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Trends in Asthma Prevalence in Canadians, Asthma Course Trajectories in Children, and the Effect of Maternal Gestational Diabetes Mellitus on the Risk of Asthma in the Offspring

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Abstract

Asthma causes substantial public health burden. An enhanced understanding of asthma burden, asthma course and identification of intervenable risk factor is warranted.

The objectives of this research were to: 1) examine the age, period and cohort effects on asthma prevalence among Canadian adults during 1994–2011 (manuscript one); 2) identify the trajectories of asthma exacerbation and their predictors in children with incident asthma (manuscript two); and 3) examine the effect of maternal gestational diabetes mellitus on the risk of asthma in offspring (manuscript three).

Longitudinal data from 13,616 individuals in the National Population Health Survey, household component were used to address objective one using generalized estimating equations. Data from 403 children with asthma in the National Longitudinal Survey of Children and Youth (NLSCY) were used to address objective two using latent class growth modeling and multinomial logistic regression. Pooled logistic regression was performed on data from 19,933 children in the NLSCY to address objective three.

By age, asthma prevalence was 12% in 20-year-olds, 6% in 50–60-year-olds, and 8% in 80-year-olds in Canadian adults. By period, asthma prevalence increased from 5% in 1994/1995 to 11% in 2010/2011. There was some evidence of cohort effect on asthma prevalence. Three distinct trajectories of asthma exacerbation were identified in children with incident asthma: *low increasing* (21.3% of children), *medium decreasing* (45.8% of children) and *high decreasing* (32.8% of children). Number of siblings at home and age at asthma diagnosis predicted trajectory group membership. The adjusted hazard ratio for the association between maternal gestational

diabetes mellitus and incident asthma in the offspring was 1.25 (95% confidence interval [CI]: 1.03, 1.51).

Our findings suggest the presence of age, period and cohort effects on prevalence of asthma in Canadian adults. Children with incident asthma apparently follow three distinct trajectories of asthma exacerbations. Gestational diabetes mellitus appears to increase the risk of asthma in the offspring. The findings from this research provide further insights into trends in asthma burden in Canadian adults, asthma exacerbation trajectories in children that would aid physicians in prognosticating its course, and potential opportunity for prevention of asthma in children.

Keywords: Asthma Prevalence; Asthma Exacerbation; Trajectories; Gestational Diabetes Mellitus; Canada

Summary for Lay Audience

Asthma causes a huge health burden. A better understanding of asthma course and its risk factors is needed. First, we studied the prevalence of asthma by age and time in adults. We then researched the patterns of an asthma attack and their associated factors in children with asthma. We looked if mothers' diabetes during pregnancy increased the risk of asthma in children. We used data from two Canadian national surveys. Our study began with 13,616 adults, 403 children with asthma and 19,933 children without asthma.

Asthma prevalence in adults was 12% at 20 years, 6% at 50–60 years and 8% at 80 years. Asthma prevalence increased from 5% in 1994/1995 to 11% in 2010/2011. Such pattern over time differed by age. Three different patterns of asthma attack course were found in children with asthma. The patterns were: a) low increasing (21.3%), b) medium decreasing (45.8%) and c) high decreasing (32.8%). Number of siblings at home and age at asthma diagnosis were associated with both *medium decreasing* and *high increasing* patterns. Diabetes during pregnancy increased the chance of asthma in children.

Co-Authorship Statement

All chapters of this doctoral research dissertation were written by Sharifa Nasreen as part of the fulfillment requirements for her Doctor of Philosophy from the Department of Epidemiology and Biostatistics. Chapter 3 was based on study using secondary data from the National Population Health Survey (NPHS), and chapters 4 and 5 were based on secondary data from the National Longitudinal Survey of Children and Youth (NLSCY). Both NPHS and NLSCY data are held by Statistics Canada and were accessed at the Research Data Center at Western University. Ms. Nasreen conducted all statistical analyses using these datasets.

Ms. Nasreen's supervisory committee (Dr. Igor Karp, Dr. Piotr Wilk and Dr. Tara Mullowney) provided guidance in the conceptualization of the research questions, study design, conduct of analyses and interpretation of results. Ms. Nasreen drafted the full text of all manuscripts and the supervisory committee members were listed as co-authors as they critically reviewed the manuscripts and assisted in clarification of concepts, interpretation of results, and revising the manuscripts. Sharifa Nasreen was the primary author of each manuscript.

Dedication

This dissertation is dedicated to my loving parents

Hasina Begum and Faiz Uddin Ahmed

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List of Abbreviations

ADA	American Diabetes Association
ADPSG	International Association of Diabetes and Pregnancy Study Group
aHR	Adjusted hazard ratio
aOR	Adjusted odds ratio
APC	Age-period-cohort
apRR	Adjusted pooled relative risk
AP	Attributable proportion due to interaction
APGAR	Appearance-Pulse-Grimace-Activity-Respiration
AvePP	Average posterior probability
BAMSE	Barn/Children, Allergy and Milieu in Stockholm, an Epidemiological study
BIC	Bayesian Information Criterion
BMI	Body mass index
CCDSS	Canadian Chronic Disease Surveillance System
CCHS	Canadian Community Heath Survey
CDA	Canadian Diabetes Association
CDE	Controlled direct effect
CI	Confidence interval
CO	Carbon monoxide
DAG	Directed Acyclic Graph
DNA	Deoxyribonucleic acid
ECD	Early Childhood Development
ESS	Enquête Sociale et de Santé

ETS	Environmental Tobacco Smoke
FEV_1	Forced expiratory volume at 1 min
FMI	Fraction of missing information
GBTM	Group-based trajectory modeling
GDM	Gestational Diabetes Mellitus
GEE	Generalized estimating equations
GLT	Glucose loading test
HbA1c	Hemoglobin A1c
HR	Hazard ratio
ICAM	Intracellular Adhesion Molecule
ICD	International Classification of Diseases
ICON	International Consensus on Pediatric Asthma
IgE	Immunoglobulin E
IQR	Interquartile range
IRR	Incidence rate ratio
ISAAC	International Study of Asthma and Allergies in Childhood
MICE	Multivariate imputation using chained equations
NDDG	National Diabetes Data Group
NDE	Natural direct effect
NICE	National Institute for Health and Care Excellence
NLSCY	National Longitudinal Survey of Children and Youth
NO	Nitric oxide
NO_x	Nitrogen oxides

NO_2	Nitrogen dioxide
NPHS	National Population Health Survey
OCC	Odds of correct classification
OGTT	Oral glucose tolerance test
OR	Odds Ratio
$PM_{2.5}$	Particulate matter ≤2.5 μm in aerodynamic diameter
PM_{10}	Particulate matter ≤10 μm in aerodynamic diameter
PMK	Person Most Knowledgeable
pOR	Pooled odds ratio
QIC	Quasi-likelihood under the independence model criterion
RDC	Research Data Centre
RERI	Relative Excess Risk due to Interaction
RR	Risk ratio/relative risk
SD	Standard deviation
SE	Standard error
SO_2	Sulphur dioxide
SSHRC	Social Science and Humanities Research Council
Th1	T-helper cell 1
Th2	T-helper cell 2
UK	United Kingdom
US	United States
USA	United States of America
WHO	World Health Organization

1. Chapter 1: Introduction and Objectives

1.1 Thesis Organization

Chapter 1 presents an overview of the thesis, including the introduction, rationale, research objectives and data sources. Chapter 2 presents a review of the relevant literature related to asthma and each of the objectives. Chapter 3 addresses Objective 1. A version of Chapter 3 is in press in *Annals of Epidemiology*. Chapter 4 addresses Objective 2. A version of Chapter 4 has been published in *Annals of Allergy, Asthma and Immunology*. Chapter 5 addresses Objective 3. A version of Chapter 5 is under review in a peer-reviewed journal. Finally, Chapter 6 provides an integrated discussion and conclusion. Other relevant information is provided in the appendices.

1.2 Introduction

Asthma is a chronic inflammatory disease of the airway characterized by recurrent attacks of breathlessness or wheezing. Asthma affected an estimated 242–305 million people worldwide in 2017 and resulted in a 4.9% increase in age-standardized years lived with disability since 2007 [1]. Globally, asthma ranked 25th among the leading causes of disease burden and was the 16th highest rank cause of years lived with disability contributing an estimated 18.9–29.7 million disability-adjusted life years lost across all ages in 2016 [2, 3]. Despite reductions in asthma-associated mortality between 2007 and 2017 [4], and in hospitalization rates between 2001 and 2015 [5], asthma remains a chronic disease of great public health importance. Asthma causes substantial economic burden through direct (e.g. physician visits, emergency visits, hospitalization, diagnostics, ambulance services, nursing services, devices and medications) and indirect (e.g., lost productivity at work and school, travel and waiting time in outpatient care and lost future potential income) costs [6]. Asthma also results in intangible costs related to pain or suffering, impairment of quality of life, limitations of physical activities and study or job

performance, job changes and psychological effects [7, 8]. Furthermore, asthma is associated with higher rates of attention-deficit/hyperactivity disorder, depression, behavioural disorders, and learning disabilities in children [9].

This doctoral research sought to explore and advance the knowledge base on three epidemiological aspects of asthma of public health importance - trends in asthma prevalence in adults, the course of asthma in children with asthma, and the role of mother's gestational diabetes mellitus as a potential intervenable risk factor of asthma development in offspring. All three themes are grounded in the ultimate goal of epidemiology –that is, prevention and control of diseases, such as asthma.

1.3 Study Rationale

Asthma affects an estimated 3.8 million Canadians accounting for substantial medical and economic burden [10, 11]. The prevalence of asthma in Canadians increased considerably from 1996 to 2012, and the prevalence differed by age: it peaked in adolescents and young adults, decreased in middle-aged adults, and then increased in elderly persons [10, 12]. Studies have generally examined and reported age-standardized or age-specific asthma prevalence estimates using non-model-based approaches. However, there is a dearth of literature on studies formally examining the effects of age and period on asthma prevalence and the differential effect of period across ages using the theoretical and analytical *age*, *period and cohort* framework. Examining the age, period and cohort effects employing the age, period and cohort framework would provide insights into the observed trends in asthma prevalence in Canadians.

The clinical course of asthma follows periods of relapse and remission. However, it remains unknown if there are any particular trajectories in asthma course. It is possible that there are qualitatively distinct trajectories of asthma course, particularly of asthma exacerbations,

among children with asthma. Identifying these trajectories and their predictors could enhance physicians' ability to better prognosticate and manage the course of asthma.

A number of risk factors of asthma are known [13]. A growing body of evidence suggests that not only factors one is exposed to after birth but also intrauterine exposure to maternal conditions such as gestational diabetes mellitus (GDM) may lead to asthma in the offspring [14-18]. However, results from previous studies are inconclusive [19]. Thus, the role of GDM in the etiology of asthma in children remains unclear and warrants further investigation.

This proposed doctoral research will enhance our understanding of several important aspects of asthma, particularly the observed trends in asthma occurrence in Canadians, the trajectories of asthma course, and the role of GDM in the etiology of asthma in the offspring.

1.4 Research Objectives

1) To examine the effects of age and period on asthma prevalence among Canadian adults during 1994/1995–2010/2011 and to assess if the period effect differed by age
2) To explore trajectories of asthma course in Canadian children with incident asthma:
    a) To identify the trajectories of asthma exacerbation
    b) To identify the predictors of the trajectories
3) To investigate the effect of maternal gestational diabetes mellitus on the risk of asthma in the offspring:
    a) To examine the total effect of maternal gestational diabetes mellitus on the risk of asthma in the offspring

b) To estimate the controlled direct effect of gestational diabetes mellitus on the risk of asthma in the offspring after accounting for the mediation by cesarean section delivery

c) To assess the joint effect of maternal gestational diabetes mellitus and maternal smoking during pregnancy on the risk of asthma in the offspring

1.5 Data Sources

This thesis employed two databases to address the research objectives. Each data source is described briefly below. Additional details are provided in respective chapters.

1.5.1 The National Population Health Survey

The National Population Health Survey (NPHS), household component was a longitudinal survey conducted by Statistics Canada to collect information on sociodemographic characteristics and health of the Canadian population [20]. The NPHS was conducted every two years starting from 1994/1995 among 17,276 individuals in 10 Canadian provinces. There were 9 cycles in total with the last cycle conducted in 2010/2011. Persons living on Indian reserves and Crown lands, residents of health institutions, full-time members of the Canadian Forces living on Canadian Forces Bases, and residents of some remote areas in Ontario and Quebec were excluded. A stratified two-stage sampling design was employed using the sampling frame of the Labour Force Survey in all provinces except Québec, where Santé Québec's design for the 1992/1993 Enquête sociale et de santé (ESS) was used. Data were collected using survey questions administered through computer-assisted interviewing methods. The table of contents of the survey questionnaire for cycle 9 is included in Appendix A. The questionnaire is available at: http://www23.statcan.gc.ca/imdb/p3Instr.pl?Function=getInstrumentList&Item_Id=75087&UL=1V&. Data from the NPHS were used to address Objective 1.

1.5.2 The National Longitudinal Survey of Children and Youth

The National Longitudinal Survey of Children and Youth (NLSCY) was a longitudinal survey conducted by Statistics Canada and Human Resources and Skills Development Canada [21]. A sample of Canadian children living in any of the 10 provinces of Canada was followed every two years to monitor their development and well-being from infancy to adulthood. The first cycle was conducted in 1994/1995 among 22,831 children aged 0–11 years. Out of the 22,831 children surveyed in cycle 1, 16,903 children were followed through the final survey (cycle 8) in 2008/2009 when they were 14–25 years old. These children comprised the 1994 original cohort (Appendix A). From cycle 2, a new cohort of children aged 0–1 year was included in each subsequent cycle and followed for a variable time to monitor early childhood development (ECD). These children comprised the ECD cohorts. The NLSCY used a multi-stage cluster sampling to select households for the survey. The Labour Force Survey's sampling frame was used to select the sampling unit, households. The original cohort contained a maximum of two children from each household. One person most knowledgeable (PMK) about the child was selected from each household. For children less than 14 years of age, most of the information were collected from the PMK. Data were collected through computer-assisted interviewing methods and paper questionnaires. Computer-assisted interviewing method comprised of computer-assisted personal interviewing or computer-assisted telephone interviewing. The table of contents of the survey questionnaire for cycle 8 is included in Appendix B. The questionnaire is available at: http://www23.statcan.gc.ca/imdb/p3Instr.pl?Function=getInstrumentList&Item_Id=88288&UL=1V&. The child-level response rates at different cycles are included in Appendix C. Data from the NLSCY were used for Objectives 2 and 3.

1.5.3 Ethical Approval and Data Access

Ethical approval was not needed as the study relied on anonymous and confidential secondary data from Statistics Canada. However, the proposal for this study was approved by the Social Science and Humanities Research Council (SSHRC), Canada (see Appendix D) to gain access to the data in Statistic Canada's Research Data Centre (RDC) at Western University. Data are only accessible to researchers with approved projects who have been sworn in under the Statistics Act of Canada as deemed employees.

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2. Chapter 2: Literature review

2.1. Asthma

2.1.1. Asthma in Children

2.1.1.1.Definition

The International Consensus on (ICON) Pediatric Asthma defines pediatric asthma as “a chronic inflammatory disorder associated with variable airflow obstruction and bronchial hyperresponsiveness. It presents with recurrent episodes of wheeze, cough, shortness of breath, and chest tightness” [1]. Chronic inflammation, airway hyperresponsiveness and airway remodeling are central to the complex pathophysiology of asthma. Expiratory wheezing and intermittent dry cough are the most common symptoms of asthma in children; intermittent nonfocal chest pain are reported more in younger children while shortness of breath, chest congestion and tightness are commonly reported in older children [2].

2.1.1.2.Asthma Classification and Phenotypes

Being a heterogeneous disease with different phenotypes and clinical presentations, asthma in children can be classified in various ways [2]. Based on the natural history, asthma is classified into two common types: 1) Recurrent wheezing asthma: It is transient nonatopic wheezing asthma that occurs in early preschool years, causes recurrent wheeze or cough primarily due to common respiratory viral infections and usually resolves or improves during preschool and lower school years and 2) Chronic asthma: It is persistent atopy-associated asthma that begins in early preschool years, associated with allergy and has the highest risk for persistence into later childhood and often adulthood. Asthma can also be classified according to disease severity into two classes: intermittent or persistent; according to asthma control while being managed and treated into three classes: well controlled, not well controlled, and very poorly controlled; and

according to treatment response and medication requirements into four classes: easy-to-treat (well controlled with low levels of daily controller therapy), difficult-to-treat (well-controlled with multiple and/or high levels of controller therapies), exacerbators (continue to have severe exacerbations despite being well controlled), and refractory (continue to have poorly controlled asthma despite multiple and high levels of controller therapies) [2]. However, disease severity can reflect multiple factors such as inherent severity of the disease, resistance to treatment and treatment adherence and it can be difficult to differentiate between these factors. Classification based on asthma control has more clinical utility in guiding treatment and is thus recommended [1].

Having significant individual variability over time together with heterogenous nature in disease manifestation, different asthma/wheeze phenotypes have been proposed or identified from longitudinal studies. Three asthma phenotypes were proposed in children with asthma: transient wheezing phenotype with symptoms limited to the first 3–5 years of life, non-atopic wheezing of the toddler and pre-school aged children phenotype having wheezing due to respiratory syncytial virus in the first years of life and more likely to continue wheezing up to 13 years of life, and IgE-mediated wheezing phenotype, also known as the classic asthma phenotype, associated with allergic sensitization [3]. In the Tucson Children's Respiratory Study, a birth cohort study following children from birth to 6 years of age, one third of the children developed lower respiratory tract illness with wheezing by three years of age and 40% of them continued to wheeze at six years of age [4]. However, only 14% of the children with wheeze during the first 2 years of life had asthma, defined as "at least four episodes of wheeze in the last 12 months or at least one episode of wheezing during the same period in combination with occasional or regular treatment with inhaled glucocorticosteroids" in Barn/Children, Allergy and

Milieu in Stockholm, an Epidemiological study (BAMSE), another population-based birth cohort study [5]. Following children from the Tucson Children's Respiratory Study through adolescence showed that the patterns of wheezing prevalence and levels of lung function are established by 6 years of age [6]. Respiratory viruses, such as respiratory syncytial virus, parainfluenza virus and rhinovirus have been commonly identified in children with lower respiratory tract illness with wheeze during the first year of life [7, 8].

2.1.1.3.Diagnostic Challenges in Children

The diagnosis of asthma in children, particularly in preschool children is challenging [9, 10]. History of symptoms, physical examination and objective evidence of airway obstruction helps in the diagnosis and determining the severity of asthma. The diagnostic challenge in children relates to both clinical diagnosis and lung function tests to provide evidence of airway obstruction. Many symptoms of asthma are not asthma-specific, and common symptoms such as recurrent cough and wheeze can be present in a range of other pediatric diseases, including upper airway diseases, congenital structural bronchial diseases, bronchial/tracheal compression, endobronchial diseases, oesophageal/swallowing problems, diseases causing pulmonary suppuration, bronchopulmonary dysplasia, tracheomalacia and pulmonary oedema secondary to left-to-right shunting or cardiomyopathy [11]. Clinical diagnosis of asthma requires careful consideration of symptoms and their frequency, severity, and pattern together with age of the child and presence of known risk factors. Furthermore, lung function assessment in children aged 2–6 years remains challenging. Different lung function tests such as spirometry, multiple inert gas washout, plethysmography, interrupter resistance and impulse oscillometry have been assessed in preschool children, with varying results [12]. Resistance and spirometry are feasible in young children aged 3–6 years with success increasing with age but require time, patience and

technical skills [13, 14]. Asthma diagnosis in children aged less than two years is particularly difficult due to absence of objective lung function measurements and specific biomarkers. Spirometry is not often feasible in children less than 4 or 5 years of age. Even when feasible, spirometry can not provide definitive diagnosis of asthma. Indeed, small airway dysfunction associated with asthma was found in children with mild asthma symptoms and normal spirometry [15]. Normal forced expiratory volume at 1 min (FEV_1) has also been reported in children with severe persistent childhood asthma [16]. But even in older children (7–12 years), objective measurements for bronchial hyperresponsiveness only "marginally increased the diagnostic accuracy after symptom history had been taken into account" [17].

2.1.2. Asthma in Adults

Asthma in adults has two distinct phenotypes: early-onset phenotype that originates in childhood by 12–13 years of age, and late-onset phenotype that starts later in adulthood without any symptoms during childhood [18-20]. Most of the adult asthma cases have its onset earlier during childhood [21]. Adults with early-onset asthma are more likely to be atopic and have higher frequency of asthma attacks, and adults with late-onset asthma are more likely to be females, smokers and have higher levels of airflow obstruction, less atopy and shorter duration of disease [20]. Late-onset asthma can be mild or severe, and generally has worse prognosis and poorer response to the standard asthma treatment compared with childhood- or early-onset asthma [20, 22, 23]. Late-onset asthma in adults has been further classified into five different phenotypes based on cluster analysis studies: eosinophilic inflammation-predominant asthma, mild-to-moderate well-controlled asthma, obese noneosinophilic asthma, smoking asthma, and severe and obstructive asthma [24].

2.1.3. Overdiagnosis and Underdiagnosis of Asthma

Challenges in asthma diagnosis can lead to both overdiagnosis and underdiagnosis [25]. Asthma was excluded in one-third of Canadian adults with a physician-diagnosed asthma following objective evaluation using spirometry and methacholine challenge test [26]. Overdiagnosis was associated with older age at diagnosis, higher FEV_1 percent of predicted, being male, lack of daily use of asthma medication and lack of daily use of inhaled corticosteroids [26]. Another recent study also reported that current asthma was ruled out in one-third of the adults with physician-diagnosed asthma, and these patients were nearly 12% less likely to undergo airflow limitation test at the time of diagnosis in the community [27]. Asthma overdiagnosis has also been reported among British children by general practitioners in primary care [28]. However, some of the patients with physician-diagnosed asthma may have outgrown asthma over the course of time. Asthma overdiagnosis is not surprising because use of heterogenous diagnostic criteria by the physicians and lower rates of diagnostic tests have been reported over the last few decades. A study was conducted to compare the reported practices with the Canadian Consensus recommendations among five specialty groups of physicians: family physicians/general practitioners, respirologists, internists, pediatricians and allergists/clinical immunologists [29]. This study was done in 10 provinces and 2 territories in 1996–1997. While virtually 100% respondents reported using medical history and physical examination for diagnosis, use of objective measurement of airflow obstruction varied greatly among physicians in different speciality. A lower rate of use of spirometer to assist with diagnosis was reported by physicians in pediatrics and family practice for both children aged six years or younger (2.4% and 13.6%, respectively) and adults and children over six years of age (31.1% and 42.7%, respectively), while the highest proportion of spirometry use was reported by physicians in respirology for both

groups (21.3% for children aged six years or younger and 97.9% for adults and children aged more than six years). The rate of use of spirometry among primary care physicians (pediatricians and family physicians) has been reported in other studies conducted in the United States in last two decades [30-32]. Different diagnostic criteria and lower rate of use of spirometry to diagnose asthma at primary care remains low even lately although the majority of the asthma cases are diagnosed at the primary care level. A survey among pediatric pulmonologists and general pediatricians from 25 different countries including the United States and Canada reported heterogeneity in the diagnostic criteria used by the physicians to diagnose pediatric asthma and 64% of the general pediatricians did not use any diagnostic tests whereas 91% of the pulmonologists used spirometry before and after bronchodilator as part of their diagnosis [33].

On the other hand, asthma has also been found to remain undiagnosed in both children and adults [34-36]. While "all that wheezes is not asthma" [37], underdiagnosis remains a frequent problem in children in whom asthma tends to be misdiagnosed as chronic bronchitis, bronchiolitis or pneumonia, leading to inadequate or inappropriate therapy [38]. More than one-thirds of Norwegian children with wheeze but without a physician-diagnosed asthma was deemed to have asthma [39]. A case of cough variant asthma has been reported to remain undiagnosed for 16 years in an adult patient [40]. Asthma in older adults (aged 64 years or more) is often underdiagnosed and undertreated. The cause of the underdiagnosis is multifactorial: reduced symptom perception, an assumption that dyspnea is normal in old age, misattribution of symptoms to other causes (e.g., congestive cardiac failure), under use of diagnostic tools including spirometry, self-limitation of activities, social isolation, depression and misconception that adult-onset asthma is rare [41].

2.1.4. Measuring Asthma Occurrence in Epidemiologic Studies

In absence of gold standard for defining and diagnosing asthma, measuring occurrence of asthma, including prevalence in population studies has been challenging. As a result, different operational definitions based on symptoms, physician diagnosis, medication use, bronchial hyperresponsiveness or spirometry with or without specific time frame, alone or in combination, have been used in epidemiological studies on childhood asthma. Indeed, 60 different definitions to diagnose asthma in children aged 6–18 years were found in 122 cohort studies published during 1998–2008, resulting asthma prevalence estimates ranging between 15.1% and 51.1% [42]. On the other hand, a review of 117 cross-sectional prevalence studies published during 2010 through 2013 reported that 34 studies used 8 different definitions of "lifetime asthma", 54 studies used 12 different definitions of "diagnosed asthma" and 61 studies used 29 different definitions of "current asthma" [43]. Furthermore, poor agreement between bronchial hyperresponsiveness and clinical assessment of asthma by a physician has also been noted in population-based studies that compared the validity of asthma symptom questionnaires and/or bronchial hyperresponsiveness testing against asthma diagnosis from clinical examination by a physician or self-report of physician-diagnosed asthma [44, 45].

The choice of instruments and methods used in population-based studies depends on the objective and targeted effect measures as well as on practicalities such as feasibility, cost and time. Written questionnaires are typically used in surveys to measure asthma and respiratory symptoms in the population. A measurement tool with good validity and reliability can ensure accurate measurement of asthma. Since the symptoms of asthma are non-specific and often subject to individual perception, this can lead to errors in reporting. The International Study of Asthma and Allergies in Childhood (ISAAC) developed a video questionnaire and compared it

with a written questionnaire among 13-14 years old Canadian children to assess the prevalence of asthma symptoms (wheezing). The prevalence of wheezing ever, current wheeze, wheeze on exercise, and nocturnal wheeze was higher based on the responses to the written questionnaire compared with the video questionnaire among children with diagnosed asthma and there was limited agreement between the questionnaires [46]. Video questionnaire had a slightly lower accuracy than the written questionnaire when evaluated against a clinical diagnosis of asthma [47]. Reported physician-diagnosed asthma in questionnaire may be preferable in terms of feasibility but is not a robust method of assessing disease burden because the diagnostic criteria may vary from physician to physician and depend on the availability of diagnostic tests at point of care. However, earlier studies conducted during 1980s reported low sensitivity and high specificity of reported physician-diagnosed asthma when validated against bronchial challenge test [45]. Parent report of asthma in 7-year-old children had a 79.8% estimated sensitivity and 80.8% estimated specificity when validated against a pediatric allergist diagnosis of asthma in a cohort study [48], while parent report of physician-diagnosed asthma in school children aged 9–12 years had a 75% estimated sensitivity and 92% estimated specificity when compared against clinical diagnosis and reversible bronchoconstriction or positive methacholine challenge [49]. Using general practitioner recorded asthma (from patients records in General Practice Research Database) as the gold standard, parent report of a doctor-diagnosed asthma in children aged less than 9 years of age had an 88.5% estimated sensitivity and 95.7% estimated specificity in UK [50]. In addition, there is the potential that asthma remission status may not be informed by the physicians.

Use of health administrative databases remain another preferred source of data for studies ascertaining disease burden, including asthma. While validated case definitions can reduce false

positive and help objective diagnosis, use of health administrative data is not free from disadvantages. Notable drawbacks are exclusion of cases for individuals not seeking medical care, seeking care from physicians who do not report services and individual or population not covered by unified single-payer health care system.

2.1.5. Etiology of Asthma

The etiology of asthma remains largely unknown, leading to a lack of primary preventive options. However, two general theories regarding the origin have been suggested, and several specific risk factors have been identified.

2.1.5.1.Fetal Origin of Adult Disease Hypothesis

The fetal origin hypothesis, also known as the Barker hypothesis or developmental plasticity hypothesis, was first postulated by David J. P. Barker [51]. Fetal programming or impaired intrauterine growth and development have been implicated in the origin of diseases such as coronary heart disease, stroke, hypertension and non-insulin-dependent diabetes mellitus [52-56]. Fetal origin of hypertension has also been implicated in animal models where prenatal exposure to maternal general and protein undernutrition were associated with increased systolic blood pressure and mean arterial blood pressure [57]. Several studies have suggested that asthma has its origin in fetal life and infancy similar to other common chronic diseases [58]. Developmental influences on airway structure and airway inflammation could possibly play a part in asthma, particularly intrauterine exposures that lead to postnatal airway inflammation [59]. It is also possible that fetal nutrition and environmental exposures causing epigenetic modifications of DNA expression could exert indirect effects on airway and lung growth.

2.1.5.2.Hygiene Hypothesis

The hygiene hypothesis proposes that "the decreasing incidence of infections in western countries and more recently in developing countries is at the origin of the increasing incidence of both autoimmune and allergic diseases" [60]. In 1989, a study reported an inverse relationship between family size and development of atopic disorders, hay fever or eczema suggesting that reduced cross-infection opportunity in the family due to declining family size, better household amenities and higher personal cleanliness led to the observed increase in atopic diseases [61]. It was proposed that allergic diseases were prevented by early childhood infections transmitted by unhygienic contact with older siblings or prenatally from mother infected through contact with older children, thereby postulating the 'hygiene hypothesis' of atopic diseases [61]. As a result, different factors affecting microbial exposure such as water and food, sanitation, antibiotics, vaccination, birth practices and farm living have been investigated along with changes in lifestyle factors such as dietary practices. Animal models and some intervention trials in human have provided the proof of the principle of hygiene hypothesis with possible underlying mechanisms [60]. However, infectious disease specialists have expressed concerns that the term 'hygiene hypothesis' will adversely affect infectious disease risk perceptions and the importance of the risk control measures among the general population. It has been suggested that the hypothesis should rather be renamed as 'microbial exposure' or 'microbial deprivation' hypothesis to focus on the impact of pathogens on atopic diseases to dissipate the possible negative impact on good hygiene behaviour [62]. There is another emerging hypothesis that involves microorganisms but in the opposite direction from the hygiene hypothesis. This relatively new overarching 'microbiome hypothesis' suggests that certain microbiome pathogens

could possibly be “determinants of asthma development, persistent, severity and risk of exacerbations” [63].

2.1.5.3.Risk Factors of Asthma

The risk factors of asthma have been extensively investigated over the last couple of decades and continues to be investigated to generate further knowledge. Several comprehensive reviews, including systematic reviews and meta-analyses have summarized and/or synthesized existing evidence on the role of different risk factors.

A wide range of demographic, developmental, lifestyle, infection, medication, diet and inhaled exposures have been implicated as risk factors for childhood asthma development. Such factors include age (nonlinear), sex (age dependent), family history, genetics, urbanization, high-income lifestyle, low birth weight, fast infant weight gain, preterm birth, cesarean section delivery, atopic sensitization, rhinitis, stress, high body mass index (BMI), sedentary behavior, infections with respiratory syncytial virus, rhinovirus, pertussis, paracetamol, beta-agonists, antibiotics, environmental tobacco exposure, child smoking, air pollution, occupational exposure, house dust mite and molds [64]. An extensive review of existing literature in 2008 reported different prenatal (maternal smoking, diet and nutrition, stress, use of antibiotics and cesarean section delivery) and childhood (allergic sensitization, environmental tobacco smoke, exposure to animal, breastfeeding, decreased lung function in infancy, family size and structure, socio-economic status, antibiotics, infections and sex) risk factors of asthma [65].

Parental asthma, prenatal environmental tobacco smoke, and prematurity were found to be well-established risk factors for childhood asthma in a recent systematic review and meta-analysis. However, there were also mild-to-moderate causal effects of pregnancy related

(maternal weight gain or obesity, maternal use of antibiotics or paracetamol, and maternal stress), perinatal (birth by cesarean section delivery), or postnatal (severe respiratory syncytial virus infection, overweight or obesity, indoor exposure to mold or fungi, and outdoor air pollution) factors on childhood asthma that warranted confirmation in further appropriately designed prospective or interventional studies [66]. Another systematic review of literature on the association between development of asthma in children up to 9 years of age and different exposures, namely second-hand smoke, inhaled chemicals, damp housing/mold, dietary exposures, respiratory virus infection and medications included 135 papers including 15 systematic reviews, 6 meta-analyses and 14 intervention studies [67]. This review suggested that observational studies likely suffered from publication bias, reverse causation bias and confounding. While consistent evidence of the association between asthma and second-hand smoke, inhaled chemicals, mold, ambient air pollutants, some deficiencies in maternal diet and respiratory virus infections were found, less consistent evidence of exposures to pets, breastfeeding and infant dietary exposures as risk factors for asthma were noted. Furthermore, the consistent association observed between early life exposure to antibiotics and paracetamol and childhood asthma might reflect reverse causation [67].

History of early childhood wheezing before two years of age, male sex, low birth weight, childhood allergy, single parent, maternal smoking during pregnancy, maternal medication use, parental atopy and low socioeconomic status increased the risk of incidence of physician-diagnosed asthma in preschool children [68]. Maternal asthma, young age, smoking, previous miscarriages, high number of previous deliveries, cesarean section, low gestational age, and low ponderal index (birth weight/birth length^3) were associated with an increased risk of asthma before 3 years of age, while only maternal asthma, low gestational age and low ponderal index

were associated with an increased risk of asthma at 3 years of age or later suggesting different risk factors for early and late-onset asthma [69]. However, increasing ponderal index was associated with an increased risk of asthma in adolescents [70].

Studies have also examined the association between fetal growth indicators and other prenatal factors and the risk of asthma using anti-asthma medications in children. Maternal asthma, male child, maternal smoking during pregnancy, increased number of cigarettes smoked per day, having older siblings, maternal age <21 years, and maternal non-cohabitation were associated with an increased risk of receiving a prescription for asthma (both a β-agonist and an inhaled glucocorticoid) in infants during the first year of life in a birth cohort study in Denmark [71]. In this study, increasing birth weight, preterm births, lower gestational age, placental weight ≥750 g and ponderal index ≥2.7 were also associated with an increased risk of receiving asthma medications. In another study, being the first-born child, maternal age more than 44 years, involuntary childlessness for more than a year, maternal smoking during pregnancy, maternal diabetes mellitus of any kind, pre-eclampsia, cesarean section, instrumental vaginal delivery, preterm birth, low birth weight, small-for-gestational age, APGAR score <7 at 5 minutes, respiratory problems, mechanical ventilation, sepsis and/or pneumonia and neonatal phototherapy and/or icterus were associated with an increased prescription of anti-asthmatic among Swedish children [72]. Prescription of asthma medication were used as a surrogate measure for asthma in these studies. Asthma medications are prescribed for treating wheezing due to other causes as well and have high sensitivity but low specificity.

Sex of the Child

There is an age-dependent effect of sex on the risk of asthma. Asthma is more common in boys until 13 years of age and thereafter is more prevalent in girls [64]. Biological sex differences as

well as sociocultural and environmental differences have been implicated in the differential sex effect on asthma [73]. Biological sex difference is caused by factors such as sex hormones, genetic susceptibility, differential lung development and immunological factors. A complex interplay among the sex hormones likely play a major role; estrogen and progesterone may increase the prevalence and severity of asthma in females and androgens may be protective. Genetic factors lead to increased female susceptibility for asthma. Sex differences in lung development and maturation, and physical growth of lung from birth into adulthood also affect asthma susceptibility and severity in females. Sex hormones also play an immunomodulatory role in the sex differences [73].

Parental History of Asthma

Parental asthma is a well-known risk factor of asthma [66, 74]. A systematic review and meta-analysis of 33 studies reported that children with maternal asthma had a higher odds of asthma compared with children without maternal asthma (OR 3.04, 95%CI: 2.59, 3.56) and children with paternal asthma had a higher odds of asthma compared with children without paternal asthma (OR 2.44, 95%CI: 2.14, 2.79); maternal asthma conferred greater risk than paternal asthma (3.04 vs 2.44, p=0.037) [75]. However, the effects were attenuated when the analysis was limited to physician-diagnosed asthma or in children aged 5 years or older although maternal asthma conferred greater risk than paternal asthma. It has been suggested that non-genetic *in utero* and/or post-natal factors may play a key role in transmission of asthma susceptibility from mother to child.

Exposure to Cigarette Smoking

Passive smoking is associated with increased asthma incidence and severity of asthma, and it has been suggested that the duration of exposure plays an important factor in asthma induction [76,

77]. A systematic review and meta-analysis of evidence from 79 prospective studies suggests that exposure to pre or postnatal maternal, paternal or household smoking increased the risk of incident asthma in childhood by 21% to 85% and the strongest effect was from maternal smoking during pregnancy on asthma in children aged two years or younger [78].

Active smoking also increases the risk of asthma in adolescence (RR 3.9, 95% CI: 1.7, 8.5), and the highest risk of asthma from active smoking (RR 8.8, 95% CI: 3.2, 24.0) was among children who smoked regularly and had exposure to maternal smoking during pregnancy [79]. Smoking causes pathophysiologic changes in the airways, including inflammation and airway hyperresponsiveness leading to new-onset asthma. A ban on smoking in workplaces or public places was associated with both an immediate reduction in hospital attendance for asthma [–10·1% (95% CI: –15·2, –5·0), p=0·0001] and an annual rate reduction [–7·5% per year (95% CI: –16·0, 0·9), p=0·081] in hospital attendance for asthma [80].

Pre-pregnancy Body Mass Index and Excess Maternal Gestational Weight Gain

Higher pre-pregnancy body mass index (BMI) and excess maternal gestational weight gain were associated with an increased risk of asthma [81-84]. Obese (BMI>30) mothers had a higher odds (OR 1.44, 95% CI: 1.12, 1.86) of having a child with asthma at 3 years of age [81]. Maternal BMI ≥35 (aOR 1.87, 95% CI: 0.95, 3.68) and excessive gestational weight gain of ≥25 kg were associated with doctor-diagnosed asthma ever during the first seven years of childhood [82]. Each 1-kg/m^2 increase in maternal BMI was associated with a 2% to 3% higher odds of childhood asthma [84]. Higher maternal BMI was also associated with an increased risk of childhood asthma medication (inhaled corticosteroid) use [85]. Four different biological mechanisms have been suggested in the association between maternal obesity and childhood asthma. Maternal obesity exerts effects through maternal and infant excess pro-inflammatory

factors/cytokines or reduction of anti-inflammatory factors, altered maternal/gut colonization, and possibly through pregnancy complications and childhood obesity [86-88].

Pregnancy Complications

Pregnancy complications such as hemorrhage, anemia, cervix insufficiency, placental dysfunction, rhesus immunization, preterm contractions, and preeclampsia and hyperemesis increased the odds of incidence of asthma in children [89].

Preterm/premature Birth

A systematic review and meta-analysis based on 19 (5 cross-sectional, one case-control and 13 cohort) studies reported higher odds of asthma in children (OR 1.37, 95% CI: 1.30, 1.43) with preterm delivery (gestational age <37 weeks) compared with children born at term [90]. However, the effect was found to be greater in studies with a younger study population compared with studies in older population. Although the underlying mechanisms are not well understood, three possible pathways (models) were suggested. The first model suggested that preterm delivery per se increased the risk of asthma through anatomical and immunological immaturity. According to the second model, there might be common genetic and environmental determinants of asthma and preterm delivery, while both preterm delivery and those determinants independently also increase the risk of asthma with the possibility that preterm birth modifies the relationship between environmental exposures and asthma. The third model suggests that the association between preterm delivery and asthma might be due to an association between prenatal and postnatal exposures. A meta-analysis of data of 147,252 children from 31 European birth cohorts also reported that preterm birth was associated with an increased risk (pooled OR 1.40, 95% CI: 1.18, 1.67) of asthma in school-aged children (aged 5–10 years) [91].

Cesarean Section Delivery

A number of studies have found a positive association between cesarean section delivery and asthma in children [92-102]. Some of these studies also examined the association separately for planned/elective and emergency/acute cesarean section delivery and/or according to the timing of cesarean section delivery in relation to membrane rupture. In one such study, the adjusted HR for the association between emergency cesarean section and asthma was 1.59 (95% CI: 1.44, 1.75) and the adjusted HR for the association between planned cesarean section and asthma was 1.42 (95% CI: 1.25, 1.61), compared with spontaneous vaginal delivery [95]. In another study, the adjusted HR for the association between acute cesarean section delivery and asthma was 1.06 (95% CI: 1.02, 1.10) and the adjusted HR for the association between elective cesarean section and asthma was 1.24 (95% CI: 1.20, 1.28), compared with vaginal delivery [98]. It has also been suggested that the risk of asthma following cesarean section delivery depends on when it was performed with regard to membrane rapture. In yet another study, the adjusted incidence rate ratio for the association between cesarean section delivery performed before rupture of membranes and asthma was 1.20 (95% CI: 1.16, 1.23) and the adjusted incidence rate ratio for the association between cesarean section delivery after rupture of membranes and asthma was 1.12 (95% CI: 1.09, 1.16), compared with vaginal delivery [99]. However, one study reported that the risk of asthma during the first 7 years of life was decreased by 7% in children born by cesarean section (aHR 0.93, 95% CI: 0.60, 1.40) [102].

Nevertheless, systematic reviews and meta-analyses examining evidence from different studies suggest that there was a positive association between cesarean section delivery and the risk of asthma in children There was a higher odds of childhood asthma (pOR 1.20, 95% CI: 1.14, 12.6) in a meta-analysis of findings from 23 (one cross-sectional, four case-control and 17

cohort) studies [104]. Cesarean section was associated with a higher odds of asthma (pOR 1.18, 95% CI: 1.05, 1.32 from 13 studies) and hospitalization for asthma (pOR 1.21, 95% CI: 1.12, 1.31) in another meta-analysis [105].

Children born by vaginal delivery are exposed to maternal vaginal and intestinal microbiota whereas children born by caesarean section delivery are exposed to skin and environmental microbiota leading to differential acquisition of microbiota shortly after birth. Cesarean section delays and alters the development of intestinal flora in child thereby altering immune development [106] that may increase the risk of atopic disease in line with the hygiene hypothesis [107]. Cesarean section delivery also delays the development of upper respiratory tract microbiota in infancy, including reduced colonization of health-associated commensals and hence could play a role in the development of asthma [108-110]. It is also possible that cesarean section causes transient tachypnea in the newborn that increases the risk of asthma.

Low Birth Weight

Low birth weight (birth weight <2500 g) is associated with an increased risk of childhood asthma. A meta-analysis of 13 cohort studies also suggested that children with low birth weight are at increased risk of childhood asthma (RR 1.15, 95% CI: 1.08, 1.22) compared with children with normal birth weight [111]. Another meta-analysis of 18 studies in children and adults also suggested a higher odds of asthma in both children (OR 1.28, 95% CI: 1.09, 1.50) and adults (OR 1.25, 95% CI: 1.12, 1.39) with low birth weight compared with those with normal birth weight (2500–4000 g) [112]. There was also a higher odds of asthma at age 3–9 years with decreasing birth weight [OR (per 100g) 1.04, 95% CI: 1.03, 1.05] in twins, and lower birthweight twin pair had a higher odds of asthma compared with heavier co-twins within twin pairs [113]. It is suggested that low birth weight might lead to developmental adaptations

resulting in impaired lung growth with smaller airways and decreased lung volume leading to asthma.

Respiratory Tract Infections

Wheezing episodes due to viral respiratory infections by respiratory syncytial virus, human rhinovirus, metapneumovirus, parainfluenza virus, corona virus have been associated with an increased likelihood of subsequent development of childhood asthma [114-116]. This contradicts the hygiene hypothesis. Whereas, lower respiratory tract infections in early infancy is associated with reduced IgE levels and day-care attendance during early infancy reduced the risk of allergen sensitization, conforming to the hygiene hypothesis [117-119].

Antibiotic Use

There is evidence that use of antibiotics within the first 6 months of life increases the risk of asthma and allergy at 6 years of age [120], however, a study suggested that the association observed between early antibiotic and wheezing is likely due to confounding rather than causal [121]. It is likely that the effect of infections on the occurrence of asthma or allergic diseases depend on specific pathogen, severity of infection, cumulative number of infections and the stage of immune development of the child [114].

Breastfeeding

The association between childhood asthma and breastfeeding remained ambiguous for some time because some studies reported benefit, while other studies reported no benefit or even an increased risk of asthma in breastfed babies. A systematic review and meta-analysis reported that breastfeeding was associated with reduction in asthma/wheezing, however, the protective effect seemed strong at 0–2 years of age and decreased thereafter [122].

Body Mass Index and Growth of the Child

Boys with high body mass index (BMI≥85th percentile) at 2–3 years of age had an increased risk of incident asthma (HR 1.6, 95% CI: 1.1, 2.4) compared with their counterparts up to 14 years of age [123]. A rapid growth in BMI during the first 2 years of life increased the risk of incident asthma (HR 1.3, 95% CI: 1.1, 1.5) up to 6 years of age compared with children with a less pronounced early childhood weight gain [124]. Children having a persistent high BMI during childhood or a high BMI at 6 to 7 years of age had a higher odds of dyspnea (OR 1.68, 95% CI: 1.18, 2.39) at 8 years of age. However, a high BMI at an earlier age was not related to a higher odds of asthma symptoms such as dyspnea and bronchial hyperresponsiveness at 8 years if the child became normal weight by 6 or 7 years [125]. A 3-unit increase in BMI was associated with an increased risk of asthma in middle-aged males and females (RR 1.21, 95% CI: 1.16, 1.26) using asthma prescription as a surrogate marker of incident asthma [126]. Obesity likely increases proinflammatory cytokines such as interleukin-6, leptin, tumor necrosis factor α, tumor growth factor β1, eotaxin as well as modifies atopy and Th1-Th2 imbalance ultimately increasing airway hyperreactivity; obesity also decreases expiratory residual volume and functional residual capacity that reduces peripheral airway diameter and smooth muscle structure and function [127].

Low Physical Activity

Children with low physical activity (no team sports played, sports participation ≤once per week and television viewing ≥1 hour per day) had an increased risk of incident asthma (OR 1.32, 95% CI: 0.95, 1.84) compared with children with high physical activity (≥1 team sport played, sports participation ≥2 times per week and television viewing <1 hour per day) as suggested by the results from a systematic review and meta-analysis of three cohort studies [128]. An inverse

relationship between leisure-time physical activity in rural environment and asthma symptoms in children aged 10–12 years was reported from a cross-sectional study [129].

Air Pollution

The strength of evidence on the association between several traffic-related air pollutants such as nitrogen oxides (NO_x), nitric oxide (NO), nitrogen dioxide (NO_2), particulate matters [≤10 μm and ≤ 2.5 μm in aerodynamic diameter (PM_{10} and $PM_{2.5}$)], sulphur dioxide (SO_2), carbon monoxide (CO), ozone, black carbon and new-onset asthma is variable across studies [130]. A systemic review and meta-analysis of findings from 14 cohort studies, 2 nested case-control studies in a birth cohort and two cross-sectional studies reported an increased risk of childhood asthma due to prenatal exposure to NO_2 [pooled OR 1.07 (95% CI: 1.01, 1.14)], PM_{10} [pooled OR 1.08 (95% CI: 1.05, 1.12)] and SO_2 [pooled OR 1.02 (95% CI: 0.98, 1.07)] [131]. Exposure to higher concentrations of NO, NO_2, and CO during pregnancy and the first year of life was associated with incident childhood asthma; aOR 1.08 (95% CI: 1.04, 1.12) for a 10-μg/m^3 increase of NO, 1.12 (95% CI: 1.07, 1.17) for a 10-μg/m^3 increase in NO_2, and 1.10 (95% CI: 1.06, 1.13) for a 100-μg/m^3 increase in CO [132]. Childhood exposure to black carbon, NO_2, NO, $PM_{2.5}$ and PM_{10} increased the risk of childhood incident asthma or lifetime prevalence of asthma in children [1.08 (95% CI: 1.03, 1.14) per 0.5 × 10−5 m−1 black carbon, 1.05 (95% CI: 1.02, 1.07) per 4 μg/m3 NO_2, 1.48 (95% CI: 0.89, 2.45) per 30 μg/m3 NO_x, 1.03 (95% CI: 1.01, 1.05) per 1 μg/m3 $PM_{2.5}$, and 1.05 (95% CI: 1.02, 1.08) per 2 μg/m3 PM_{10}] as reported by another systematic review and meta-analysis of 21 studies [133].

Four mechanisms have been attributed to the effect of air pollutants on asthma development and exacerbations: oxidative stress and damage, airway remodeling, inflammatory pathways and immunological responses, and enhancement of respiratory sensitization to

aeroallergens. However, air pollutants might exert different effects depending on the concentration. At high concentrations seen in megacities in India and China, air pollutants might have direct irritant and inflammatory effects, while at lower concentrations seen commonly in high-income countries airway inflammation, airway hyperresponsiveness and oxidative stress may play key roles [130]. However, the mechanisms in non-atopic asthma in children and adults remain largely unknown.

Risk Factors for Non-atopic Asthma/wheeze in Children

A systematic review of risk factors for non-atopic asthma/wheeze in children and adolescents evaluated 30 risk factors from 43 articles where family history of asthma/rhinitis/eczema, dampness/mold in the household and lower respiratory tract infections in childhood were identified as common risk factors of non-atopic asthma/wheeze [134].

Neonatal Risk Factors of Asthma and Asthma-associated Hospitalization

Different neonatal factors have been identified as risk factors of asthma and asthma-associated hospitalization. Lower Appearance-Pulse-Grimace-Activity-Respiration (APGAR) scores at 1- and 5-minutes following birth increased the risk of asthma in children [135, 136]. Neonatal factors such as respiratory distress syndrome with or without bronchopulmonary dysplasia, transient tachypnea of the newborn, sepsis or pneumonia, respiratory problems, mechanical ventilation, low APGAR score, neonatal icterus and neonatal phototherapy also increased the odds of hospitalization due to asthma in children [137, 138]. The association between neonatal phototherapy and hospitalization was stronger for children hospitalized two or more times.

Risk factors for Adult-onset Asthma

Active and passive cigarette smoking, female sex hormones, rhinitis, acute lower respiratory infections, obesity and stressful life events have been implicated as risk factors for adult-onset asthma [20].

2.1.6. Global Burden and Health Impact of Asthma

Asthma is one of the major chronic diseases of public health importance in the world. With significant advancement in asthma management, asthma mortality rates have declined [139]. There has been a 23.5% reduction in age-standardized asthma death rates between 2007 and 2017 worldwide [140]. Hospital admission rates for asthma has also decreased over the last several decades [139], however, there has not been any overall decline in asthma prevalence [64, 141]. Asthma affected an estimated 242–305 million people worldwide in 2017 and resulted in a 4.9% increase in age-standardized years lived with disability since 2007 [142]. Globally, asthma ranked 25th among the leading causes of disease burden and was the 16th highest rank cause of years lived with disability contributing an estimated 18.9–29.7 million disability-adjusted life years lost across all ages in 2016 [143, 144]. In children, symptom prevalence varies greatly globally, and asthma symptoms are more prevalent in affluent countries while symptoms tend to be more severe in less affluent countries [145]. Three pediatric asthma related epidemics have been reported from the developed countries during 1955–2010: “a double peaked mortality epidemic (1960s and 1980s), a hospital admission epidemic (peaked around 1990) and a steadily growing epidemic of children who report asthmatic symptoms on questionnaires” [146]. In adults, the overall prevalence of doctor diagnosed asthma and clinical or treated asthma also varied greatly among different counties in the world [147].

Asthma causes substantial economic burden through direct and indirect costs [148]. Direct costs of asthma incur through physician visits, emergency visits, hospitalization, nursing services, ambulance services, medications, devices, diagnostic tests, research and education with medication and hospitalization accounting for the major cost. Indirect costs incur through lost productivity at work and school (due to absenteeism and restricted days), travel and waiting time associated with outpatient care and lost future potential income associated with morbidity and mortality. Hospitalization and medications are the major drivers of direct cost, while work and school loss are the major drivers of indirect cost. However, the indirect cost for children with asthma is higher compared to adults because of lost productivity of parents or caregivers. A systematic review of articles published between 1966 and January 2008 demonstrated significant variation in the cost of asthma among different countries [148]. In this study, the estimated total cost from national studies in the United States, Canada and Switzerland ranged from US$654 million in Canada to US$15,248 million in the United States; the estimated direct cost ranged from US$397 per person in Canada to US$8,665 per person in the United States. Another systematic review of studies on economic burden of asthma across the globe between 2008 and 2015 also reported variation in the estimated costs across different regions of the world [149]. The estimated annual costs varied from less than US$150 per person-year (Abu Dhabi, United Arab Emirates) to more than US$3000 per person-year (United States); medication accounted for the largest direct medical cost and varied from 51% (United States) to 68% (Canada) of total cost in North America, while it varied from 45% (Spain) to 84% (Germany) of total cost in Europe. Medication costs appear to be increasing in the United States and Canada. On the contrary, out-patient costs accounted for the major portion of total costs in the Middle-East and South-East Asia. The estimated total cost of asthma in the United States in 2013 was US$81.9 billion, and

asthma accounted for an estimated UD$3 billion due to missed work and school days, US$29 billion for asthma-related mortality and US$50.3 billion in medical costs during 2008–2013 [150]. In 2013, the total direct cost of pediatric asthma in the United States was US$5.9 billion and the average annual cost per child ranged from US$1049–8039 [151]. Although asthma-related hospitalizations have declined during 2000 through 2010, pediatric asthma caused substantial medical and economic burden. Children with asthma aged 5–17 years missed 13.8 million school days per year in the United States in 2013 [152].

Asthma also results in intangible costs related to unquantifiable losses such as pain or suffering, impairment of quality of life, limitations of physical activities and study or job performance, job changes and psychological effects [153, 154]. Children with asthma have higher rates of attention-deficit/hyperactivity disorder, diagnoses of depression, behavioral disorders and learning disabilities [155]. While greater health-related quality of life impairment is generally associated with severe disease, patients with mild asthma also experience depression and impaired health-related quality of life as often as patients with severe asthma [156]. Australian adults with asthma also reported adverse health states such as poor life satisfaction, poor health status, high psychological distress and reduced activity days [157]. Even children with asthma-like symptoms but without any physician-diagnosed asthma have substantial health consequences such as missed school days, limited activities, sleep disturbances, emergency care visits and hospitalizations [158].

2.2. Asthma Prevalence

2.2.1. Asthma Prevalence in Canadians

An estimated 2.2 million Canadian adults reported physician-diagnosed asthma in 2017 Canadian Community Heath Survey (CCHS) [159]. In individuals aged 12 years or older, the

prevalence of reported physician-diagnosed asthma increased from 6.2% in 1994 to 7.5% in 1998 based on data from the NPHS; the prevalence remained around 8.4% from 2000 to 2005 based on data from the CCHS [160]. The prevalence estimates from these surveys were based on an affirmative response to the query on having health professional-diagnosed asthma as a long-term condition (expected to last or have already lasted six months or more). According to the Canadian Chronic Disease Surveillance System (CCDSS), the prevalence (age-standardized to the 2011 Canadian population) of diagnosed asthma increased from 6.5% in 2000/2001 fiscal year to 10.8% in 2011/2012 fiscal year in Canadians aged one year and older [161]. In 2011–2012 fiscal year, the prevalence of asthma varied by age: it was 15% in 20–24 years old, 10.5% in 25–29 years old, between 8% and 9% in 30–64 years old and between 9% and 10.6% in 65–84 years old. The rate of increase in prevalence over time also varied by age. CCDSS estimates are based on health administrative data and defined prevalent asthma as "having at least two visits to a physician with a diagnosis of asthma in the first diagnostic field in a two-year period, or at least one hospital separation with a diagnosis of asthma ever in any diagnostic field, coded by the International Classification of Diseases (ICD), ninth revision or ICD-9-CM 493 or ICD-10-CA J45-46" [161]. This case definition was validated against respirologist diagnosis in previous studies and was estimated to have a 84% sensitivity and 76% specificity in adults [162].

Population-based surveys are feasible methods of estimating disease burden and enable the collection of relevant socio-demographic and lifestyle information from the respondents, but disease ascertainment is dependent on self-report (as physician diagnosis is not practical) and therefore subject to reporting errors. Use of administrative data, on the other hand, provides data on diagnosis by physician, particularly if case definitions have been validated previously. However, health administrative data do not include information on cases not seeking medical

care, cases diagnosed by physicians not paid on a fee-for-service basis and who do not remit service information, and 3% of the population not included in the single-payer provincial and territorial health care plans, such as members of the Canadian Armed Forces, members of the Royal Canadian Mounted Police and individuals residing in federal correctional facilities.

An increasing trend in asthma prevalence has also been observed in studies conducted at provincial level during different spans of overlapping time periods using administrative data. In Ontario, four studies reported an increase in the prevalence while one study reported a decrease [163-166]. Overall, the age- and sex-standardized asthma prevalence (rates standardized to the 2005 Ontario population) increased from 8.5% in 1996 to 13.3% in 2005 in one study, with the highest increase observed in adolescents and young adults [163]. In another study, a gradual increase in asthma prevalence was observed during 1996–2009 among all age groups and it was projected that the prevalence of asthma will be 12.5% (95% CI: 11.3, 14.2) in 2022 [164]. In yet another study, the overall asthma prevalence decreased among 0–39 years old Ontarians, however, the prevalence decreased slightly in individuals aged <25 years and was stable or increased slightly in individuals aged more than 25 years between 1994/1995 and 2001/2002 [165]. In another study among Ontarians aged 35 years or older, the prevalence of age and sex-standardized asthma (rates standardized to the 2006 Ontario population) increased from 9.4% in 2002 to 11.9% in 2012 [166]. In British Columbia, a population-based surveillance of asthma among the working population (aged 15–64 years) with employer-paid health premium reported an increase in active asthma rates (defined as physician visit, hospitalization, workers' compensation claims or prescription of asthma during a year) from 1999 to 2003 [167]. In Manitoba, the overall prevalence of diagnosed asthma increased from 1.5% in 1984/1985 to almost 4% in 1999/2010 among all age groups; the prevalence increased from 1.3% in

1984/1985 to more than 5% during 2000–2005 among individuals aged more than 75 years [168].

2.2.2. Age, Period and Cohort Effects

Investigation of three time-related effects – age, period and cohort effects – may help understand trends in disease occurrence. The change in the frequency of disease occurrence according to age is known as the age effect [169]; age effects "describe the common developmental processes that are associated with particular ages or stages in the life course. In other words, age effects represent accumulated exposure and/or physiological changes associated with the process of aging" [170]. The period effect is the change in the frequency of disease occurrence that affects all age group because of population-wide exposures [169]. Specific phenomena such as war, famine, migration, pandemics of infectious diseases, health policies and legislations, public health interventions, new treatment, changes in awareness and lifestyle can produce period effect [171]. In epidemiology, "a cohort effect occurs when different distributions of disease arise from a changing or new environmental cause affecting age groups differently. A cohort effect, therefore, is conceptualized as a period effect that is differentially experienced through age-specific exposure or susceptibility to that event or cause (i.e., interaction or effect modification)" [170]. For example, while population prevalence of risk factors of any disease or health outcome increases or decreases over time, because of the unequal distribution across age groups, we would see different prevalence of the disease or health outcome in different age groups over time. The interaction between period and age leads to fluctuations in the outcome and is useful in epidemiologic research to better comprehend trends in disease or health outcomes, particularly to understand how different exposures impact health of population differentially across age to guide public health policy [170].

However, there is a duality in the concept of cohort effect. In sociology, cohort effect is conceptualized as the changes according to the year of birth (birth cohort), irrespective of age and calendar time. Cohort effect is considered as a structural factor that may arise from lifetime experiences, accumulated exposures over time, or differential early life exposures. A birth cohort experiences same historical and social events at the same age as they move together in life [171]. "As a result, the conditions, barriers, and resource that each cohort is born into and in which they live their collective lives may uniquely shape the patterns of experiences of health and mortality for that cohort" [170]. As such, age and period effects are considered as confounders of the cohort effect, and therefore seeks to disentangle the separate effects of age, period and birth cohort [172]. This conceptualization of age-period-cohort (APC) effect also leads to the identification problem that results from the presence of two simultaneous conditions: 1) age, period and cohort variables are mathematically linearly related to each other (age=period−cohort), and 2) APC variables are linearly related to the outcome that is APC variables are treated as independent and additive factors in a linear model [172]. Different approaches have been proposed and used to overcome the non-identifiability problem although not without some controversies [170, 171, 173].

A large number of studies have used the sociological perspective of cohort effect traditionally using historical cross-sectional data to form synthetic cohorts that included different individuals at each calendar period with the assumptions that synthetic cohorts mimic true cohorts. Few studies have used the epidemiologic concept of cohort and assessed age, period and cohort effects using data from prospective studies on 'true' (i.e., non-synthetic) cohorts [174]. The use of interaction between period and age in statistical models conforming to the

epidemiologic concept is free from the identification problem encountered in the sociological concept.

2.2.3. Studies on Asthma Prevalence using Age, Period and Cohort Effect Analytic Framework

2.2.3.1.Outside Canada

The effects of age, period and cohort on asthma prevalence have been examined in the United States and Japan. A study assessing the age, period and cohort effects on asthma prevalence in Japanese school children aged 6–17 years from 1984 to 2004 found that the prevalence peaked at 13 and 14 years in boys and girls, respectively, followed by marked decline afterwards [175]. There were upward trends in asthma prevalence among Japanese children born during 1968 through 1997. Period effect was also observed with a decline in the prevalence from 1984 followed by an abrupt increase in 1999 and then declined again. Among Californian adults (aged ≥18 years), age effects on lifetime asthma prevalence peaked in young adulthood, then flattened in 40–60 years old followed by a decline in older adults in 1984–1992 and 1994–2011 [176]. There was a positive trend from 1984 to 2003 followed by flattening of the trend starting from 2004. A positive trend in asthma prevalence was also observed in Californian adults born during 1949–1953. Both these studies attempted to disentangle the separate effects of age, period and cohort from a sociological perspective of cohort effect.

2.2.3.2.Canada

No studies in Canada have explored effects of age, period and cohort on asthma prevalence formally using age, period and cohort theoretical and analytic framework. One recent study assessed the association between fine particulate matter $PM_{2.5}$ with asthma incidence among individuals aged >44 years in Canada between 2007 and 2014 and attempted to separate the

effects of age from the effects of risk factors in relation to year [177]. However, this study employed data from the Canadian Community Health Survey and possibly suffered from the typical identification problem because age, period and birth cohort were all modeled as linearly related to the outcome. This study reported that "The age group 45–64 had the highest number of cases for asthma incidence (65%)", and "A two-year increase of 10 $\mu g/m^3$ in $PM_{2.5}$ was associated with an increased risk of 2.24% (95% CI: 0.93%; 5.38%) in asthma incidence". The effects of age, period and cohort on asthma occurrence are not comprehensible.

There is a dearth of published literature explicitly using the age, period and cohort effect theoretical and analytic framework to examine the effects of age, period and cohort in asthma prevalence in Canadian adults. Age-standardized or age-specific asthma prevalence estimates reported in previous studies using non-model-based approaches suggest age and period effects on asthma prevalence and that period effect might differ across age groups, although the studies did not take into account several relevant factors. It is unknown whether age, period and cohort effects on asthma prevalence exist when employing formal age, period and cohort effect theoretical and analytical framework and after accounting for different socio-demographic factors.

2.3. Asthma course

2.3.1. Asthma Course and Prognostic Factors in Children

The course of asthma is characterized by periods of relapse and remission. Estimates of remission rates in childhood asthma reported in literature vary from 11% to 49% [178-186]. The wide variation in remission likely resulted from differences in study population, definition of remission and follow-up period (Table 2.1). Evidence suggests that clinical remission does not equate to complete remission as children with remission based on symptoms and medication use

may continue to have subclinical active disease and likely associated airway remodeling [182]. Indeed, when followed for 15 years, children with asthma have been found to have up to 15 years gap in asthma activity, which was defined as two years or more between asthma healthcare claims [187]. Among children aged 5 years or younger, 41% had 2–4 years of gap, 23% had 5–9 years and 5% had 10–15 years of gap in asthma activity; among children aged 6–17 years, 42% had 2–4 years of gap, 25% had 5–9 years and nearly 6% had 10–15 years of gap in asthma activity.

Different sociodemographic, environmental, clinical and diagnostic prognostic factors for childhood asthma have been identified. A review of the prognostic factors of asthma in children differentiated prognostic factors for preschool- and school-aged children [188]. In this review, male sex, atopy, severe respiratory syncytial virus bronchiolitis in infancy, exposure to passive cigarette smoking, increased inflammatory markers and no or delayed anti-inflammatory treatment worsened the prognosis in preschool children; female sex, severe asthma with persistent lung function abnormalities, severe bronchial hyper-responsiveness, active or passive cigarette smoking and outdoor pollution worsened the prognosis of asthma in school aged children. In a study on individuals aged under 40 years, a family history of asthma or allergy decreased the chance of remission throughout life (HR 0.79, 95% CI: 0.64, 0.99), while early contact with older children increased the chance of remission in childhood asthma (HR 1.50, 95% CI: 1.10, 2.04 [189]. Asthma remission was positively associated with male sex (OR 2.66, 95% CI: 1.00, 7.03) but inversely associated with sensitization to furred animals (OR 0.14, 95% CI: 0.04, 0.55) and more severe asthma at 7 to 8 years of age (OR 0.19, 95% CI: 0.07, 0.54) in another study that followed children with asthma from 7 to 19 years of age [185]. In children followed from 9 to 26 years, airway hyperresponsiveness (OR 3.00, 95% CI: 1.71, 5.26),

sensitization to house dust mites at 13 years of age (OR 2.41, 95% CI: 1.42, 4.09) and female sex (OR 1.71, 95% CI: 1.04, 2.82) were associated with persistence of wheezing from 9 to 26 years of age, while airway hyperresponsiveness (OR 3.03, 95% CI: 1.65, 5.55), sensitization to house dust mites at 13 years of age (OR 2.18, 95% CI: 1.18, 4.00) and earlier age at wheezing onset (OR 0.89 per year increase in age at onset, 95% CI: 0.85, 0.94) predicted asthma relapse [181]. Another study assessing remission of asthma from birth to 44 years of age reported that individuals in remission had younger mean age at asthma onset (7.8 vs. 15.9 years) and a shorter duration of asthma (5.6 vs. 16.1 years) than patients with current asthma; age at onset was associated with remission in patients with asthma [190].

Table 2. 1: Summary of studies on asthma remission for children having asthma diagnosed during childhood and followed through childhood or into adulthood

Study/location	Study sample	Age at diagnosis	Follow-up	Definition of remission	Remission, percentage
Kjellman et al., 2000/Sweden [178]	55 children with asthma during 1973–1976	5–14 years	Until aged 25–35 years	Remission: free from asthma symptoms and medication during the year prior to the last follow-up Complete remission: absence of symptoms and medication both at the last and the penultimate visit	Remission: 16% Complete remission: 11%
Halász et al. 2002/Hungary [179]	155 individuals with diagnosed asthma in childhood	<18 years	≥28 years of age	Symptom free (no frequent cough, dyspnea, or asthma attacks)	43%
Robertson, 2002/Australia [180]	317 children with episodic, persistent and severe asthma	7 and 9 years	42 years of age	Free of wheezing in past three years	40%
Sears et al., 2003/New Zealand [181]	613 children with asthma born between April 1972 and March 1973	9 years	26 years of age	Free of wheezing at 26 years (absence of wheezing after wheezing had been reported at two or more successive prior assessments)	15%
Vonk et al., 2004/Netherlands [182]	119 allergic asthmatic children aged 5–14 years during 1966–1969	5–14 years	Until aged 32–42 years with a mean follow-up 30 years	Complete remission: having no current wheeze and no asthma attacks in the previous 3 years, no use of inhaled corticosteroids, normal lung function (FEV1 .90% predicted), and absence of BHR (PC10 .16 mg/ml) Clinical remission: absence of wheeze and asthma attacks and no use of inhaled corticosteroids	Complete remission: 22% Clinical remission: 30% Total: 52%

Taylor et al., 2005/New Zealand [183]	176 children with asthma	9–15 years	18 years of age	Absence of reported wheezing that had been current at ≥2 prior assessments	39%
To et al.,2007/Canada [184]	34,216 children born in 1994 and had diagnosed asthma before 6 years of age	Before 6 years of age	6-year follow-up up to 11 years of age	No hospitalization or physician visit for asthma during 6-year follow-up	49%
Andersson et al., 2013/Sweden [185]	248 children with asthma enrolled in 1996	7–8 years	19 years of age	No use of asthma medication and no wheeze during the past 12 months as reported at endpoint and in 2 annual surveys preceding endpoint (i.e., for ≥3 years).	21%
Bag et al., 2013/Turkey [186]	52 children with persistent allergic asthma	2–10 years	For 10–22 years after enrollment	Clinical remission: no attack, no use of quick-reliever medications in the previous year and no admission to the emergency department for asthma	39%

2.3.2. Asthma Exacerbation in Children

Asthma exacerbation is an acute or subacute episode of progressive increase in asthma symptoms such as shortness of breath, cough, wheezing or chest tightness, associated with airflow obstruction [1, 191]. Asthma exacerbations cause considerable morbidity in children and result in unscheduled visits seeking acute care, including emergency department visit, hospitalization and even death [192]. Asthma exacerbations in children lead to school absenteeism and parental loss of workdays [193, 194]. Among children with asthma, children missing school days were more likely to experience asthma exacerbation or seek urgent or emergency care compared to children without missed school days for asthma [194]. Nearly half of school-aged children with asthma in the United States missed one or more school days in 2013 and more than half had one or more asthma attacks in 2016 [152]. Among children with asthma, the prevalence of asthma attacks (62%), emergency department/urgent care center visits (31%), and hospitalization (10%) were higher in children aged 0–4 years compared to children aged 12–17 years (45%, 10% and 3%, respectively) [152]. The estimated cost of missed school days in children in the United States amounted to US$0.9 billion in 2013 causing substantial economic burden to the society [150].

Asthma causes substantial burden in Canadian children. During 2013–2014 fiscal year (extending from April 1 to March 31), the overall prevalence of diagnosed asthma among Canadians aged 1–19 years was approximately 15%; the prevalence was 5%, 13%, 18% and 20% among 1–4, 5–9, 10–14 and 15–19 year-olds, respectively [195]. More than 9% of Ontarian children aged 2–17 years with asthma had one or more emergency department visits from April 2003 to March 2005 [196], while approximately 10% of children with acute asthma visiting emergency department required hospitalization in Alberta during 2004/2005 fiscal year [197].

Asthma accounted for more than 6,000 hospitalizations among Canadians aged 1–19 years resulting in a hospitalization rate of 79 per 100,000 population during 2015–2016 fiscal year [198]. Hospitalization rates provide insights into the rate of severe asthma exacerbations.

Poor asthma control, severe exacerbation in the previous year, viral respiratory tract infections, allergen sensitization, virus-allergen interaction, exposure to second-hand smoke, acute exposure to pollutants such as NO_2, and genetic factors have been implicated as risk factors for exacerbations in children [115, 199]. A systematic review of findings from 68 studies reported several factors associated with asthma attacks in children aged 5–17 years: previous asthma attacks were associated with greatly increased risk of asthma attack; suboptimal drug regimen, comorbid atopic/allergic disease, African-American ethnicity, poverty and vitamin D deficiency were associated with moderately increased risk of attack; and exposure to environmental tobacco smoke, younger age, obesity and low parental education were associated with slightly increased risk of asthma attacks [200]. Prevention of asthma exacerbations decreases emergency department visit, school absenteeism, parent's missed work and prevents future exacerbations [199].

2.3.3. Studies on Asthma Course in Children

Studies on asthma course could be instrumental in providing insights into asthma prognosis and identifying opportunities to intervene early to alter the course. Published literature in the field of asthma course in children have mostly focused on asthma development using trajectories of wheeze, cough or atopy. A few studies have explored patterns of wheeze or wheeze and cough to identify wheeze phenotypes [201-208] (Table 2.2). Some of these studies also examined the association between wheeze phenotypes and childhood outcomes, including cough, wheeze, asthma, atopy, bronchial hyperresponsiveness and lung function [201-203, 205, 207]. These

studies followed children from birth or pre-school age from a time when they were not diagnosed with asthma. Other studies have identified trajectories of asthma prevalence [209, 210] or combined wheeze and atopy as measures of asthma in children [211] using group-based trajectory modeling or with pre-defined asthma patterns [212] to identify asthma phenotypes and used age of the child as the time axis (Table 2.2). However, none of these studies examined the trajectories of asthma course in children with incident asthma using time since asthma diagnosis as the time scale, and consequently they do not provide adequate information on the course of asthma after diagnosis.

Table 2.2: Summary of studies on asthma course in children

Study/country	Population	Duration and frequency of follow up	Variable used for trajectory/measures	Statistical method	Trajectory classes
Henderson et al., 2008/UK [201]	6265 children in Avon Longitudinal Study of Parents and Children (ALSPAC) born to mothers with expected dates of delivery between April 1991 to December 1992	Birth to 7 years, at seven time points (6, 18, 30, 42, 54, 69 and 81 months after birth)	Wheezing/mother-reported	Group-based trajectory modeling	Six phenotypes: never/infrequent wheeze (59.3%), transient early wheeze (16.3%), prolonged early wheeze (8.9%), intermediate onset wheeze (2.7%), late onset wheeze (6.0%), and persistent wheeze (6.9%)
Spycher et al., 2008/UK [202]	1650 white children in Leicester recruited in 1990	Enrolled at 0-5 years, followed up in 1992-1994	Chronic cough (cough apart from cold) and wheezing/parent-reported	Group-based trajectory modeling	Five phenotypes: persistent cough, transient cough, atopic persistent wheeze, nonatopic persistent wheeze, and transient viral wheeze
Savenije et al., 2011/UK, Netherlands [203]	5760 children from Avon Longitudinal Study of Parents (ALSPAC) study and 2810 children from Prevention and Incidence of Asthma and Mite Allergy (PIAMA)	0–8 years of age, at 6, 18, 30, 42, 54, 69, 81 and 91 months after birth in ALSPAC study and at 12, 24, 36, 48, 60, 72, 84 and 96	Wheezing/parent-reported	Group-based trajectory modeling	Five phenotypes in PIAMA study: never/infrequent wheeze (75.0%), transient early wheeze (16.7%), intermediate onset wheeze (3.1%), late onset wheeze (1.7%), and persistent wheeze (3.5%)

	study born to mother recruited during 1991-1992	months after birth in PIAMA study			
Chen et al., 2012/USA [204]	689 children from the Columbia Center for Children's Environmental Health (CCCEH) birth cohort study, data collected between October 1998 to May 2011	0–8 years, followed up at 6, 12, 24, 36 ,60, 84, and 108 months or at 3, 9, 15, 18, 21, 30, 48, and 72 months	Wheezing or whistling in chest/parent-reported	Group-based trajectory modeling	Four phenotypes: never/infrequent (47.1%), early-transient (37.5%), early-persistent (7.6%), and late-onset (7.8%).
Granell et al., 2016/UK [207]	12,303 children from Avon Longitudinal Study of Parents (ALSPAC) and Children birth cohort study	Birth to 16 ½ years of age, at 14 time points-annually from 6 to 198 months	Wheezing/parent-reported	Group-based trajectory modeling	Six phenotypes: never/ infrequent (59.9%), preschool-onset remitting (18.7%), mid childhood-onset remitting (7.5%), school age–onset persisting (4.3%), late childhood–onset persisting (4.7%), and continuous wheeze (4.9%).
Tse et al., 2016/USA [208]	1,623 children from a birth cohort study	Birth to 9 years of age, followed annually from 1 through 9 years of age	Wheezing/parent-reported	Group-based trajectory modeling	Three phenotypes: never/infrequent wheeze (74.1%), early transient wheeze (12.7%), and persistent wheeze (13.1%).

Soto-Ramirez et al., 2013/UK [210]	1456 children in Isle of Wight birth cohort enrolled from January 1989 to February 1990	0–18 years, followed up at 1 or 2, 4, 10 and 18 years	Asthma/parent-reported	Group-based trajectory modeling	Three trajectories separately for asthma and wheezing as well as for boys and girls. Asthma trajectories: Boys: developing asthma (18.2%), growing out of asthma (27.6%), and never/infrequent asthma (54.2%); Girls: developing asthma (11.3%), intermittent asthma (12.4%), and never/infrequent asthma up to age 18 years (76.3%).
Sbihi et al., 2017/Canada [209]	68,195 birth cohort born from 1999 to 2002 in Metropolitan Vancouver, British Columbia	0–10 years (1999–2009)	Asthma (physician billing and hospital discharge records)/administrative data	Group-based trajectory modeling	Four trajectories: nonasthma trajectory (88.8%), late-onset chronic asthma trajectory (4.1%), early-onset chronic asthma trajectory (1.5%), and transient asthma trajectory (5.6%)
Panico et al., 2014/UK [211]	11,632 children from the Millennium Cohort Study (MCS) of infants born from September 2000 to January 2002	Up to 7 years, followed up thrice at 3, 5 and 7 years	Wheeze, and other atopic symptoms (eczema and hay fever)	Group-based trajectory modeling	Four trajectories: low levels of wheeze and other atopic symptoms (54%), low levels of wheeze and high prevalence of other atopic symptoms (29%), high prevalence of both wheeze and other atopic symptoms

					(9%), and high levels of wheeze and low levels of other atopic symptoms (8%)
Wu et al., 2012/USA [212]	13,256 children in Tennessee born during 1995-1996	0–10 years, followed up at 7-8 years and 9-10 years	Asthma (physician-diagnosed or asthma-specific prescription use)/administrative data	"Lasagna" plot	Seven pre-defined developmental patterns based on asthma status at three age periods: 3.5–5.5 years, 7–8 years and 9–10 years. Patterns: asthma at all three age periods (24%), asthma at first two age periods (8%), asthma at first and third age period (5%), asthma at first age period alone (17%), asthma at second and third age periods (14%), asthma at second age period alone (12%), and asthma at third age period alone (20%).
Yii et al., 2017/Singapore [213]	177 patients with uncontrolled and severe asthma enrolled in 2011	Followed for five years for annual severe exacerbations	Severe exacerbations (hospitalization or ED visit for asthma and systematic corticosteroids ≥3 days)/Nationwide electronic records	Group-based trajectory modeling	Three trajectories: infrequent severe exacerbations (58.5%), nonpersistently frequent severe exacerbations (32.0%), and persistently frequent severe exacerbations (9.5%)

2.3.4. Studies on Asthma Exacerbation Trajectories

Studies on asthma exacerbation trajectories among individuals with asthma are scarce. To our knowledge, only one published study sought to identify latent trajectories of severe exacerbation rates and factors associated with the trajectories among adult patients with difficult, severe and uncontrolled asthma presenting to a specialist asthma clinic in Singapore [213]. Severe exacerbation was defined as events requiring hospitalization or emergency department visit for asthma and systemic corticosteroids for ≥3 days and data were obtained from electronic records of prescriptions, emergency department consults and inpatient discharges. Three clinically distinct trajectories of severe exacerbation over a five-year period were identified: infrequent (few intermittent severe exacerbations), nonpersistently frequent (frequent severe exacerbations at baseline with gradual decline in subsequent years) and persistently frequent (yearly frequent severe exacerbations). Since the follow-up of patients with uncontrolled and severe asthma in that study began some time after asthma diagnosis, asthma course trajectories from asthma diagnosis were not identified. Considering the fact that the majority of the asthma diagnosed in adults has origin in childhood, it would be difficult to study the trajectories after incident diagnosis in adults without following them from childhood.

The trajectories of asthma exacerbation in children with incident asthma remain understudied. Considering the waxing and waning nature of asthma course, it is likely that among children with asthma there could be qualitatively distinct classes of underlying asthma exacerbation trajectories instead of following a uniform disease course. Identifying the trajectories and their predictors could enhance physicians' ability to better prognosticate the course of asthma at the time of asthma diagnosis.

2.3.5. Methods for Studying the Longitudinal Course/Trajectory of Asthma

There are two fundamental methods to study the longitudinal course of different health outcomes. One method examines the average course in the population, and the other classifies population into groups that follow a specific trajectory. These two fundamental methods correspond to the two methodological approaches commonly used: traditional hierarchical modeling [214, 215] and group-based trajectory modeling (GBTM) [216]. These methods describe individual-level heterogeneity in the course of different health outcomes. Hierarchical models estimate the average developmental trend and the random variation around the average trend using a single set of parameters for the population. Individual variation is described as the variation around the population mean. This is based on the assumption that the parameters are continuously distributed throughout the population according to the multivariate normal distribution. This is suitable for diseases where population members follow a common pattern of either increase or decline, although at different rates. When the course of a disease evolves over time or age and a common growth process does not ensue, it is more reasonable to assume that there would be qualitatively distinct trajectories across subpopulations rather than everyone will have increasing or decreasing course of the disease. Such qualitatively distinct trajectories would not be distinguishable by the traditional growth curve modeling using hierarchical models. Asthma, having periods of remission and relapse, would likely violate the assumption of having a common course for everyone in the population. GBTM helps describing complex disease course by identifying groups of individuals with similar trajectories and explaining individual-level heterogeneity in terms of group differences [217, 218]. Trajectory groups are used as tools to approximate the unknown distribution of trajectories across population as these trajectory groups are latent, not observed.

2.4. Gestational Diabetes Mellitus as a Risk Factor for Asthma in the Offspring

2.4.1. Gestational Diabetes Mellitus

2.4.1.1.Definition and Diagnostic Criteria

Until recently, gestational diabetes mellitus (GDM) had long been defined as any glucose intolerance that begins or is first detected during pregnancy [219]. However, this definition was imprecise, as it did not differentiate between undiagnosed pre-existing diabetes and new onset diabetes during pregnancy and whether the new-onset diabetes persisted after the pregnancy. The American Diabetes Association currently defines GDM more precisely as "diabetes that is first diagnosed in the second or third trimester of pregnancy that is not clearly either pre-existing type 1 or type 2 diabetes", and recommends testing for undiagnosed diabetes at first prenatal visit in women with risk factors while testing for GDM during 24–28 weeks of gestation without previously known diabetes [220]. Nevertheless, there is a lack of international consensus on the diagnostic criteria for GDM (Table 2.3). The Canadian Diabetes Association (CDA) recommends early screening (<20 weeks of gestation) in women with high risk of undiagnosed type 2 diabetes [221]. The CDA recommended preferred approach for GDM diagnosis during 24–28 weeks of gestation consists of an initial 50g glucose challenge test, followed by if abnormal with a 75g oral glucose tolerance test [221]. GDM is diagnosed if one plasma glucose value is abnormal. The CDA also includes an alternate one-step approach (Table 2.3).

Table 2. 3: Diagnostic criteria for gestational diabetes mellitus

Organization	Diagnostic criteria
Canadian Diabetes Association (CDA) 2013 [221, 222]	*Preferred approach:* 50g glucose challenge test with plasma glucose 1-hour later- • 7.8–11.0 mmol/L: 75g OGTT measure when fasting and at 1-hour and 2-hour. Any one the following value is met or exceeded - Fasting: ≥5.3 mmol/L - 1-hour: ≥10.6 mmol/L - 2-hour: ≥9.0 mmol/L • ≥11.1 mmol/L Alternate approach: If one of the following values is met or exceeded after 75g OGTT plasma glucose is measured when fasting and at 1- and 2-hour - Fasting: ≥5.1 mmol/L - 1-hour: ≥10.0 mmol/L - 2-hour: ≥8.5 mmol/L
American Diabetes Association (ADA) 2018 [223]	*One-step strategy* 75-g oral glucose tolerance test (OGTT) when fasting and at 1-hour and 2-hour. Any of the following values are met or exceeded- • Fasting: 92 mg/dL (5.1 mmol/L) • 1-hour: 180 mg/dL (10.0 mmol/L) • 2-hour: 153 mg/dL (8.5 mmol/L) *Two-step strategy* Step 1: Perform a 50-g glucose loading test (GLT) (nonfasting), with plasma glucose at 1-hour. If the plasma glucose level measured 1-hour after the load is ≥130mg/dL, 135mg/dL, or 140mg/dL (7.2mmol/L, 7.5mmol/L, or 7.8mmol/L), then proceed to a 100-g OGTT. Step 2: The 100-g OGTT should be performed when the patient is fasting.

<table>
<tr><td></td><td>The diagnosis of GDM is made if at least two* of the following four plasma glucose levels (measured fasting and 1-hour, 2-hour, 3-hour during OGTT) are met or exceeded:
<table>
<tr><td></td><td>Carpenter-Coustan</td><td>National Diabetes Data Group</td></tr>
<tr><td>Fasting</td><td>95 mg/dL (5.3 mmol/L)</td><td>105 mg/dL (5.8 mmol/L)</td></tr>
<tr><td>1-hour</td><td>180 mg/dL (10.0 mmol/L)</td><td>190 mg/dL (10.6 mmol/L)</td></tr>
<tr><td>2-hour</td><td>155 mg/dL (8.6 mmol/L)</td><td>165 mg/dL (9.2 mmol/L)</td></tr>
<tr><td>3-hour</td><td>140 mg/dL (7.8 mmol/L)</td><td>145 mg/dL (8.0 mmol/L)</td></tr>
</table>
*The American College of Obstetricians and Gynecologists recently noted that alternatively one elevated value can be used for diagnosis</td></tr>
<tr><td>World Health Organization (WHO) 2016 [224]</td><td>One or more of the following plasma glucose level when fasting or at 1 and 2 h after ingestion of 75g oral glucose load:
Fasting plasma glucose: 5.1–6.9 mmol/L (92–125 mg/dl)
1-hour: ≥ 10.0 mmol/L (180 mg/dl)
2-hour: 8.5–11.0 mmol/L (153–199 mg/dl)</td></tr>
<tr><td>National Institute for Health and Care Excellence (NICE) 2015 [225]</td><td>In women with risk factors, 2-hour glucose tolerance test (OGTT) with either of the following plasma glucose level:
Fasting plasma glucose: ≥ 5.6 mmol/L
2-hour: ≥ 7.8 mmol/L</td></tr>
<tr><td>International Association of Diabetes and Pregnancy Study Groups (ADPSG) 2010 [226]</td><td>One or more of the following plasma glucose level when fasting or at 1 and 2 h after ingestion of 75g oral glucose load:
Fasting plasma glucose: ≥ 5.1 mmol/L (92 mg/dl)
1 h: ≥ 10.0 mmol/L (180 mg/dl)
2 h: ≥ 8.5 mmol/L (153 mg/dl)</td></tr>
</table>

2.4.1.2.Prevalence of GDM

Globally, the prevalence estimates of GDM vary from <1% to 28% [227, 228]. In high-income countries, the prevalence estimates vary between 1.7% and 11.6% [229]. The overall prevalence of GDM is estimated to be 5.4% (range 3.8% to 7.8%) in Europe [230], 10.1% (95% CI: 6.5%, 15.7%) in Eastern and Southeastern Asia [231], and ranges from 0% to 13.9% in six African countries [232]. An estimated 21.4 million women aged 20–49 years giving live births in 2013 were diagnosed with hyperglycemia in pregnancy comprising known diabetes in pregnant women, previous undiagnosed diabetes in pregnancy and GDM, however, the majority (84%) of the cases were likely to be GDM [233]. An increased trend in GDM prevalence has been observed worldwide during last few decades [234-237]. Some of the countries in Asia experienced an increasing trend in GDM prevalence [236]. In Canada as well, the rate of GDM has increased considerably from 40.8/1000 deliveries in 2004/05 to 54.5/1000 deliveries in 2010/11 [238]. The rising global trend in GDM prevalence is likely to continue with the increase in important risk factors such as increased maternal age and obesity.

2.4.1.3.Risk Factors of GDM

Several risk factors for GDM have been identified. Overweight and obesity were associated with a higher odds of GDM in pregnant women (OR 2.14, [95% CI: 1.82, 2.53] among overweight, OR 3.56 [95% CI: 3.05, 4.21] among obese and OR 8.56 [95% CI: 5.07, 16.04] among severely obese) compared with pregnant women with normal weight in a systematic review and meta-analysis of findings from 20 studies [239]. Increased age (35 years or older), minority ethnic family origin with a high prevalence of diabetes (e.g., African Middle Eastern, Asian, Hispanic or Indigenous), using corticosteroid medication, having prediabetes, GDM in a previous pregnancy, history of giving birth to a macrosomic baby (weighing 4.5 kg or more), family

history of diabetes (first degree relative with diabetes) and polycystic ovary syndrome or acanthosis nigricans are known risk factors of GDM [221, 225, 240].

A higher incidence of GDM was associated with systolic blood pressure higher than 109 mmHg and diastolic blood pressure higher than 65 mmHg in first trimester [241]. Women with prehypertension (systolic blood pressure 140 mmHg/diastolic blood pressure 80–89 mmHg) or hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or use of antihypertensive medication) during early pregnancy (<20 weeks) was associated with increased odds of GDM (OR 1.56 [95% CI: 1.16, 2.10] and OR 2.04 [95% CI: 1.14, 3.65], respectively); women with prepregnancy prehypertension or hypertension also had a higher odds of GDM (OR 1.44 [95% CI: 0.95, 2.19] and OR 2.01 [95% CI: 1.01, 3.99], respectively) [242]. Pregnant women carrying a male fetus have a higher risk (RR 1.04, 95% CI: 1.02, 1.06) of developing GDM [243]. Different pre-pregnancy lifestyle factors have also been implicated as risk factors for GDM: dietary patterns (Western dietary pattern, high glycemic load, low carbohydrate diet), food (red meat, processed and unprocessed red meat, sugar -sweetened cola, fried food) and nutrients (heme iron, animal fat, cholesterol intake, monounsaturated fatty acids, animal proteins, potatoes) [244, 245]. Vitamin D deficiency was also associated with an increased risk of GDM (OR 1.53, 95% CI 1.33, 1.75) in a systematic review and meta-analysis of evidence from observational studies [246]. In addition, maternal history of low birth weight, low stature, low level of physical activity, excessive weight gain during pregnancy, parity, previous fetal malformation, previous miscarriage/still birth and low socioeconomic status were found to be associated with GDM [247-250].

There have been conflicting results for the association between smoking during pregnancy and GDM [251-253]. A systematic review and meta-analysis reported an OR 1.03

(99% CI: 0.85, 1.25) for the association between smoking during pregnancy and GDM from unadjusted results in nine studies, however, the 99% confidence interval for the odds ratios was compatible with a 15% decreased odds to a 25% increased odds of GDM [254]. The association between GDM and smoking in this systematic review from the adjusted results in four studies among five distinct populations was OR 0.95, 99% CI: 0.85, 1.07. Another recent systematic review and meta-analysis of results from 12 studies reported similar findings (pooled OR 0.98, 95% CI: 0.88, 1.10); the OR for light smoking (1–10 cigarettes/day) was 1.10 (95% CI: 0.97, 1.25) and the OR for heavy smoking (≥10 cigarettes/day) during pregnancy was 1.02 (95% CI: 0.67, 1.53) compared with non-smoking [255].

2.4.1.4.Adverse Consequences of GDM

GDM is associated with different short- and long-term adverse consequences in the mother, fetus and offspring. Adverse outcomes include pre-eclampsia, cesarean section delivery, preterm delivery and future type 2 diabetes in mother; fetal macrosomia (birth weight >4.5 kg) and large for gestational age in fetus; and perinatal mortality, obesity and metabolic syndrome (a cluster of risk factors such as high blood pressure, high fasting blood sugar, excess body fat around the waist, and low HDL cholesterol or high triglyceride levels) in the offspring [256-263]. A growing body of evidence suggests that GDM may also increase the risk of asthma in the offspring.

2.4.2. Rationale for Studying GDM as a Risk Factor for Asthma

There are several pathways that could link maternal GDM and asthma in the offspring (Figure 2.1). One pathway may involve fetal hyperglycemia resulting from maternal hyperglycemia. Fetal hyperglycemia then causes fetal hyperinsulinemia. Maternal diabetes mellitus has substantial effect on the growth of the fetal lung. Fetal hyperinsulinemia leads to neonatal

surfactant deficiency [264], which could increase the risk of respiratory distress syndrome and ultimately to asthma in the offspring [265, 266]. Fetal hyperglycemia also causes fetal immune dysregulation and fetal hypoxia. Dysregulated cytokine profiles have been detected in the cord blood of neonates born to mothers with diabetes mellitus, suggesting disruption of fetal immune development. Insulin resistance developed during GDM modifies placental transcriptome with a dominance of genes that regulate inflammatory responses and endothelial function, thereby increasing the markers and mediators of inflammation, such as interleukins, leptin and tumor necrosis factor [267]. Umbilical cord C-reactive protein and intracellular adhesion molecule (ICAM-1), markers of subclinical inflammation, were also higher in offspring of mothers with type 1 diabetes compared with offspring of mothers without diabetes [268]. Intrauterine hypoxia also occurs as a complication of diabetic pregnancy. Fetal erythropoietin concentration, a marker of fetal hypoxia, directly correlates with maternal HbA1c levels, and increased amniotic fluid erythropoietin level is indicative of fetal hypoxia in diabetic pregnancy [265, 269]. Intrauterine hypoxia and immune system dysregulation both are associated with asthma.

A second pathway could involve cesarean section delivery. Evidence suggests that cesarean section could possibly play a role in childhood asthma development by affecting intestinal and respiratory microbiota leading to altered immune development [106-110]. It is also possible that cesarean section increases the risk of asthma through transient tachypnea in the newborn [270, 271].

A third pathway could operate through preterm birth that leads to respiratory distress syndrome and subsequently asthma in offspring [272, 273].

Overall, the net effect of these postulated pathways is not known. Additionally, there may be other pathways that are not known yet.

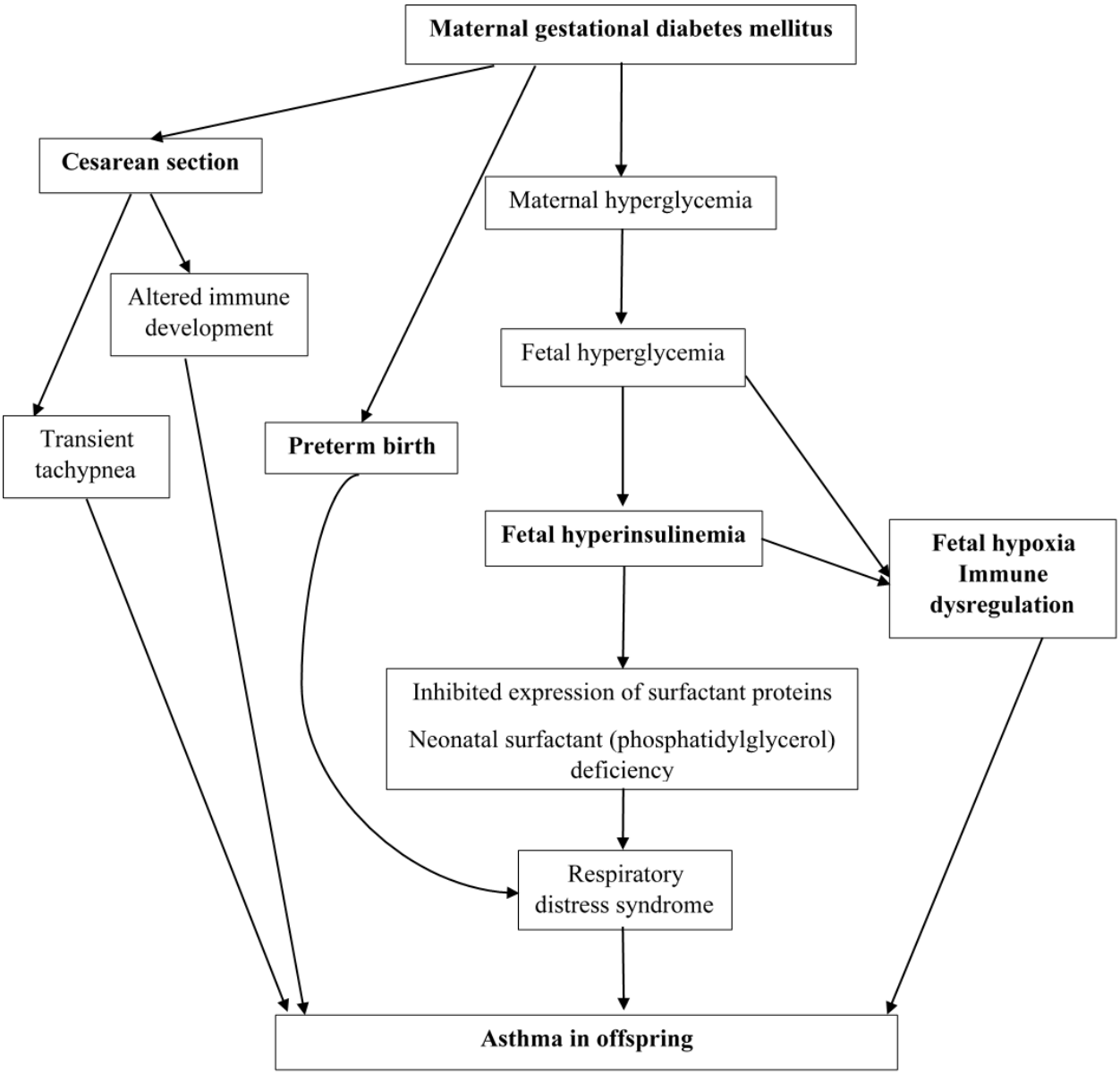

Figure 2. 1: Pathways between gestational diabetes mellitus and asthma in offspring

2.4.3. Studies on GDM as a Risk Factor for Asthma in Children

A growing number of studies have investigated the role of maternal diabetes mellitus in pregnancy in wheezing and asthma in offspring [274] but the results are inconclusive.

A study using population-based registers (Swedish Hospital Discharge Register and Swedish Medical Birth Register) among Swedish children born between 1987 and 1999 compared 14,803 children hospitalized (by the end of 2001) for asthma after 2 years of age with 1,386,029 children born during the same time to identify risk factors of asthma [138]. The children were followed up between 2 to 13 years with an average follow-up of 6.8 years. Maternal diabetes during pregnancy (any type) was associated with a higher odds (OR 1.20, 95% CI: 1.02, 1.42) of hospitalization for asthma. However, it is not clear if any (and if yes, which) factors were adjusted for to obtain the estimate. A subsequent study was conducted to validate the findings of the associations between the risk factors and asthma in children aged between 2 years and less than 15 years using two linked population-based registers (Swedish Medical Birth Register and Swedish Prescribed Drug Register) [72]. In this second validating study, 61,256 Swedish children born between 1 January 1990 and 30 June 2003 and prescribed and redeemed anti-asthmatic medication between 1 July 2005 and 31 December 2005 were compared with 1,338,319 children born in Sweden during the same time. Forty percent of children registered in the drug registry had asthma diagnosis in the prescription. A total of 16,257 children were born to mothers with diabetes and 916 among them received asthma medication. Maternal diabetes mellitus of any kind was associated with a higher odds (aOR 1.19, 95% CI: 1.12, 1.28) of prescription of anti-asthmatic medication after adjusting for year of birth, maternal age, parity, smoking and involuntary childlessness. However, anti-asthmatic medication was used as a

surrogate for childhood asthma and some of the children may have been prescribed anti-asthmatic medication for reasons other than asthma.

A study conducted among 1,401 children born to pregnant mothers who were enrolled in a study on the perinatal risk of asthma in infants of asthmatic mothers in the United States [120]. This study particularly examined the association between early antibiotic use and risk of childhood asthma. Pregnancy related information were collected from the mothers before 24 weeks of gestation using a questionnaire. Mothers were interviewed between September 2003 and January 2007 at their child's sixth birthday to determine the child's asthma status in terms of physician-diagnosed asthma. A total of 164 children reported asthma by six years of age and the prevalence of maternal diabetes was 1.6%. Maternal diabetes was associated with a higher odds of asthma in children by 6 years of age in the unadjusted model (OR 3.63, 95% CI: 1.46, 9.04). However, the final adjusted model did not include maternal diabetes following the model inclusion criteria used in the study using backward elimination process. So, the association between maternal diabetes and asthma in children remains undetermined after controlling for confounders.

Another population-based study aimed to identify early life factors for parent-reported physician diagnosed incidence asthma in 8,499 preschool children following them up to 4 to 5 years of age [275]. The cumulative incidence of asthma was 13.7% during the 4-year study period. Prenatal problem defined as history of diabetes or high blood pressure during pregnancy had 31.8% prevalence and prenatal problem was associated with an increased risk of asthma (HR 1.20, 95% CI:1.06, 1.36) in bivariate analysis. Being combined with high blood pressure during pregnancy, the effect of maternal diabetes on risk of asthma in offspring remains obscure even in

the unadjusted model. Moreover, prenatal problem was not included in the final multivariable model that was selected using modified stepwise methods.

In a population-based birth-cohort study the Study of Asthma, Genes and Environment (SAGE) among 3,574 Canadian children born in Manitoba in 1995, parent-reported asthma was present in 12.4% children at 7–8 years of age and 1.4% children had maternal history of diabetes mellitus (type 1, type 2 or GDM requiring insulin or controlled by diet) [276]. Children with maternal diabetes mellitus had a higher odds (OR: 1.95, 95% CI: 0.98, 3.86) of having reported asthma compared with children having mothers without diabetes mellitus. This study adjusted for family history of asthma, atopy, residence location and home exposure to mold, environmental tobacco smoke but did not consider some important confounders such as sex of the child, maternal age, maternal education, maternal smoking during pregnancy and household income. This study was also unable to differentiate between type 1, type 2 diabetes and GDM, and it is not clear if mothers were asked if they had diabetes during pregnancy. Some of the mothers may have had prepregnancy diabetes while some others may also have diabetes developed after birth of the child.

In another registry-based birth cohort study, 1,018,302 children born in Finland between 1991 and 2008 were followed up to 7 years of age or 2009 [277]. Information on all specialized health care outpatient and inpatient visits in public hospitals were collected from Hospital Discharge Register and information on children entitled to asthma medication reimbursement were collected from Finland's Social Insurance Institution database. A child was considered to have asthma if the child had record of asthma medication reimbursement; 3.9% children received reimbursement for asthma medication and 5.1% required hospital care for asthma. Maternal diabetes mellitus was present in 1.4% of children born very preterm (<32 weeks), 2.2% of

children born moderately preterm (32–33 weeks), 2.4% of children born late preterm (34–36 weeks) and 0.9% of children born at term (≥37 weeks). Among children born moderately preterm (32–33 weeks), children born to mothers with diabetes mellitus (GDM, type 1 and type 2 diabetes) were at an increased risk of asthma [HR 1.62, 95% CI: 1.02, 2.58] by 7 years of age compared with children born to mothers without diabetes. There was also weak evidence of an increased risk of asthma in term (≥37 weeks) babies (HR 1.09, 95% CI: 0.99, 1.21). The following potential confounders were controlled for in this study: mother's age, smoking, first delivery, assisted reproduction technology, antenatal steroid, number of fetuses, premature rupture of membranes, level of hospital, mode of delivery, sex of the child, gestational weight, admission to neonatal unit, ventilator and antibiotic therapy.

In yet another study, children born between 1995 and 2009 in hospitals in the United States were followed from 5 years of age for a median duration of 8.1 years using electronic medical records [278]. In that study, 3,856 children had exposure to maternal prepregnancy type 2 diabetes, 21,832 children had exposure to maternal GDM, and 118,908 children had no exposure to maternal diabetes. During the follow-up, 19.5% children with exposure to GDM had asthma diagnosed. Children with exposure to maternal GDM had an increased risk of asthma (HR 1.09, $p<0.0001$) after adjusting for maternal age, parity, race/ethnicity, education, household income, history of comorbidity, asthma, smoking during pregnancy and sex of the child. Furthermore, the adjusted HR for the association between maternal GDM and asthma was 1.15 ($p<0.0001$) for children whose mothers required antidiabetic medication for GDM during pregnancy compared with children without exposure to GDM, and the adjusted HR for the association was 1.06 ($p=0.01$) for children whose mothers did not use medication for GDM during pregnancy compared with children without exposure to GDM.

A recent population-based cohort study was conducted among 216,197 children born between 1991 and 2014 in a tertiary referral hospital to assess the association between GDM and long-term respiratory related hospitalizations of the offspring [279]. This study used data from two linked databases: the computerized perinatal database of the Obstetrics and Gynecology Department and the computerized hospitalization database of the Soroka University Medical Center, Israel. Children were followed up to 18 years of age or January 2014. The prevalence of GDM was 4.9%. A total of 5,481 children were hospitalized for asthma during the study period; 22 children had mothers with pharmacologically-treated GDM, 242 children had mothers with diet-treated GDM, and the remaining children did not have exposure to maternal GDM. The risk of asthma-associated hospitalization during childhood was lower in children born to mothers with pharmacologically-treated GDM (HR 0.94, 95% CI: 0.61, 1.42) or diet-treated GDM (HR 0.93, 95% CI: 0.82,1.06) compared with children born to mothers without GDM. While the point estimate suggested a lower risk of asthma-associated hospitalization, the 95% confidence interval indicates that the risk could be plausibly ranging from a 39% decrease to a 42% increase, so a substantial positive association in children born to mothers with pharmacologically-treated GDM was also compatible with their data. The following potential confounders were adjusted in this study: maternal age, hypertensive disorders of pregnancy (e.g. chronic hypertension, gestational hypertension and preeclampsia), gestational age, macrosomia (birth weight ≥4000 g), maternal smoking status, gender of the child and maternal ethnicity. However, this study included women who were diagnosed with diabetes during the first two trimesters of pregnancy and may have included some women with prepregnancy diabetes.

Studies have also examined the association between maternal diabetes and wheezing in children. A population-based study among 15,609 children examined the association between

different maternal medical conditions or procedures during pregnancy and/or at birth and wheezing by 6–7 years of age [280]. Data were collected by administering questionnaire to parents. Among the children, 9.5% had transient early wheezing (no wheezing in the first two years of life and no wheezing in the last 12 months), 5.4% had persistent wheezing (wheezing in the first two years of life and wheezing in the last 12 months), 6.1% had late-onset wheezing (no wheezing in the first two years of life but wheezing in the last 12 months) and the remaining 79% were non-wheezers (no wheezing in the first two years of life and in the last 12 months). The prevalence of maternal diabetes (pregestational or GDM) was 1.5%. Children born to mothers with diabetes mellitus had a higher odds [OR 1.72, 95% CI: 0.99, 3.00] of persistent wheezing compared with children born to mothers without diabetes mellitus at 6–7 years of age. The wide confidence interval was probably because of the low frequency of diabetes in mothers. Another study pooling 85,509 children from 14 European birth cohorts examined the association between maternal complications in pregnancy and wheezing in the offspring up to 12–24 years of age [281]. In this study, cohort-specific prevalence of ever wheezing (at least one episode of wheezing) varied from 20% to 47% and recurrent wheezing (at least four episodes of wheezing) from 3% to 14%. Maternal diabetes was defined as prepregnancy diabetes or overt diabetes or glucose intolerance in pregnancy. The prevalence of maternal diabetes varied between 0.8% and 19% among different cohorts. In the pooled analysis, there was an increased risk of ever wheezing [adjusted pooled relative risk (apRR): 1.04, 95% CI: 0.97, 1.13] and an increased risk of recurrent wheezing (apRR: 1.24, 95% CI: 0.86, 1.79) up to 12–24 months of life in children with maternal diabetes mellitus. However, there was evidence of heterogeneity (p=0.027) across the cohorts for the association between diabetes mellitus and recurrent wheezing.

2.4.4. Cesarean Section Delivery as a Potential Intervenable Mediator in the Pathway between Gestational Diabetes Mellitus and Asthma in the Offspring

Given that GDM is a known risk factor for cesarean section delivery [256] and there is a positive association between cesarean section delivery and asthma in children [95, 106], the effect of maternal GDM on the risk of asthma in the offspring may be partially mediated through cesarean section delivery. Recently, there has been an alarming increasing trend in delivery by cesarean section globally [282, 283]. An estimated 29.7 million (21% of global births) births occurred through cesarean section in 2015 worldwide. While the increase in cesarean section was driven by an increase in the proportion of births in health facilities and increase in cesarean section use within health facilities, a substantially higher proportion of births have occurred in low obstetric risk births without medical indications [283]. Cesarean section can lead to a range of short-term and long-term adverse consequences for both mothers and children even though it can be a life-saving intervention in medically indicated situations [284]. Different clinical and non-clinical interventions have been evaluated and recommended to reduce unnecessary cesarean section deliveries [285-287]. As such, cesarean section delivery could be a potential intervenable mediator to reduce the risk of asthma in children.

2.5. Summary

The current literature indicates gaps in knowledge in the three important areas of asthma epidemiology pertaining to the objectives of this doctoral research. Specifically, it indicates the need for examination of the age, period and cohort effects on the prevalence of asthma in Canadian adults using age, period and cohort theoretical and analytic framework. The course of asthma in children since asthma diagnosis in terms of asthma exacerbation using group-based trajectory modeling remains unknown. There remains considerable uncertainty regarding the role

of maternal GDM in the risk of asthma in the offspring. Overall, the existing literature suggests the need for further research to address these gaps in knowledge.

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3. Chapter 3: Age, Period and Cohort Effects on Asthma Prevalence in Canadian Adults, 1994–2011[1]

3.1. Introduction

Asthma affects an estimated 339 million people globally [1]. In Canada, around 2.4 million (8%) persons were estimated to have asthma in 2014 [2]. The Canadian Chronic Disease Surveillance System (CCDSS) reported that in 2011/2012 fiscal year, the prevalence of asthma differed by age: it decreased from 15% in 20–24 years old to 8.3% in 35–44 years old, remained stable at less than 9% in 45–64 years old before increasing in old age from 9.2% in 65–69 years to 10.6% in 80–84 years [3]. Similar age distribution of asthma prevalence was observed during 2000/2001 through 2011/2012 fiscal years in adults: the prevalence was higher in the 20–29 years old, decreased in 30–59 years old and then increased again in individuals aged 60 years and older [3]. The prevalence of asthma in Canadians aged one year and older increased from 6.5% in 2000/2001 fiscal year to 10.8% in 2011/2012 fiscal year [3]. In adults, during this period, the prevalence increased in all age groups but the rate of increase differed by age suggesting some age-period interaction [3]. The estimated prevalence of asthma with recent symptoms or medication use among Canadians aged 12 years or older also increased from 5.1% in 1994 to 6.5% in 2005 [4].

Variation in trends in estimated disease prevalence can be explicated in light of three time-related effects: age, period and cohort effects. Age effect is the change in the frequency of disease occurrence according to age [5], while period effect is the change in the frequency of

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disease occurrence caused by factors such as health policies and legislations, public health interventions and new treatment that affect all age groups [5, 6]. Cohort effect is conceptualized in epidemiology as a period effect that is differentially experienced across ages (i.e., interaction between calendar time and age) because of differential distribution of environmental or other factors across age groups [7]. However, in sociology, a cohort effect is conceptualized as the change according to the year of birth (birth cohort), irrespective of age and calendar time [6].

Above mentioned non-model-based results from the CCDSS shed some light on age, period and cohort effects on asthma prevalence, but these effects have yet to be estimated within a formal age, period and cohort analytic framework while accounting for socio-demographic factors. Examining the effects of age, period and cohort can provide insights into the observed trends in asthma prevalence and help identify subgroups with high asthma burden. We took the opportunity to examine the effects of age, period and cohort on asthma prevalence in Canada using data from a national longitudinal survey. The objectives of our study were to examine the effects of age and period on asthma prevalence among Canadian adults during 1994/1995–2010/2011 fiscal years and to assess if the period effect differed by age (cohort effect) adopting the epidemiological perspective of cohort effect.

3.2. Methods

3.2.1. Data Source

We utilized data from the National Population Health Survey (NPHS), household component conducted by Statistics Canada. Details of the NPHS are available elsewhere [8]. Briefly, the NPHS used stratified multi-stage sampling method and included 17,276 individuals aged 12 years or older in 10 Canadian provinces in first cycle in 1994/1995 fiscal year. These respondents were longitudinally followed every two years until cycle 9 in the 2010/2011 fiscal

year to collect information on socio-demographic factors, chronic health conditions, lifestyle factors and health services utilization. Response rates decreased from 92.8% in cycle 2 to 69.7% in cycle 9.

3.2.2. Study Sample

NPHS participants aged 18–80 years and living in Canada during survey cycles were included in this study. The final analytical sample comprised of 13,616 individuals in cycle 1, 12,334 in cycle 2, 11,296 in cycle 3, 10,364 in cycle 4, 9,391 in cycle 5, 8,593 in cycle 6, 8,205 in cycle 7, 7,194 in cycle 8 and 6,764 in cycle 9 (contributing a total of 87,757 observations).

3.2.3. Outcomes and Covariates

Health professional-diagnosed asthma (hereafter asthma) was self-reported by the respondents at each survey cycle. Asthma was ascertained from an affirmative response to the question "We are interested in 'long-term conditions' that have lasted or are expected to last 6 months or more and that have been diagnosed by a health professional. Do you have asthma?" asked at each survey. We also used a more conservative definition 'active asthma', which was a binary variable defined as self-reported asthma and one or both of the following conditions: (1) self-reported presence of wheezing, asthma symptoms or asthma attack in last 12 months and (2) intake of asthma medication in the last one month (in the first survey cycle) or intake of asthma medication in the last 12 months (in the remaining survey cycles).

Age and period were treated as continuous variables. Covariates controlled for included: sex, province of residence, country of birth, race, educational attainment, household income, exposure to environmental tobacco smoke and smoking status. Sex was categorized into "male" and "female"; province of residence was categorized into "Atlantic" (New Brunswick, Nova

Scotia, Prince Edward Island and Newfoundland and Labrador) and “non-Atlantic” (Ontario, Quebec, Manitoba, Saskatchewan, Alberta and British Columbia) provinces considering previously reported higher childhood asthma prevalence in Atlantic provinces [9]; country of birth was categorized into “Canada” and “outside Canada”; race was categorized into “white” and “non-white”; and educational attainment was categorized into “less than secondary school graduation”, “secondary school graduation”, “some post-secondary” and “post-secondary graduation”. Household income was adjusted based on total reported household income in past 12 months and the number of people living in the household and was categorized into the following groups by Statistics Canada [10]: “lowest” (income <$15,000 and 1–2 persons; <$20,000 and 3–4 persons; <$30,000 and ≥5 persons), “lower middle” (income $15,000–$29,000 and 1–2 persons; $20,000–$39,000 and 3–4 persons; $30,000–$59,000 and ≥5 persons), “upper middle” (income $30,000–$59,000 and 1–2 persons; $40,000–$79,000 and 3–4 persons; $60,000–$79,000 and ≥5 persons) and “highest” (income ≥$60,000 and 1–2 persons; ≥$80,000 and ≥ 3 persons). Exposure to environmental tobacco smoke (ETS) was categorized into “exposed” and “not exposed” based on current exposure. A respondent was considered to be “exposed” from an affirmative response to the question “Does anyone in this household smoke regularly inside the house?” A respondent’s smoking status was categorized into “never”, “former” and “current” from the categories (daily smoker, occasional smoker [former daily smoker], always an occasional smoker, former daily smoker, former occasional smoker and never smoked) of a derived variable created by Statistics Canada. The derived variable was created based on responses to the following three questions “At the present time do you smoke cigarettes daily, occasionally or not at all?” “Have you ever smoked cigarettes at all?” and “Have you ever smoked cigarettes daily?” Covariate information collected at each survey cycle were

used, except race and country of birth information that were collected at enrollment (survey cycle 1).

3.2.4. Missing Data

Data were missing for some of the variables from non-participation in one or more surveys because of either loss to follow-up or intermittent nonparticipation (resulting in 'non-monotone' missingness). The variable-wise rate of missing data was calculated based on the total observations (87,757) contributed by the respondents across all survey cycles. Among all observations, 89% had information on all variables; <1% of observations had missing information on asthma and race; while 2–3% of observations had missing information on educational attainment, exposure to ETS and smoking status. We created a separate household income category for 9.28% of observations with missing information on this variable.

3.2.5. Statistical Analysis

Descriptive statistics for covariates at survey cycle 1 and across survey cycles were calculated as a mean (SD) or percentage. Age was categorized into groups (18–25, 26–30, 31–35, 36–40, 41–45, 46–50, 51–55, 56–60, 61–65, 66–70, 71–75 and 76–80 years) for descriptive statistics. Prevalence of asthma and active asthma according to age group across the survey cycles were calculated. Generalized estimating equations (GEEs) with autoregressive correlation structure were used to examine the age, period and cohort effects while accounting for repeated measures. Specifically, modified Poisson regression models were fitted in the GEE framework to estimate prevalence ratio with a robust error variance [11]. Age was centered around its grand mean, and age and an age-squared term were included in the models to allow for potential non-linear relationship between age and both outcomes [12]. Cubic age term was considered but excluded because it was not statistically significant for both outcomes and its inclusion in the model

decreased model fit based on the quasi-likelihood under the independence model criterion (QIC) goodness of fit statistic for GEE models (Supplementary Table, S Table 3.1) [13]. In Model 1, asthma was regressed on age, age^2 and period to estimate age and period effects, and interaction terms between age and period and age^2 and period were included to estimate the cohort effect on asthma.

In Model 2, sex, province of residence, country of birth, race, educational attainment, household income, exposure to ETS and smoking status were added to Model 1 to estimate age, period and cohort effects while controlling for these covariates. Similar models were used for active asthma. We performed sensitivity analysis for active asthma excluding observations from survey cycle 1 as the recall period for asthma medication intake was one month in survey cycle 1 compared with 12 months in survey cycles 2–9.

We performed model-based standardization, also known as G-computation, to estimate the prevalence of the outcomes (asthma and active asthma) standardized to the population distribution of the covariates [14, 15]. This involved four steps: expansion of dataset, outcome modeling, prediction, and standardization by averaging [14].

Expansion of dataset: In the first step, three new expanded datasets were created: one for the age effect, one for the period effect and the other for the cohort effect (age-period interaction). For the age effect, the new expanded dataset contained the original data (with 87,757 observations) and seven copies of it. The original data was kept unchanged. Age was set to different values in the seven copies: '20' in the 1st copy, '30' in the 2nd copy, '40' in the 3rd copy, '50' in the 4th copy, '60' in the 5th copy, '70' in the 6th copy and '80' in the 7th copy. In all seven copies, the outcome was deleted and assigned a missing value to reflect unobserved

counterfactual outcome. For the period effect, the new expanded dataset contained the original data (with 87,757 observations) and nine copies of it. The original data was kept unchanged. Period was set to different survey cycles in the nine copies: 'cycle 1' in the 1st copy, 'cycle 2' in the 2nd copy, 'cycle 3' in the 3rd copy, 'cycle 4' in the 4th copy, 'cycle 5' in the 5th copy, 'cycle 6' in the 6th copy, 'cycle 7' in the 7th copy, 'cycle 8' in the 8th copy and 'cycle 9' in the 9th copy. In all nine copies, the outcome was deleted and assigned a missing value to reflect unobserved counterfactual outcome. For the cohort effect, the new expanded dataset contained the original data (with 87,757 observations) and 21 copies of it. The original data was kept unchanged. Both age and period were set to different values in these 21 copies: each of the seven age values described in the expanded dataset for the age effect (20, 30, 40, 50, 60, 70 and 80) were set at three different periods (survey cycles 1 [1994/1995], 5 [2002/2003] and 9 [2010/2011]). The outcome was deleted and assigned a missing value to reflect unobserved counterfactual outcome in all 21 copies.

Outcome modeling: In the second step, the outcome was modeled adjusted for the covariates using Model 2 described above in each expanded new dataset. Only original data in the expanded datasets contributed to the estimation of the parameters of the model because the outcome is missing in the copies.

Prediction: In the third step, the parameter estimates from the original data were used to predict the probabilities of unobserved counterfactual outcomes in the copies in each expanded dataset. The predicted probabilities represent counterfactual estimates of the population prevalence of the outcome.

Standardization by averaging: In the last step, we computed average of the predicted probabilities in each copy in the expanded datasets to obtain standardized prevalence. For the effect of age, the prevalence was standardized for period and the covariates; for the effect of period, the prevalence was standardized for age and the covariates; and for the cohort effect, the prevalence was standardized for the covariates. Standardized prevalences were then plotted to depict age, period and cohort (age-period interaction) effects, respectively.

Data analyses were conducted in SAS software v 9.4 (SAS Institute, Cary, North Carolina) [16]. GEE was conducted with GENMOD procedure in SAS [17]. Standardized survey sampling weights were used in all analyses to take into account the unequal probabilities of selection.

3.3. Results

3.3.1. Socio-demographic Characteristics of the Respondents

At cycle 1, the mean age of the respondents was 43 years, which increased to 55 years in cycle 9. Nearly half of the respondents were male; the majority were born in Canada, were white and did not have exposure to environmental tobacco smoke; 30% were current smoker (Table 3.1). Across survey cycles, the mean age was 48 years (Table 3.1).

Table 3. 1: Characteristics of respondents at cycle 1 and across survey cycles, National Population Health Survey, 1994/1995-2010/2011

Characteristics	**Cycle 1**	**Across survey cycles**
	N= 13,616	**N=87,757**
Age in years, mean (SD*)	43.1 (15.8)	48.2 (14.9)
Male (%)	49.3	51.1
Country of birth, Canada (%)	78.8	80.0
Race		
White (%)	89.6	90.3
Non-white (%)	9.7	9.1
Missing (%)	0.7	0.6
Province of residence, Atlantic (%)	8.2	8.2
Educational attainment		
Less than secondary school graduation (%)	25.1	19.4
Secondary school graduation (%)	16.4	14.3
Some post-secondary (%)	25.7	25.6
Post-secondary graduation (%)	32.5	38.5
Missing	0.3	2.3
Household income		
Lowest income (%)	16.4	9.1
Lower middle income (%)	28.0	19.7
Upper middle income (%)	35.1	32.7
Highest income (%)	15.4	29.3
Missing (%)	5.1	9.3
Exposure to environmental tobacco smoke		
Unexposed (%)	60.7	72.5
Exposed (%)	35.2	24.4
Missing	4.1	3.1
Smoking status		
Never smoked (%)	36.2	33.5

Former smoker (%)	29.5	40.0
Current smoker (%)	30.2	24.6
Missing (%)	4.1	2.9

*SD, standard deviation

3.3.2. Asthma Prevalence

The prevalence of asthma increased from 5.2% in 1994/1995 to 9.0% in 2010/2011, across all age groups but the rate of increase differed among age groups (Table 3.2). The prevalence of active asthma across all age groups also increased from 4.6% in 1994/1995 to 7.0% in 2010/2011 (Table 3.3).

Table 3. 2: Prevalence of asthma among respondents according to age groups across the survey cycles, National Population Health Survey, 1994/1995-2010/2011

Age group, years	Cycle 1 (1994/1995), N=13596	Cycle 2 (1996/1997), N=12329	Cycle 3 (1998/1999), N=11289	Cycle 4 (2000/2001), N=10310	Cycle 5 (2002/2003), N=9313	Cycle 6 (2004/2005), N=8534	Cycle 7 (2006/2007), N=8114	Cycle 8 (2008/2009), N=7125	Cycle 9 (2010/2011), N=6718
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
18-25	140 (7.2)	101 (7.6)	81 (9.5)	37 (8.9)					
26-30	109 (7.7)	93 (8.2)	78 (8.0)	80 (9.2)	70 (8.0)*	46 (9.4)	21 (11.6)		
31-35	88 (5.0)	107 (7.0)	106 (8.5)	94 (8.9)	73 (8.7)	76 (9.7)	69 (9.5)	55 (10.7)	39 (14.5)
36-40	78 (4.8)	96 (5.9)	94 (5.9)	90 (6.7)	95 (8.6)	87 (9.3)	60 (7.4)	59 (8.8)	69 (11.4)
41-45	50 (3.6)	63 (4.5)	86 (6.3)	105 (7.6)	105 (7.6)	84 (6.9)	95 (8.6)	74 (8.9)	72 (9.9)
46-50	58 (4.7)	63 (5.2)	51 (4.5)	57 (4.8)	70 (6.2)	92 (8.0)	100 (8.5)	86 (7.7)	73 (7.5)
51-55	28 (2.9)	35 (3.7)	62 (6.2)	77 (7.7)	60 (6.0)	71 (7.2)	79 (7.3)	101 (9.8)	92 (8.9)
56-60	39 (4.6)	46 (5.6)	43 (5.5)	44 (5.5)	55 (6.8)	63 (7.6)	75 (8.7)	45 (5.4)	67 (7.4)
61-65	40 (5.3)	38 (5.3)	40 (5.4)	42 (6.1)	49 (7.2)	42 (6.3)	45 (6.6)	58 (8.0)	81 (10.5)
66-70	37 (5.4)	39 (5.9)	48 (8.0)	39 (6.6)	36 (6.4)	36 (6.4)	49 (8.0)	43 (7.5)	42 (7.5)
71-75	27 (4.72)	35 (6.0)	26 (4.7)	37 (7.1)	42 (8.3)	43 (8.6)	34 (7.1)	31 (6.6)	31 (6.2)
76-80	16.5 (4.5)	20 (5.2)	31 (7.4)	41 (9.1)	30 (7.3)	31 (8.3)	32 (8.2)	36 (9.8)	36 (9.7)
Total	712 (5.2)	735 (6.0)	748 (6.6)	743 (7.2)	685 (7.4)	673 (7.9)	658 (8.1)	588 (8.3)	601 (9.0)

*18–24 years and 26–30 years age groups combined because frequencies for 18–24 years were not reportable

Table 3. 3: Prevalence of active asthma among respondents according to age groups across the survey cycles, National Population Health Survey, 1994/1995-2010/2011

Age group, years	Cycle 1 (1994/1995), N=13596	Cycle 2 (1996/1997), N=12329	Cycle 3 (1998/1999), N=11289	Cycle 4 (2000/2001), N=10310	Cycle 5 (2002/2003), N=9313	Cycle 6 (2004/2005), N=8534	Cycle 7 (2006/2007), N=8114	Cycle 8 (2008/2009), N=7125	Cycle 9 (2010/2011), N=6718
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
18-25	123 (6.4)	81 (6.1)	50 (5.9)	30 (7.1)					
26-30	95 (6.7)	69 (6.1)	61 (6.2)	49 (5.7)	46 (5.3)*	30 (6.1)	12 (6.9)		
31-35	82 (4.6)	86 (5.6)	91 (7.3)	72 (6.8)	55 (6.6)	59 (7.6)	55 (7.6)	42 (8.2)	22 (8.4)
36-40	61 (3.8)	74 (4.6)	79 (5.0)	75 (5.6)	81 (7.3)	59 (6.3)	43 (5.3)	46 (6.9)	52 (8.7)
41-45	47 (3.4)	48 (3.5)	71 (5.1)	80 (5.8)	67 (4.8)	63 (5.1)	69 (6.2)	52 (6.3)	54 (7.4)
46-50	44 (3.6)	51 (4.3)	34 (3.0)	47 (4.0)	60 (5.3)	69 (6.0)	79 (6.7)	66 (5.9)	55 (5.6)
51-55	22 (2.3)	26 (2.8)	56 (5.6)	67 (6.6)	44 (4.4)	51 (5.2)	56 (5.2)	70 (6.8)	76 (7.3)
56-60	36 (4.2)	39 (4.7)	37 (4.8)	39 (4.9)	45 (5.6)	56 (6.7)	66 (7.6)	34 (4.1)	51 (5.7)
61-65	39 (5.2)	33 (4.7)	36 (4.9)	36 (5.2)	43 (6.3)	38 (5.7)	36 (5.2)	51 (7.0)	65 (8.5)
66-70	36 (5.2)	34 (5.2)	37 (6.1)	32 (5.4)	29 (5.2)	29 (5.1)	40 (6.5)	36 (6.3)	40 (7.1)
71-75	27 (4.6)	31 (5.3)	24 (4.3)	31 (6.0)	37 (7.5)	38 (7.6)	23 (4.8)	27 (5.9)	25 (5.0)
76-80	16 (4.4)	17 (4.4)	25 (5.9)	35 (7.8)	24 (6.1)	25 (6.6)	27 (7.1)	33 (9.1)	31 (8.3)
Total	630 (4.6)	589 (4.8)	601 (5.3)	592 (5.7)	532 (5.8)	517 (6.1)	506 (6.2)	457 (6.4)	472 (7.0)

*18–24 years and 26–30 years age groups combined because frequencies for 18–24 years were not reportable

3.3.3. Age, Period and Cohort Effects on Asthma Prevalence

Asthma prevalence was negatively associated with age and positively associated with age^2 variables (Table 3.4, Model 1). There was also a positive association between asthma prevalence and period. Asthma prevalence was negatively associated with period-age interaction term suggesting some cohort effect. Similar results were observed after controlling for the covariates (Table 3.4, Model 2).

Model-based standardization demonstrated the curvilinear relationship between asthma prevalence and age. The standardized prevalence of asthma was 12% at 20 years, 6% at 50–60 years and 8% at 80 years (Figure 3.1a). There was a gradual increase in standardized asthma prevalence with period from 5% in 1994/1995 to 11% in 2010/2011 (Figure 3.1b). Period effect differed across individuals of different age (Figure 3.1c). While the standardized asthma prevalence increased between 1994/1995 and 2002/2003, and between 2002/2003 and 2010/2011 for everyone, individuals aged 20 years had the highest standardized asthma prevalence and steepest increase in standardized prevalence across three survey cycles. Individuals aged 80 years had the least increase in standardized asthma prevalence.

Table 3. 4: Age, period and cohort effects on prevalence of asthma among Canadian adults, National Population Health Survey, 1994/1995-2010/2011

	Model 1		Model 2[a]	
	Coefficients (95% confidence intervals)	***P*-value**	**Coefficients (95% confidence intervals)**	***P*-value**
Intercept	-3.1147 (-3.2458, -2.9837)	<0.0001	-3.2814 (-3.4793, -3.0835)	<0.0001
Age	-0.0017 (-0.0066, 0.0032)	0.49	-0.0038 (-0.0089, 0.0013)	0.15
Age^2	0.0006 (0.0003, 0.0009)	<0.0001	0.0005 (0.0002, 0.0008)	0.0007
Period	0.0937 (0.0763, 0.1111)	<0.0001	0.0964 (0.0780, 0.1148)	<0.0001
Period*age	-0.0014 (-0.0024, -0.0003)	0.01	-0.0011 (-0.0021, 0.0000)	0.05
Period*age^2	-0.0000 (-0.0001, 0.0000)	0.31	-0.0000 (-0.0001, 0.0000)	0.47
Sex				
Female			0.2749 (0.1293, 0.4206)	0.0002
Male			Reference	
Race				
Non-white			-0.0791 (-0.4273, 0.2690)	0.66
White			Reference	
Country of birth				
Outside Canada			-0.2748 (-0.5269, -0.0226)	0.03
Canada			Reference	
Province of residence				
Atlantic			-0.1747 (-0.3047, -0.0447)	0.0085
Non-Atlantic			Reference	
Highest education attained				
Less than secondary school graduation			0.0719 (-0.0928, 0.2366)	0.39
Secondary school graduation			-0.0703 (-0.2674, 0.1269)	0.48
Some post-secondary			-0.0170 (-0.1370, 0.1030)	0.78

Post-secondary graduation		Reference	
Household income			
Lowest income		0.1263 (0.0218, 0.2308)	0.02
Lower middle income		0.0790 (0.0062, 0.1518)	0.03
Upper middle income		0.0444 (-0.0133, 0.1022)	0.13
Missing		0.0326 (-0.0520, 0.1172)	0.45
Highest income		Reference	
Exposure to environmental tobacco smoke			
Yes		-0.0070 (-0.0654, 0.0515)	0.82
No		Reference	
Smoking status			
Current smoker		0.0740 (-0.0279, 0.1759)	0.15
Former smoker		0.0718 (-0.0087, 0.1523)	0.08
Never smoked		Reference	
GEE fit statistic			
QIC	47859.5443	46526.5118	

[a] Adjusted for sex, race, country of birth, province of residence, educational attainment, household income, exposure to environmental tobacco smoke and smoking

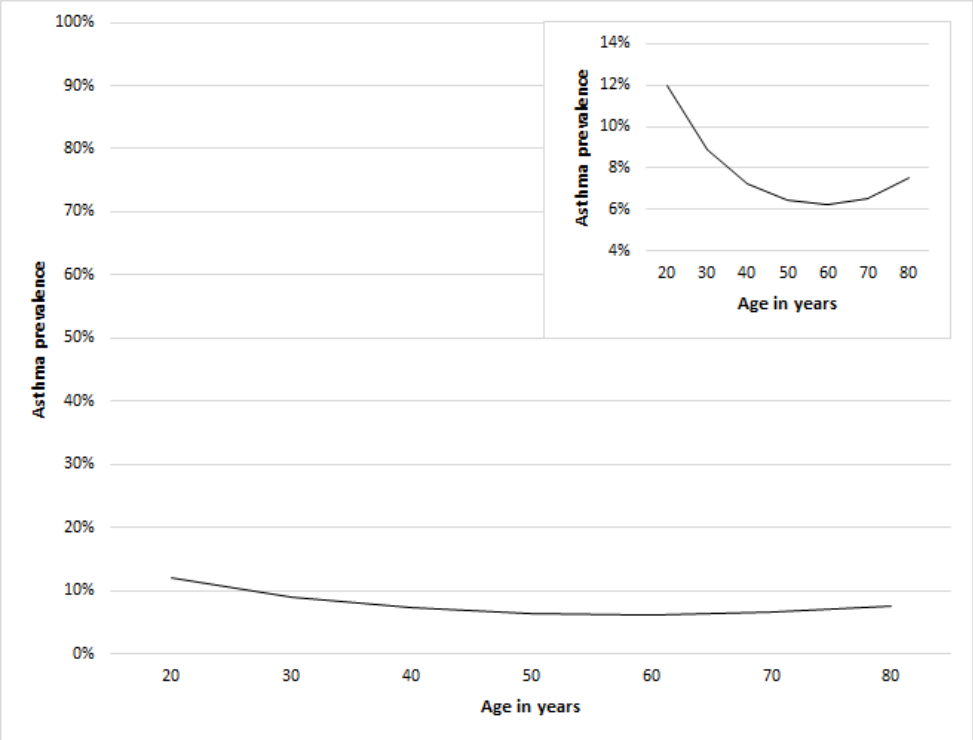

Figure 3.1a. Age effect on asthma prevalence

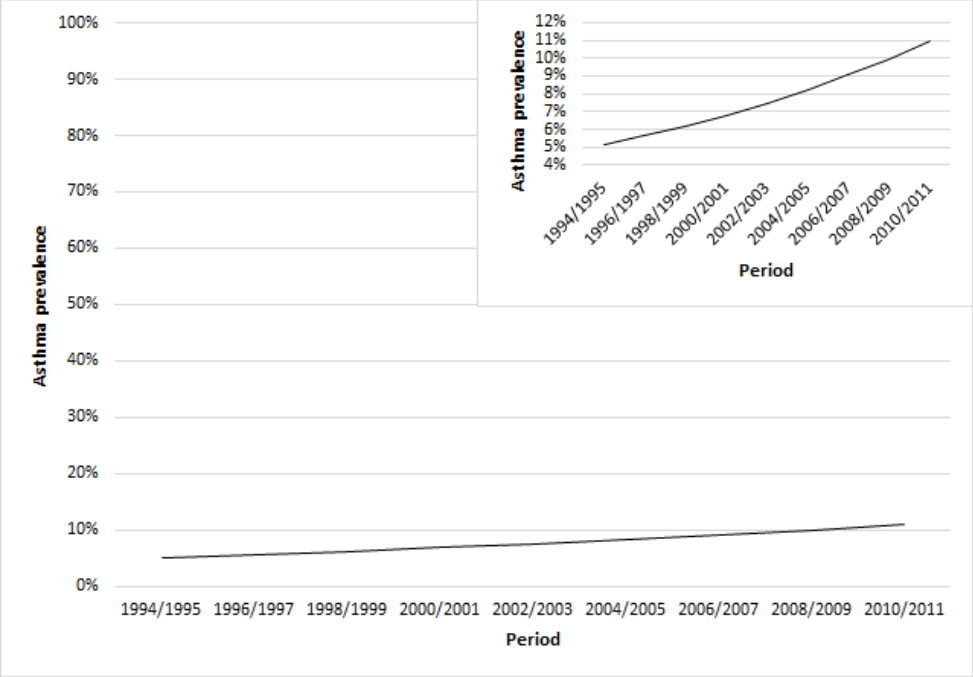

Figure 3.1b. Period effect on asthma prevalence

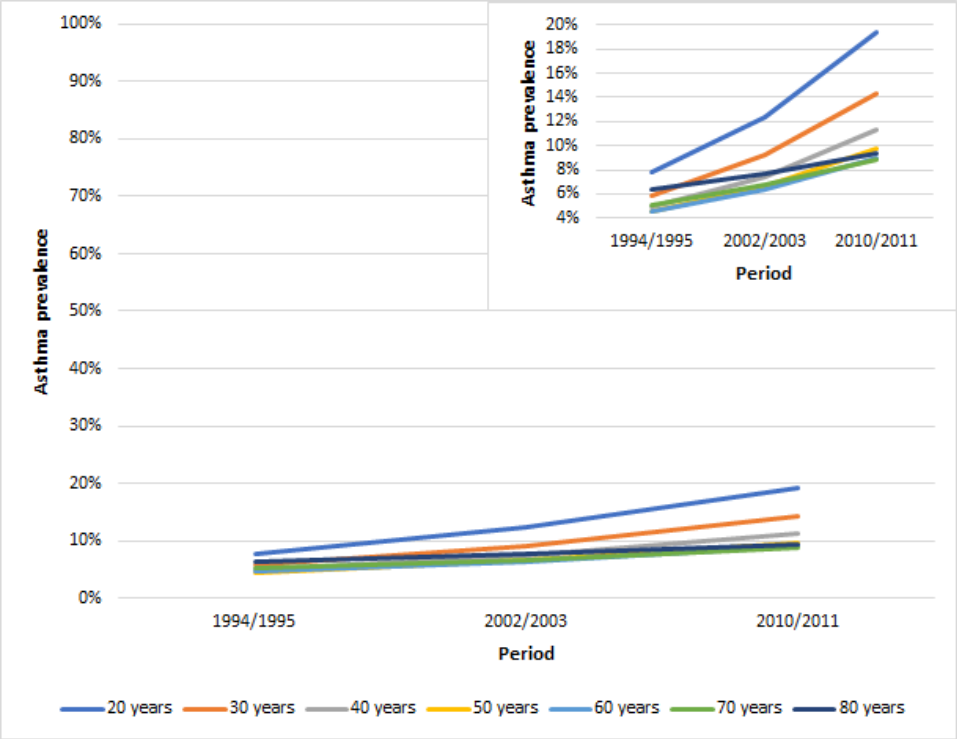

Figure 3.1c. Period effect on asthma prevalence according to age

Figure 3. 1: Model-based standardized prevalence of asthma among Canadian adults, National Population Health Survey, 1994/1995-2010/2011. a: age effect, b: period effect, c: period effect according to age

3.3.4. Age, Period and Cohort Effect on Active Asthma Prevalence

Active asthma prevalence was negatively associated with age and positively associated with age^2 variables (Table 3.5, Model 1). There was also a positive association between active asthma prevalence and period. The interaction term between period and age^2 was negatively associated with active asthma prevalence suggesting presence of some cohort effect. After controlling for the covariates, age and period effects on active asthma prevalence remained similar to the results from the unadjusted model (Table 3.5, Model 2). Period-age^2 interaction term was negatively associated with active asthma prevalence. Sensitivity analysis excluding observations from survey cycle 1 yielded similar results (Supplementary Table, S Table 3.2).

Model-based standardization demonstrated the curvilinear relationship between active asthma prevalence and age. The standardized prevalence of active asthma was 8% at 20 years, 5% at 50–60 years and 6% at 80 years (Figure 3.2a). There was a gradual increase in standardized active asthma prevalence with period from 4.5% in 1994/1995 to 8% in 2010/2011 (Figure 3.2b) but was lower and the slope of increase was less steep compared with the slope of increase in standardized prevalence of asthma. The period effect differed across individuals of different age between 1994/1995 and 2002/2003, and between 2002/2003 and 2010/2011 (Figure 3.2c). Individuals aged 20 years had the highest standardized prevalence across three survey cycles. The increase in standardized active asthma prevalence was least steep in individuals aged 80 years.

Table 3. 5: Age, period and cohort effects on prevalence of active asthma among Canadian adults, National Population Health Survey, 1994/1995-2010/2011

	Model 1		Model 2[a]	
	Coefficients (95% confidence intervals)	***P*-value**	**Coefficients (95% confidence intervals)**	***P*-value**
Intercept	-3.2547 (-3.3898, -3.1195)	<0.0001	-3.5602 (-3.7811, -3.3393)	<0.0001
Age	-0.0016 (-0.0068, 0.0037)	0.56	-0.0042 (-0.0096, 0.0013)	0.13
Age^2	0.0006 (0.0003, 0.0009)	<0.0001	0.0005 (0.0002, 0.0008)	0.0005
Period	0.0788 (0.0598, 0.0977)	<0.0001	0.0828 (0.0629, 0.1026)	<0.0001
Period*age	-0.0003 (-0.0015, 0.0009)	0.60	-0.0000 (-0.0012, 0.0012)	0.98
Period*age^2	-0.0001 (-0.0001, -0.0000)	0.04	-0.0000 (-0.0001, 0.0000)	0.08
Sex				
Female			0.3282 (0.1729, 0.4835)	<0.0001
Male			Reference	
Race				
Non-white			-0.2020 (-0.5612, 0.1572)	0.27
White			Reference	
Country of birth				
Outside Canada			-0.3038 (-0.5595, -0.0482)	0.02
Canada			Reference	
Province of residence				
Atlantic			-0.1802 (-0.3335, -0.0270)	0.02
Non-Atlantic			Reference	
Highest education attained				
Less than secondary school graduation			0.1794 (-0.0033, 0.3620)	0.05
Secondary school graduation			0.0353 (-0.1871, 0.2576)	0.76
Some post-secondary			0.0447 (-0.0708, 0.1602)	0.45

Post-secondary graduation		Reference	
Household income			
Lowest income		0.1099 (-0.0107, 0.2306)	0.07
Lower middle income		0.0623 (-0.0310, 0.1556)	0.19
Upper middle income		0.0205 (-0.0499, 0.0910)	0.57
Missing		0.0683 (-0.0366, 0.1732)	0.20
Highest income		Reference	
Exposure to environmental tobacco smoke			
Yes		-0.0055 (-0.0784, 0.0674)	0.88
No		Reference	
Smoking status			
Current smoker		0.1781 (0.0431, 0.3132)	0.0097
Former smoker		0.1801 (0.0614, 0.2989)	0.0029
Never smoked		Reference	
GEE fit statistic			
QIC	40614.2094	39453.5812	

[a] Adjusted for sex, race, country of birth, province of residence, educational attainment, household income, exposure to environmental tobacco smoke and smoking

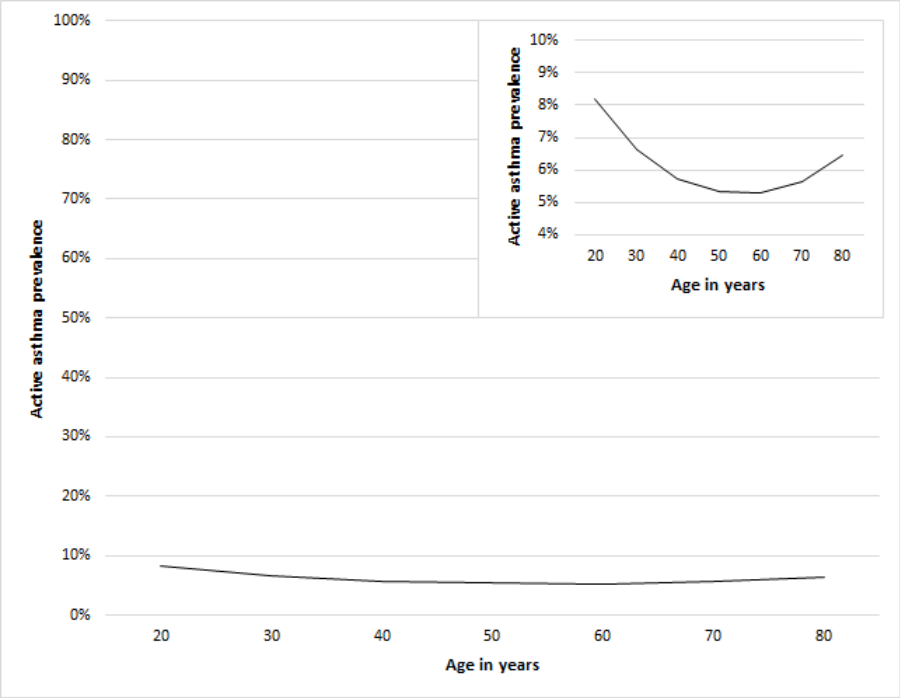

Figure 3.2a. Age effect on active asthma prevalence

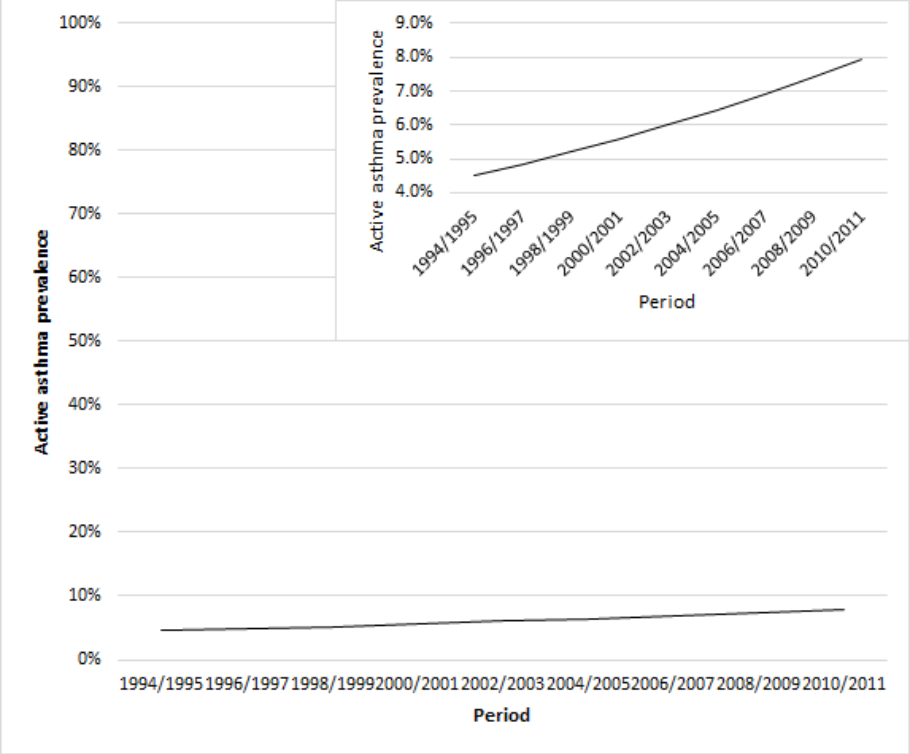

Figure 3.2b. Period effect on active asthma prevalence

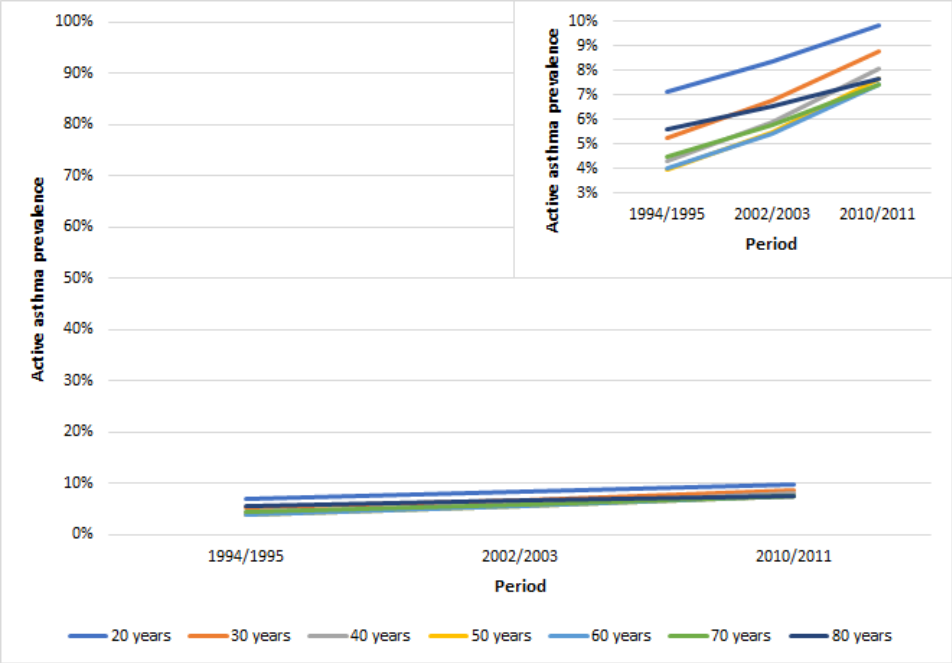

Figure 3.2c. Period effect on active asthma prevalence according to age

Figure 3. 2: Model-based standardized prevalence of active asthma among Canadian adults, National Population Health Survey, 1994/1995-2010/2011. a: age effect, b: period effect, c: period effect according to age

3.4. Discussion

Using a national longitudinal survey, this study examined the age, period and cohort effects on the prevalence of asthma, including active asthma, among Canadian adults for 16 years while controlling for socio-demographic factors. Our findings suggest that the prevalence of asthma and active asthma among Canadian adults differed by age (age effect), increased over time (period effect) and the period effect was somewhat different among individuals of different age during the study period (cohort effect).

The age effect on the prevalence of asthma and active asthma among Canadian adults indicates that the prevalence was highest among young adults, lowest for middle-aged adults and then increased slightly in old age. Our finding is similar to the non-model-based estimates from the studies that did not use formal age, period and cohort framework but suggested age effect on asthma prevalence among Canadians in 2011/2012 fiscal year [3], Ontarians during 1996–2015 [18, 19] and the study showing age effect on active asthma prevalence in 2011/2012 fiscal year [3]. However, these studies used administrative data and prevalent asthma was defined as at least two physician visits with a diagnosis of asthma within two consecutive years, or at least one hospitalization with a diagnosis of asthma; active asthma was defined as prevalent asthma with at least one physician visit or asthma hospitalization in a year. Additionally, the time frame of these studies differed from our study, although there was some overlap. The decreasing prevalence of asthma until middle age could be related to a similar relationship between asthma incidence and age. Indeed, in Canadians during 1996 through 2015, asthma incidence decreased with age in young and middle-aged adults before increasing again in older adults [3, 20]. Comparable age effects on asthma incidence have also been observed in Swedish adults [21]. Nevertheless, the reduction of asthma incidence has to be substantial to reduce the prevalence in young and

middle-aged adults in our study considering the chronic nature of asthma. It is possible that asthma remained undiagnosed, resulting in a lower prevalence of asthma in young and middle-aged adults in our study. Some young and middle-aged adults with asthma in our study remained symptom-free leading to lower prevalence of active asthma compared with older adults. Forty percent of adults aged 18–64 years with asthma in Ontario had two or more years of gaps in asthma activity compared with adults 65 years and older during 15 years of follow-up [22]. Different rates of asthma remission have been reported in adults in different settings: 6% in middle-aged adults and elderly individuals in Italy [23], 30% in Italian young adults [24], 14.6% in Swedish adults [21] and 18.6% in adults in northern Europe [25]. On the other hand, the increased prevalence of asthma, including active asthma in older adults may reflect increased incidence, and uncontrolled or frequent symptomatic asthma with declining lung functions and a low remission rate [26-29], as well as changes in lifestyle and increased access to health care and medication through government funded health care system in Canada. Indeed, age effect can arise from a combination of biological process and social experiences [6]. In addition, it is also possible that chronic obstructive pulmonary disease was misdiagnosed as asthma in older adults because of the overlap in clinical symptoms between these two conditions [30].

The prevalence of asthma increased over the course of 16 years among Canadian adults in our study similar to the temporal trends of asthma prevalence reported previously in Canada [19, 31]. Contrary to our finding of an increasing prevalence of active asthma, the age-standardized active asthma prevalence was reported to decrease slightly in Canadians from 2.8% in 2000/2001 fiscal year to 2.3% in 2011/2012 fiscal year in the CCDSS [3]. Active asthma in the CCDSS was defined as having at least one physician claim in the first diagnostic field or at least one hospital admission for asthma in any diagnostic field in a given fiscal year. The

decreasing trend in active asthma prevalence in the CCDSS might reflect improving asthma management and control, thereby reducing the need for medical care and hospitalization. The increasing active asthma prevalence in our study might reflect the milder cases, cases that were under control by taking medication not necessitating medical care or cases that did not seek medical care and not hospitalized. The prevalence of 'current asthma', defined as still having asthma among those with ever diagnosed asthma by a health professional using data from surveys, in adults also increased in the United States from 7.2% in 2000/2001 to 8.5% in 2008/2009 [32]. The cause behind this increasing secular trend remains unclear. The increasing prevalence, despite decreasing incidence of asthma [3], and decreased asthma-associated mortality [3, 33], likely reflect better asthma management and the chronic nature of asthma. It is also possible that asthma was over diagnosed because of increased awareness or, in adults 35 years and older, because of 'diagnostic exchange' in the sense that the increased asthma prevalence was driven by a decrease in the prevalence of bronchitis [34]. As such, the increased prevalence would reflect an artifact rather than true increase in asthma prevalence. In our study, across all survey cycles, the prevalence of active asthma was lower than the prevalence of asthma, which is expected as all asthma cases may not experience frequent symptoms or require regular intake of asthma medications. The increasing prevalence has implications for public health policy makers to address health care needs and planning asthma management. Future studies should seek to identify the underlying factors for the observed temporal trend beyond the sociodemographic and lifestyle factors controlled for in our study.

In our study, the increase in prevalence of asthma over time somewhat differed by age, reflected by the unparallel slopes of prevalence for different ages across three survey cycles and steeper slopes in young adults in the graphs with standardized prevalence. Similar to our

findings, the increase in age-standardized prevalence of asthma over time differed by age in the CCDSS [3]. However, the difference in period effect according to age in our study was largely attenuated for the restricted definition of active asthma albeit some variation in the slopes for prevalence over period was observed.

3.4.1. Strengths and Limitations

The use of data from a population-based longitudinal survey gave us the opportunity to assess the effects of age, period and cohort over a period of 16 years. We were able to adjust for potential confounding by some socio-demographic factors that are not usually available in administrative data. Furthermore, we were able to include more asthma cases, including active asthma cases because medical care delivered by physicians outside fee-for-service and asthma cases not seeking medical care would not be captured by administrative data, including the CCDSS [3]. Model-based standardization enabled us to visualize population-wide effect of age and period on prevalence of asthma, including active asthma, and to assess the variation in period effect across different ages using population standardized prevalence.

Asthma diagnosis, symptoms and medication intake were self-reported by the respondents and has the potential for errors in reporting. Compared to respondents with frequent or severe symptoms, respondents with milder symptoms or longer symptom-free periods may underreport asthma and/or asthma symptoms, which may result in an underestimation of the prevalence of asthma or active asthma. There is a potential for overestimation of active asthma prevalence in survey cycle 1 because of the shorter recall time for asthma medication between survey cycle 1 and the remaining survey cycles. However, we performed a sensitivity analysis excluding observations from survey cycle 1 and the results were similar. Our study was limited to adults aged 18–80 years. An age cut-point of 80 years was chosen because of fewer

respondents with asthma beyond this age and to minimize recall error. Furthermore, we did not control for environmental risk factors of asthma (such as air pollution) because of lack of data on them in the source database. Age, period and cohort effects may vary across different populations and settings and the findings from this study may not be generalizable beyond the study period and the Canadian population.

3.4.2. Conclusion

In conclusion, our findings suggest age and period effects on the prevalence of asthma, including active asthma in Canadian adults from 1994/1995 to 2010/2011. The period effect on asthma prevalence was experienced somewhat differently across age groups indicating some cohort effect. Future research is warranted to see whether the age distribution of asthma burden, the rising temporal trend along with the variation in asthma prevalence by age continues beyond our study period and in future.

3.5. Supplementary Tables

S Table 3. 1: Model coefficients, P-value and fit statistics with inclusion of age^3 in the models

	Model without covariates		Model with covariate[a]	
	Coefficients (95% CI)	***P*-value**	**Coefficients (95% CI)**	***P*-value**
Asthma				
Intercept	-3.1264 (-3.2601, -2.9927)	<0.0001	-3.2865 (-3.4861, -3.0869)	<0.0001
Age	-0.0039 (-0.0153, 0.0075)	0.51	-0.0038 (-0.0157, 0.0081)	0.53
Age^2	0.0006 (0.0003, 0.0009)	<0.0001	0.0005 (0.0002, 0.0008)	0.0007
Age^3	0.0000 (-0.0000, 0.0000)	0.65	0.0000 (-0.0000, 0.0000)	0.98
Period	0.0943 (0.0752, 0.1134)	<0.0001	0.0954 (0.0755, 0.1154)	<0.0001
Period*age	-0.0006 (-0.0024, 0.0011)	0.47	-0.0006 (-0.0024, 0.0012)	0.51
Period*age^2	-0.0000 (-0.0001, 0.0001)	0.66	-0.0000 (-0.0001, 0.0001)	0.96
Period*age^3	-0.0000 (-0.0000, 0.0000)	0.20	-0.0000 (-0.0000, 0.0000)	0.36
GEE fit statistic				
QIC	47890.4771		46569.2255	
Active asthma				
Intercept	-3.2517 (-3.3884, -3.1149)	<0.0001	-3.5552 (-3.7756, -3.3347)	<0.0001
Age	-0.0004 (-0.0132, 0.0124)	0.96	-0.0028 (-0.0161, 0.0105)	0.68
Age^2	0.0006 (0.0003, 0.0009)	0.0001	0.0005 (0.0002, 0.0008)	0.0008
Age^3	-0.0000 (-0.0000, 0.0000)	0.83	-0.0000 (-0.0000, 0.0000)	0.8116
Period	0.0772 (0.0562, 0.0983)	<0.0001	0.0816 (0.0594, 0.1037)	<0.0001
Period*age	-0.0003 (-0.0023, 0.0018)	0.80	-0.0001 (-0.0022, 0.0020)	0.90
Period*age^2	-0.0000 (-0.0001, 0.0000)	0.29	-0.0000 (-0.0001, 0.0000)	0.34
Period*age^3	-0.0000 (-0.0000, 0.0000)	0.82	0.0000 (-0.0000, 0.0000)	0.96
GEE fit statistic				
QIC	40654.9577		39484.6341	

[a] Adjusted for sex, race, country of birth, province of residence, educational attainment, household income, exposure to environmental tobacco smoke and smoking

S Table 3. 2: Sensitivity analysis on age, period and cohort effects on prevalence of active asthma among Canadian adults, National Population Health Survey, 1994/1995-2010/2011

	Model 1		Model 2[a]	
	Coefficients (95% confidence intervals)	***P*-value**	**Coefficients (95% confidence intervals)**	***P*-value**
Intercept	-3.2310 (-3.3817, -3.0802)	<0.0001	-3.5152 (-3.7563, -3.2741)	<0.0001
Age	-0.0008 (-0.0068, 0.0052)	0.79	-0.0034 (-0.0098, 0.0031)	0.30
Age^2	0.0005 (0.0002, 0.0008)	0.0043	0.0004 (0.0000, 0.0007)	0.03
Period	0.0744 (0.0537, 0.0951)	<0.0001	0.0766 (0.0546, 0.0985)	<0.0001
Period*age	-0.0005 (-0.0019, 0.0009)	0.48	-0.0002 (-0.0016, 0.0012)	0.77
Period*age^2	-0.0000 (-0.0001, 0.0000)	0.23	-0.0000 (-0.0001, 0.0000)	0.52

[a] Adjusted for sex, race, country of birth, province of residence, educational attainment, household income, exposure to environmental tobacco smoke and smoking

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4. Chapter 4: Asthma Exacerbation Trajectories and Their Predictors in Children with Incident Asthma[1]

4.1. Introduction

Asthma, a chronic disease characterized by periodic exacerbations and remissions, accounts for substantial medical and economic burden in children. Asthma exacerbations cause considerable suffering in children and can result in unscheduled emergency department visits, outpatient visits, hospitalizations, and even death [1]. Furthermore, asthma exacerbations can have extra-medical consequences such as school absenteeism and loss of parental or caregiver's productivity [2, 3]. Much of the clinical-epidemiological literature on asthma has focused on the trajectories of wheezing to identify wheeze phenotypes and their subsequent association with asthma development in children [4-6] and a few studies followed children since birth and attempted to identify trajectories of asthma prevalence according to age [7-9]. However, none have examined the trajectories of asthma course in children using time since asthma diagnosis as the time scale to inform the course after diagnosis.

The trajectories of asthma course in terms of exacerbations in children remain understudied. It is possible that among children with incident asthma there could be qualitatively distinct groups of asthma exacerbation trajectories. Identifying the trajectory groups and their predictors could enhance physicians' ability to better prognosticate the course of asthma. The objectives of this study were to identify trajectories of exacerbation in children with incident asthma and to identify the predictors of these trajectories at the time of asthma diagnosis.

[1] A version of this chapter has been published: Nasreen S, Wilk P, Mullowney T, Karp I. Asthma exacerbation trajectories and their predictors in children with incident asthma. Ann Allergy Asthma Immunol 2019; 123: 293-300.e292

4.2. Methods

4.2.1. Data Source

The data source for this study was the National Longitudinal Survey of Children and Youth (NLSCY), Canada. Details of the NLSCY are available elsewhere [10]. Briefly, the NLSCY used a multi-stage cluster sampling to select households in 10 Canadian provinces in 1994/1995 (cycle 1) with children aged 0–11 years. Out of the 22,831 children surveyed in cycle 1, 15,405 children were followed for 14 years and surveyed every two years through the final survey (cycle 8) in 2008/2009 when they were 14–25 years old. A maximum of two children (siblings) were selected from each household. One person most knowledgeable about a child (aged 0–15 years) and older children (>15 years) responded to survey questionnaires administered to collect sociodemographic and lifestyle, environment and health-related data.

4.2.2. Study Population

An affirmative response to the question "Has this child ever had asthma that was diagnosed by a health professional?" asked to the person most knowledgeable for children aged 0–15 years in survey cycles indicated the presence of asthma. An affirmative response to the question "Have you ever had asthma that was diagnosed by a health professional?" asked to children aged >15 years in survey cycles 4–5 indicated the presence of asthma. The first-time report of asthma during survey cycles 2–8 indicated incident asthma diagnosed at some point during the two years before the survey. Children meeting the following criteria were included in our study: having a biological parent as the person most knowledgeable (parent hereafter), no asthma at survey cycle 1, and reported asthma diagnosed by a health professional during follow-up. Children with the following conditions were excluded from the study: not having a biological parent as the person most knowledgeable (n=958); asthma at survey cycle 1 (n=1,530), missing asthma information at

survey cycle 1 (n=178); no health professional-diagnosed asthma during the follow-up (n=10,617); information on asthma at less than 4 survey cycles (to be able to assess cubic pattern of the trajectories) [11] (n=1,538); and inconsistent response ("no" after "yes") on "ever diagnosed with asthma" question between surveys (n=161). Another 20 children were excluded because of: missing asthma information between surveys with a 'no' and a 'yes' response on asthma, which precluded identification of time of incident asthma; older child from households with two children to allow longer follow-up of the younger child; and children whose reported sex changed between surveys before asthma diagnosis. A total of 403 children diagnosed with incident asthma were retained for the analysis to identify trajectories during childhood. Follow-up of a child for our study started at asthma diagnosis and lasted for 6–12 years (up to 17 years of age), depending on the age at survey cycle 1 and on the age at asthma diagnosis.

4.2.3. Outcome and Predictors

'Asthma attack' was considered as the measure of asthma exacerbation. An affirmative response to the question "Has he/she had an attack of asthma in the last 12 months?" asked to parents of 0–15 year old children with asthma at each survey cycle, or "Have you had an attack of asthma in the last 12 months?" asked to 16–17 year old children with asthma in survey cycles 4–5 was considered as having an asthma attack. The following variables measured at or before incident asthma diagnosis were considered as potential predictors for trajectory group membership based on review of literature on prognostic factors in asthma [12-17] and available information in the NLSCY: sex of the child, child having allergy as a proxy for allergen sensitization or atopy of the child, at least one biological parent with a history of asthma or allergy, smoking habit of parent or spouse of the parent as a proxy for exposure to environmental tobacco smoke at home, number of siblings at home and age at asthma diagnosis. A child was considered to have allergy

if the parent reported that the child had health-professional-diagnosed allergies in survey cycles 1–3, or if the parent reported that the child had at least one of the following health-professional-diagnosed long-term conditions: food or digestive allergies, respiratory allergies such as hay fever or any other allergies in the remaining survey cycles. Parents were considered to have a history of asthma or allergy if either or both biological parents had at least one of the following health professional-diagnosed long-term conditions: food allergies or other allergies in survey cycles 1–3 or food or digestive allergies, respiratory allergies such as hay fever, any other allergies, or asthma, in the remaining survey cycles. A child was considered to be exposed to environmental tobacco smoke at home if parent or spouse reported to smoke cigarettes daily or occasionally at the time of survey. Age at the survey cycle reporting incident asthma was considered as the age at asthma diagnosis. Except for age at asthma diagnosis, predictor information from the survey cycle prior to asthma diagnosis was used, considering a 12-month recall period for asthma attack and because predictors should be established at the time of asthma diagnosis (i.e., at the beginning of period of trajectory) [18]. By our study design, children reporting incident asthma during survey cycles 2–5 and having information on asthma and asthma attack in four or more survey cycles were included. So, the predictor information from survey cycles 1–4 were used depending on the survey cycle of incident asthma report. Available information from a prior survey cycle was used to replace missing predictor data assuming the condition remained the same at the survey cycle prior to asthma diagnosis. Age at asthma diagnosis and number of siblings were treated as continuous variables, while the other predictors were represented by binary variables.

4.2.4. Statistical Analysis

Descriptive statistics on characteristics of children at asthma diagnosis were computed and summarized by means (standard deviation, SD) or medians (interquartile range, IQR) depending on the distribution of the continuous variables and by percentages for categorical variables. At first, a hierarchical logistic regression model was used to assess the overall pattern of asthma attack after diagnosis [19, 20]. Latent class growth modeling, a semi-parametric approach, was then used to identify distinct groups of children with similar patterns of asthma exacerbations over time [18, 21]. Latent class growth modeling attempts to identify trajectory groups in the population even if these trajectory groups are latent ("not identifiable ex ante on the basis of measured characteristics") [18] and thus unobservable. We first attempted to identify the number of latent trajectory groups by testing models with up to five latent trajectory groups. Each model included linear, quadratic and cubic polynomial terms for time since asthma diagnosis, so as to allow for the possibility of a cubic shaped pattern of the relation between the logit of the probability of asthma attack and time since asthma diagnosis. Among these, the model having the lowest Bayesian Information Criterion was selected (Supplementary Material, S Table 4.1) [22]. Examination of the results of statistical-significance testing of the three polynomial terms for time since asthma diagnosis revealed that the quadratic and cubic terms were not statistically-significant. Thus, these terms were dropped from the model [11, 18], so that the final model only included a linear term, suggesting a straight-line (rather than parabolic or S-shaped) pattern of the relation between the logit of the probability of asthma attack and time since asthma diagnosis. We used time since asthma diagnosis as the time axis in both hierarchical modeling and group-based trajectory modeling. Details of these analytic methods are provided in Supplementary Material, S Methods. Finally, bivariate and multivariable multinomial logistic

regression modeling was performed to identify the predictors of trajectory group membership. Multinomial logistic regression models were fitted because the outcome 'trajectory group' had more than two categories. Data on parental history of asthma or allergies and exposure to environmental tobacco smoking at home were missing in 28 (7%) and 4 (1%) children, respectively. We first performed a complete-case analysis, restricted to children having information on all predictors. We also performed sensitivity analysis after conducting 10 imputations for the missing risk factor values employing multivariate imputation using chained equations (MICE) [23]. We followed the rule of thumb regarding the number of imputations, that is, the number of imputations should be equal to or more than 100 times the largest fraction of missing information (FMI) [23].

We conducted a secondary analysis to identify asthma exacerbation trajectories restricted to children with asthma diagnosed after six years of age, as some preschool children with diagnosed asthma may outgrow their asthma after six years of age [24, 25]. To identify predictors of trajectory group membership, we fitted bivariate and multivariable logistic regression models. We performed a complete-case and sensitivity analyses, which involved conducting 15 imputations (based on the rule of thumb described above) in this subset of children for missing risk factors using MICE.

The questions on allergies for the parents were asked differently between survey cycles 1–3 and the remaining survey cycles. So, we conducted a sub-analysis for the predictors of trajectory group membership by restricting the operational definition of parental allergy to include parents having food allergy alone for the predictor parental asthma/allergy. This redefined predictor was thus named 'parental asthma/food allergy'. We conducted complete-case analysis and sensitivity analysis after multiple imputation, which involved conducting 15

imputations (based on the rule of thumb described above) for missing risk factors using MICE. Analyses were performed for all children and in the subset of children with asthma diagnosed after six years of age.

Hierarchical logistic regression modeling was performed using SAS's PROC GLIMMIX procedure with Laplace estimation to obtain maximum likelihood estimation of the parameters (SAS Institute, Inc., Cary, NC, USA) [26]. Latent class growth modeling was performed using the PROC TRAJ procedure and multinomial logistic regression in SAS [27]. Sensitivity analysis was performed using Stata software (StataCorp LP, College Station TX, USA). All statistical-significance tests were carried out at the alpha level of 0.05 (2-sided).

4.3. Results

We report findings on the trajectories and predictors following the recommended guidelines for reporting on latent trajectory studies, including studies using latent class growth modeling [28].

4.3.1. Characteristics of Children at Asthma Diagnosis

Among 403 children retained in the analysis, the median age at asthma diagnosis was six years, the majority of children (61%) were male and one-fifth (20%) of the children had allergies at or before asthma diagnosis (Table 4.1). The median duration of follow-up was 8 years (interquartile range, IQR: 4 years); 170 (42%) children contributed data for six years, 104 (26%) children contributed data for eight years, 79 (20%) children contributed data for ten years and remaining 50 (12%) children contributed data for 12 years of follow-up. Of the 403 children, 177 (44%) were aged more than six years at asthma diagnosis. Among these 177 children, 136 (77%) contributed data for six years and 41 (23%) contributed data for eight years of follow-up.

Table 4. 1: Characteristics of children at asthma diagnosis, National Longitudinal Survey of Children and Youth (NLSCY), 1994/1995–2008/2009

Characteristics	Frequency (%) (n=403)
Sex, male	246 (61)
Child has allergy	82 (20)
Parent has asthma or allergy	114 (28)
Exposure to environmental tobacco smoke at home	192 (48)
Number of siblings at home, mean (SD*)	1.02 (0.83)
Age of child at asthma diagnosis in years, median (IQR†)	6 (4)

*SD, standard deviation
†IQR, interquartile range

4.3.2. Overall Asthma Trajectory from Hierarchical Modeling

Table 4.2 presents the parameter estimates from the hierarchical logistic regression model. The fixed-effects parameter estimate for the intercept was 0.68, implying that the estimated probability of asthma attack was 0.66 at asthma diagnosis. The fixed-effects parameter estimate for time since asthma diagnosis was −0.358, implying that the odds of having had asthma attack decreased by 30% with each year increase in time since asthma diagnosis. The random-effects parameter estimates for between-child variance in both the intercept and 'growth' rate of asthma attack over time since asthma diagnosis were statistically significant (Table 4.2, random effects) suggesting that asthma attack probability at diagnosis and asthma attack probabilities across time since asthma diagnosis vary across children. The overall trajectory of asthma attack plotted from the fitted model suggested that the probability of asthma attack decreased with time after asthma diagnosis, from 0.63 at asthma diagnosis to 0.11 at 12 years following diagnosis (Figure 4.1).

Table 4. 2: Overall trajectory of asthma attack in children with asthma, National Longitudinal Survey of Children and Youth (NLSCY), 1994/1995–2008/2009

Effect	Estimate (SE*)	*p*-value
Fixed effects		
Intercept	0.68 (0.14)	<0.0001
Time†	-0.36 (0.03)	<0.0001
Random effects		
Between-child variance in intercepts	2.91 (0.49)	<0.0001
Between-child variance in 'growth' rate of asthma attack over time†	0.04 (0.02)	0.003
Fit statistics		
BIC‡	2291.93	
-2 Log Likelihood	2267.94	

*SE, standard error

†Time since asthma diagnosis

‡BIC, Bayesian information criterion

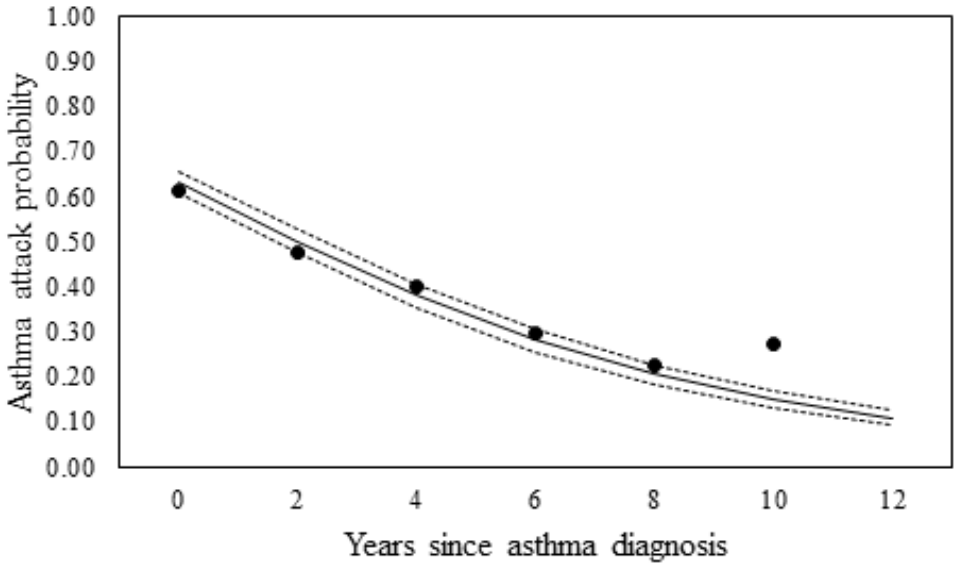

Figure 4. 1: Overall trajectory of estimated probability of asthma attack, hierarchical logistic regression model, National Longitudinal Survey of Children and Youth, Canada, 1994/1995–2008/2009. Solid line represents the point estimate of the probability, and dashed lines represent the 95% confidence interval estimates. Black circles represent observed proportion of asthma attack. Proportion at 12 years since asthma diagnosis is not reportable because of a small sample size (n<15) in this subpopulation.

4.3.3. Trajectory Groups of Asthma Attack from Latent Class Growth Modeling

Asthma attack over time was best fitted by a three-group model. Figure 4.2A presents the trajectories of each of the three groups and Supplementary Material, S Table 4.2 presents the estimates of the trajectory parameters and model adequacy information. The first trajectory group (*low increasing*) comprised of 21.3% children who had an initial low level of asthma attack probability that gradually increased after diagnosis and remained higher than the asthma attack probability for the second trajectory group from around seven years after asthma diagnosis (Figure 4.2A). The second trajectory group (*medium decreasing*) comprised of 45.8% children having a moderate level of initial asthma attack probability with initial steep decrease followed by gradual decrease with almost zero asthma attack probability at the end of 12-year follow-up. The third trajectory group (*high decreasing*) comprised of 32.8% children having very high initial asthma attack probability that decreased gradually and had a higher level of asthma attack probability than *low increasing* and *medium decreasing* trajectory groups at 12 years after asthma diagnosis. The predicted and observed trajectories for the three trajectory groups suggested good fit (Figure 4.2B). Among 104 children in the *low increasing* trajectory group, the median age of asthma diagnosis was 7 (IQR 3) years and 57 (54.8%) children had asthma diagnosed after six years of age; among 168 children in the *medium decreasing* trajectory group, the median age at asthma diagnosis was 6 (IQR 4) years and 99 (58.9%) children had asthma diagnosed before six years of age; and among 131 children in the *high decreasing* trajectory group, the median age at asthma diagnosis was 5 (IQR 5) years and 80 (61.1%) children had asthma diagnosed before six years of age.

A

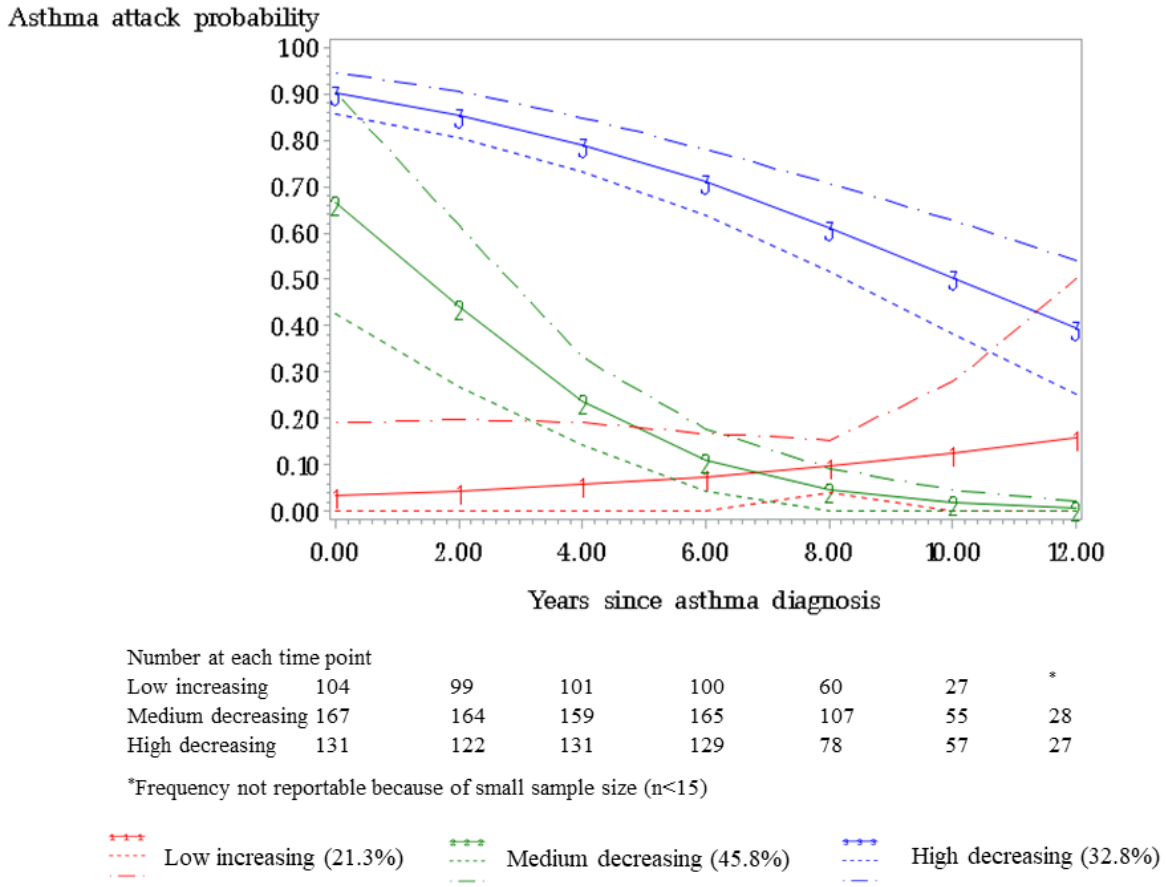

Figure 4.2A. Solid line depicts predicted trajectory and dashed line 95% confidence interval

B

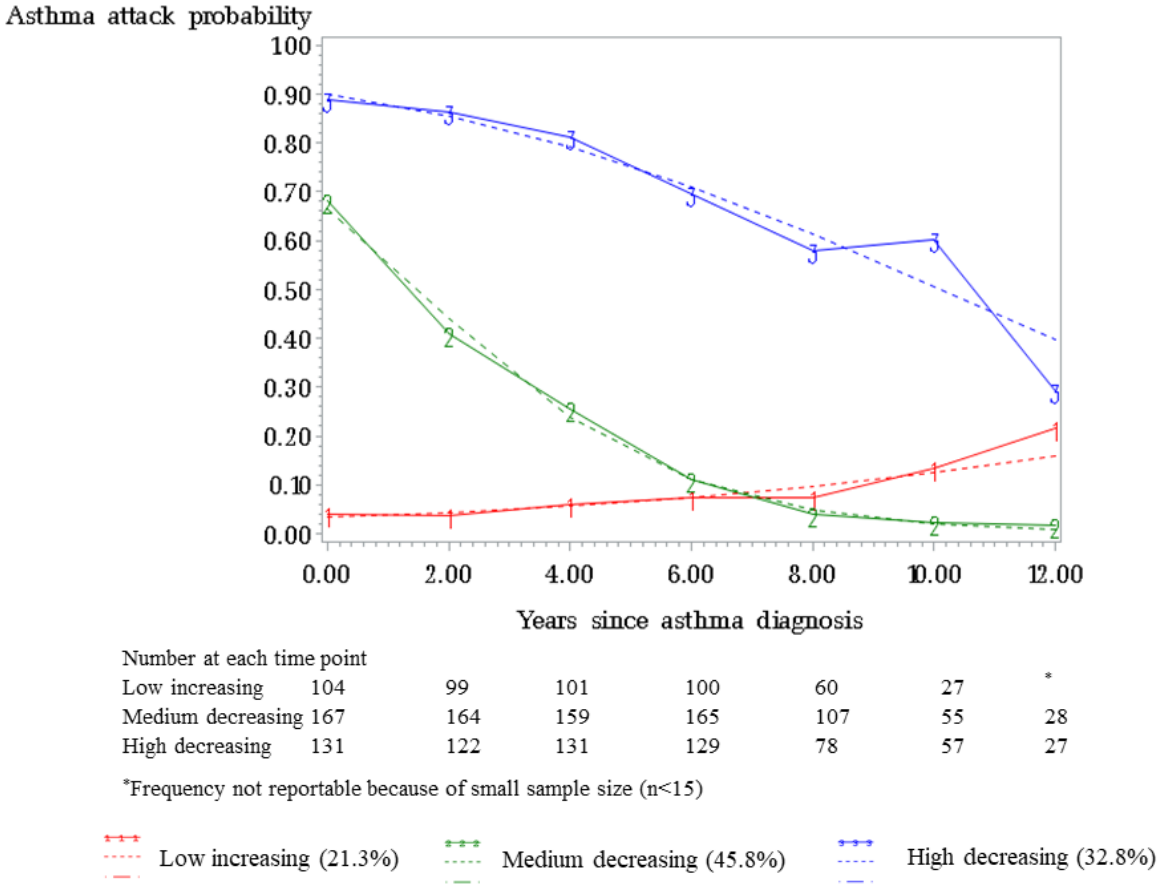

Figure 4.2B. Solid line depicts observed trajectory and dashed line the predicted trajectory

Figure 4. 2: Trajectories of asthma attack, latent class growth modeling, National Longitudinal Survey of Children and Youth, Canada, 1994/1995–2008/2009.

4.3.4. Predictors of Trajectory Groups

A total of 371 children had information on all potential predictors. According to the multivariable model, children having more siblings at home were more likely to belong to the *medium decreasing* and *high decreasing* trajectory groups, while children older at asthma diagnosis were less likely to belong to the *medium decreasing* and *high decreasing* trajectory groups than *low increasing* trajectory group (Table 4.3). The magnitude of the estimated association was largest for having more siblings. Male children were less likely to belong to the *medium decreasing* and *high decreasing* trajectory groups compared with the *low increasing* group, but the 95% confidence intervals were wide to allow meaningful interpretation. Similarly, imprecise results were obtained for children having allergy and exposure to environmental tobacco smoke at home although there were positive associations with the probability of belonging to the *medium decreasing* and *high decreasing* trajectory groups. The association between having parents with asthma or allergy and trajectory group membership was ambiguous: children having parents with asthma or allergy were less likely to belong to the *medium decreasing* trajectory group but more likely to belong to the *high decreasing* trajectory group. Sensitivity analysis with imputed data for missing predictors yielded similar results (Table 4.3).

Table 4. 3: Predictors of trajectory groups of asthma attack in children with asthma, National Longitudinal Survey of Children and Youth, 1994/1995–2008/2009

Group	Predictor	Odds ratio (95% confidence interval)			
All children*					
		Complete case analysis (N=371)		**Sensitivity analysis (N=403)**	
		Bivariate	**Multivariable**	**Bivariate**	**Multivariable**
Medium decreasing	Sex of the child, male	0.76 (0.45–1.33)	0.74 (0.42–1.29)	0.94 (0.57–1.56)	0.91 (0.54–1.53)
	Child has allergy	1.07 (0.57–2.02)	1.19 (0.62–2.30)	1.26 (0.68–2.34)	1.38 (0.73–2.60)
	Parent has asthma/allergy	0.69 (0.39–1.23)	0.67 (0.37–1.24)	0.69 (0.39–1.21)	0.64 (0.36–1.16)
	Exposure to environmental tobacco smoke at home	1.33 (0.79–2.24)	1.28 (0.75–2.18)	1.21 (0.74–1.99)	1.15 (0.69–1.91)
	Siblings at home	1.37 (0.99–1.90)	1.60 (1.11–2.30)	1.36 (0.99–1.86)	1.53 (1.08–2.16)
	Age at asthma diagnosis (years)	0.92 (0.83–1.02)	0.87 (0.78–0.98)	0.44 (0.84–1.02)	0.88 (0.79–0.98)
High decreasing	Sex of the child, male	0.83 (0.47–1.46)	0.70 (0.39–1.26)	1.01 (0.60–1.72)	0.87 (0.50–1.50)
	Child has allergy	1.02 (0.53–1.99)	1.11 (0.55–2.22)	1.11 (0.57–2.14)	1.14 (0.58–2.26)
	Parent has asthma/allergy	1.45 (0.82–2.56)	1.36 (0.75–2.49)	1.47 (0.83–2.58)	1.36 (0.76–2.44)
	Exposure to environmental tobacco smoke at home	1.41 (0.82–2.42)	1.21 (0.69–2.13)	1.27 (0.75–2.15)	1.11 (0.64–1.92)
	Siblings at home	1.26 (0.90–1.78)	1.59 (1.09–2.33)	1.34 (0.96–1.86)	1.62 (1.13–2.32)
	Age at asthma diagnosis (years)	0.83 (0.74–0.93)	0.80 (0.71–0.90)	0.85 (0.77–0.94)	0.82 (0.74–0.92)

Children with asthma diagnosed after six years of age[†]					
		Complete case analysis (N=160)		**Sensitivity analysis (N=177)**	
		Bivariate	**Multivariable**	**Bivariate**	**Multivariable**
High decreasing	Sex of the child, male	0.83 (0.44–1.56)	0.69 (0.35–1.38)	0.89 (0.49–1.61)	0.75 (0.40–1.43)
	Child has allergy	1.72 (0.85–3.50)	1.71 (0.81–3.61)	1.55 (0.78–3.08)	1.53 (0.75–3.15)
	Parent has asthma/allergy	1.28 (0.65–2.54)	1.31 (0.62–2.79)	1.26 (0.64–2.48)	1.27 (0.60–2.69)
	Exposure to environmental tobacco smoke at home	1.57 (0.83–2.98)	1.79 (0.92–3.51)	1.52 (0.83–2.79)	1.70 (0.91–3.20)
	Siblings at home	1.57 (1.03–2.41)	1.54 (0.99–2.39)	1.45 (0.97–2.17)	1.44 (0.95–2.18)
	Age at asthma diagnosis (years)	1.22 (0.94–1.59)	1.23 (0.93–1.62)	1.18 (0.93–1.49)	1.20 (0.93–1.53)

[*]Multinomial logistic regression, low increasing trajectory is the comparison group

[†]Logistic regression, low decreasing trajectory is the comparison group

4.3.5. Asthma Attack Trajectory Groups and Predictors in Children with Asthma Diagnosed after Six Years of Age

Among 177 children with asthma diagnosed after six years of age, the pattern of asthma attack over time was best represented by a two-group model. Figure 4.3A depicts the trajectories of these two groups, and Supplementary Material, S Table 4.2 depicts the estimates of the trajectory parameters and model adequacy statistics. The first trajectory group (*low decreasing*) comprised of 59.7% of children having a low level of asthma attack probability that gradually decreased during the follow-up (Figure 4.3A). The second trajectory group (*high decreasing*) comprised of 40.3% of children having very high initial asthma attack probability that decreased gradually over the eight years of follow-up and had a higher level of asthma attack probability than *low decreasing* trajectory group throughout the follow-up. The predicted and observed trajectories for the two trajectory groups suggested good fit (Figure 4.3B).

A

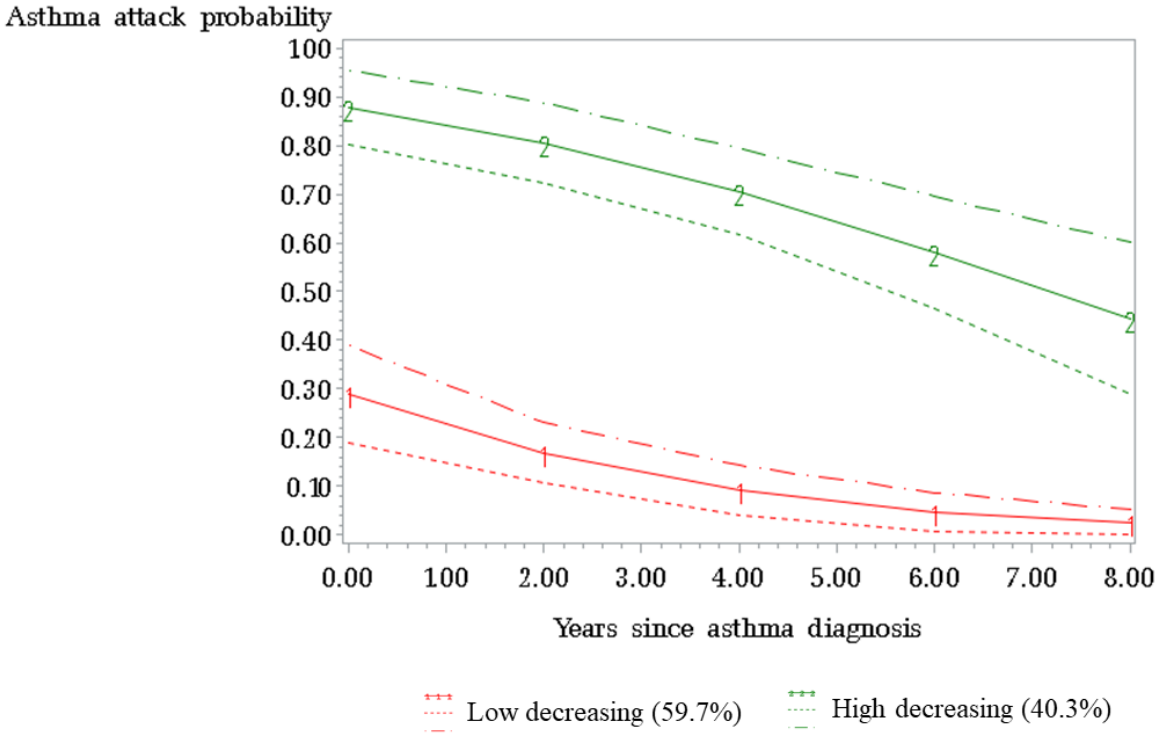

Figure 4.3A. Solid line depicts predicted trajectory and dashed line 95% confidence interval

B

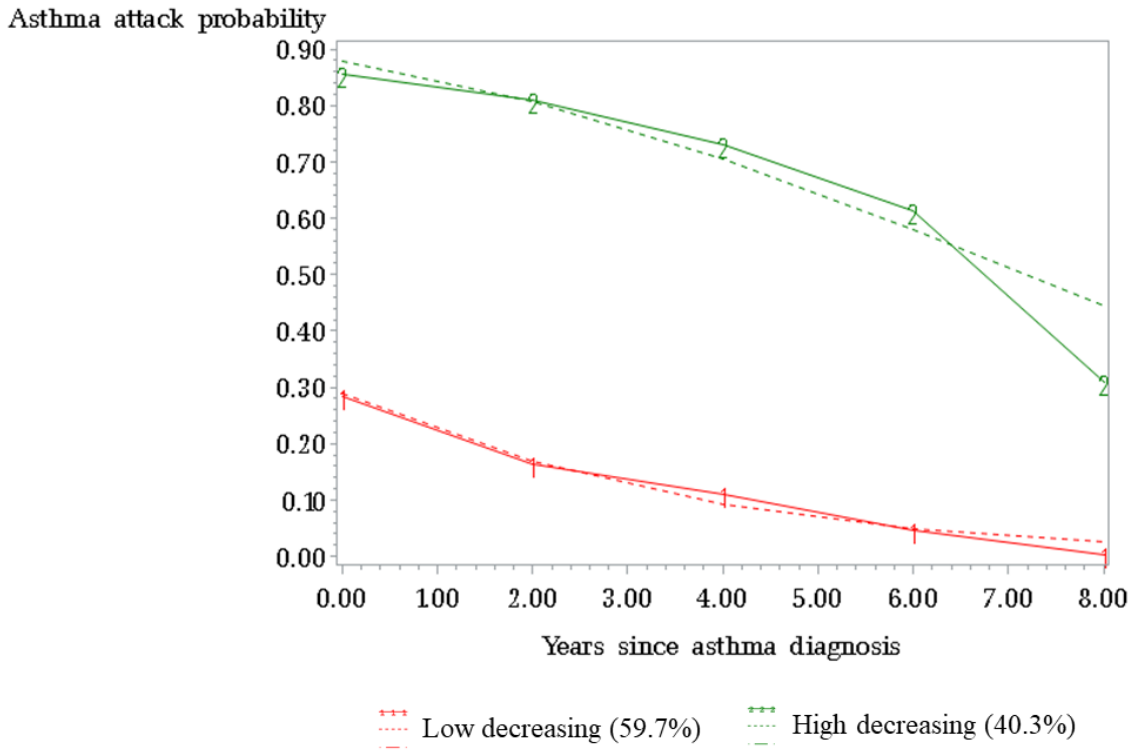

Figure 4.3B. Solid line depicts observed trajectory and dashed line the predicted trajectory

Figure 4. 3: Trajectories of asthma attack in children with asthma diagnosed after six years of age, latent class growth modeling, National Longitudinal Survey of Children and Youth, Canada, 1994/1995–2008/2009.

In the complete-case analysis (N=160), male children were less likely to belong to the *high decreasing* trajectory group, while children having allergy, having parents with asthma or allergy, children with exposure to tobacco smoke at home, having more siblings at home and children older at asthma diagnosis were more likely to belong to the *high decreasing* trajectory

group compared with the *low stable* trajectory group (Table 4.3). Similar results were obtained with imputed data.

4.3.6. Sub-analysis with parental asthma/food allergy as a potential trajectory-predictor

Among 403 children, 65 (16%) children had parents with asthma/food allergy, and among 177 children with asthma diagnosed after six years of age, 23 (13%) children had parents with asthma/food allergy. In the sub-analysis (Table 4.4), the results for the predictors of the trajectory group membership remained similar to the results presented in Table 4.3 that included parents with allergies (any type) or asthma. The estimated association between having parents with asthma and/or food allergy and trajectory group membership was as follows: children having parents with asthma or allergy were less likely to belong to the *medium decreasing* trajectory group but more likely to belong to the *high decreasing* trajectory group.

Table 4. 4: Sub-analysis for the predictors of trajectory groups of asthma attack in children with asthma, National Longitudinal Survey of Children and Youth, 1994/1995–2008/2009

Group	Predictor	Odds ratio (95% confidence interval)			
All children*					
		Complete case analysis (N=366)		**Sensitivity analysis (N=403)**	
		Bivariate	**Multivariable**	**Bivariate**	**Multivariable**
Medium decreasing	Sex of the child, male	0.85 (0.49–1.45)	0.76 (0.44–1.33)	0.94 (0.57–1.56)	0.86 (0.52–1.44)
	Child has allergy	1.24 (0.65–2.39)	1.30 (0.67–2.55)	1.26 (0.68–2.34)	1.31 (0.70–2.45)
	Parent has asthma/food allergy	0.84 (0.41–1.72)	0.77 (0.36–1.62)	0.85 (0.42–1.73)	0.79 (0.38–1.63)
	Exposure to environmental tobacco smoke at home	1.38 (0.82–2.34)	1.34 (0.78–2.29)	1.20 (0.73–1.96)	1.15 (0.69–1.91)
	Siblings at home	1.41 (1.01–1.96)	1.65 (1.14–2.39)	1.36 (0.99–1.86)	1.53 (1.08–2.16)
	Age at asthma diagnosis (years)	0.91 (0.82–1.01)	0.86 (0.77–0.97)	0.92 (0.84–1.02)	0.88 (0.80–0.98)
High decreasing	Sex of the child, male	0.87 (0.50–1.53)	0.76 (0.42–1.36)	1.01 (0.60–1.72)	0.90 (0.52–1.56)
	Child has allergy	1.11 (0.56–2.21)	1.25 (0.62–2.54)	1.11 (0.57–2.14)	1.19 (0.61–2.34)
	Parent has asthma/food allergy	1.43 (0.71–2.87)	1.20 (0.57–2.49)	1.38 (0.70–2.73)	1.19 (0.58–2.41)
	Exposure to environmental tobacco smoke at home	1.47 (0.85–2.53)	1.26 (0.72–2.23)	1.28 (0.76–2.16)	1.13 (0.66–1.93)
	Siblings at home	1.28 (0.91–1.82)	1.65 (1.12–2.42)	1.34 (0.96–1.86)	1.62 (1.13–2.32)
	Age at asthma diagnosis (years)	0.82 (0.74–0.92)	0.79 (0.70–0.89)	0.85 (0.77–0.94)	0.82 (0.73–0.92)

Children with asthma diagnosed after six years of age[†]					
		Complete case analysis (N=157)		**Sensitivity analysis (N=177)**	
		Bivariate	**Multivariable**	**Bivariate**	**Multivariable**
High decreasing	Sex of the child, male	0.84 (0.44–1.58)	0.73 (0.37–1.43)	0.89 (0.49–1.61)	0.79 (0.43–1.48)
	Child has allergy	1.71 (0.83–3.52)	1.70 (0.80–3.60)	1.55 (0.78–3.08)	1.60 (0.79–3.24)
	Parent has asthma/food allergy	-[‡]	1.07 (0.42–2.75)	1.04 (0.43–2.50)	1.06 (0.42–2.69)
	Exposure to environmental tobacco smoke at home	1.64 (0.86–3.13)	1.84 (0.93–3.61)	1.51 (0.82–2.77)	1.67 (0.89–3.12)
	Siblings at home	1.63 (1.05–2.51)	1.59 (0.94–1.64)	1.45 (0.97–2.17)	1.43 (0.95–2.17)
	Age at asthma diagnosis (years)	1.23 (0.94–1.60)	1.24 (0.94–1.64)	1.18 (0.93–1.49)	1.21 (0.94–1.54)

[*]Multinomial logistic regression, low increasing trajectory is the comparison group

[†]Logistic regression, low decreasing trajectory is the comparison group

[‡]The model did not meet the required guidelines for the results to be released from the Research Data Center

4.4. Discussion

Using data from a population-based longitudinal survey, we identified three distinct trajectories of asthma attack in children for a period of up to 12 years after incident asthma diagnosis: *low increasing*, *medium decreasing* and *high decreasing*. We also identified two predictors of the trajectory group membership: number of siblings at home and age at asthma diagnosis. Knowledge on the trajectories could help physicians foresee disease course at the time of asthma diagnosis.

While one-fifth of the children belonged to the *low increasing* trajectory group, the majority of the children belonged to the *medium decreasing* and *high decreasing* trajectory groups with substantially high probabilities of asthma attack during the initial phase of follow-up immediately after asthma diagnosis. The median age of asthma diagnosis in children was 6 years suggesting that half of the children were diagnosed when virus-induced wheezing is prevalent and symptoms may have abated soon afterwards [24, 29, 30]. The median age at asthma diagnosis was higher in children in the *low increasing* trajectory group compared with the median age at asthma diagnosis in children in the *medium decreasing* and *high decreasing* trajectory groups. Furthermore, more than half of the children in the *low increasing* trajectory group had asthma diagnosed after six years of age, whereas more than half of the children in the *medium decreasing* and *high decreasing* trajectory groups had asthma diagnosed before six years of age. Our finding of children with asthma diagnosed before six years of age belonging to the *high decreasing* trajectory group is comparable to the findings from previous studies that an earlier age at asthma onset may lead to persistent asthma in childhood [29, 31]. In addition, our findings suggest that children with preschool asthma belonging to the *medium decreasing* trajectory group grow out of asthma, and that this may happen after six years of age. The reason

for low level of exacerbation probability in children in the *low increasing* trajectory group warrants exploration in future studies. Children belonging to the *low increasing* group may require attention several years after asthma diagnosis to decrease the increasing probabilities of asthma attacks while children belonging to the *medium decreasing* and *high decreasing* trajectory groups could particularly benefit from reduction in exacerbation frequency during the initial period after diagnosis. Overall, children belonging to the *medium decreasing* trajectory group have better long-term prognosis than children belonging to the other two trajectory groups. Lack of similar studies on individuals with diagnosed asthma and with follow-up beginning right after asthma diagnosis in children or adult precluded us from comparing exacerbation trajectories identified in our study.

Having more siblings at home was positively associated with membership in the *medium decreasing* and *high decreasing* trajectory groups compared with the *low increasing* trajectory group. Having more siblings at home may have increased exposure to respiratory infections via contact with the siblings resulting in more asthma exacerbation immediately after asthma diagnosis. Our finding is similar to the finding that larger sibship was associated with severe asthma symptoms in children aged 6–7 years and 13–14 years in a worldwide study [32]. Nevertheless, our finding seems contrary to the finding from a study reporting that exposure to older siblings was associated with an increased rate of asthma remission in childhood [33]. Assessing a factor for asthma remission measured at a particular age or time does not provide information on the role of the factor over the course of asthma. In our study, children older at asthma diagnosis experienced milder asthma course as they were less likely to belong to the *medium decreasing* and *high decreasing* trajectory groups that had higher probabilities of asthma attack. In other studies, younger age was found to be a risk factor for asthma attack [34] and a

predictor of severe asthma exacerbation in children [35]. These findings are consistent with the results from our study. However, age at asthma diagnosis was only weakly associated with frequent episodic asthma in children in another study [36].

Exposure to environmental tobacco smoke is known to be positively associated with asthma severity and hospitalization with asthma exacerbation [37, 38] and negatively associated with asthma remission [14]. In our study, the estimated association between exposure to environmental tobacco smoke at home and trajectory group membership in our study was imprecise. Nevertheless, a study reported that exposure to second-hand smoke was "not associated" with frequent episodic asthma compared with infrequent asthma in children [36]. Although exposure to environmental tobacco smoke is time-varying and can change during the course of asthma, we considered exposure to environmental tobacco smoke before asthma diagnosis as a predictor to be able to predict trajectory group membership at the time of asthma diagnosis. An imprecise association was also found between allergy in child and trajectory group membership. Parent-reported allergy in a child may have led to inaccurate documentation of child's allergy status, potentially resulting in an underestimation of the association. The point estimates suggested allergy in child was a weak predictor, but the upper limits of the 95% confidence interval indicated that our data are compatible with relatively strong associations too. In addition, strong predictors of asthma course may not necessarily be strong predictors of our outcome, 'trajectory group'. Among children with asthma diagnosed after six years of age, nearly three-fifths of the children belonged to the *low decreasing* trajectory group with better prognosis compared with the two-fifths of the children belonging to the *high decreasing* trajectory group. Our results weakly support the association between exposure to environmental

tobacco smoke at home, siblings at home and age at asthma diagnosis with high decreasing trajectory group membership.

This study has several strengths. To our knowledge, this is the first study to identify trajectories of exacerbation in children following incident asthma diagnosis using group-based trajectory method that takes into account the dynamic nature of asthma course. Use of population-based data enabled us to follow children up to 12 years after asthma diagnosis. We may have been able to capture less severe asthma attacks that may not have necessitated urgent medical care and would have been excluded if administrative data were used. Asthma attacks managed at home, not seeking medical care or medical care received from non-fee-for-service physicians who do not remit service information are not captured in administrative data [39]. Information on the predictors of the trajectory groups identified in this study would be readily available to the physicians even at a primary care setting.

The findings of this study need to be interpreted in light of some limitations. Our sample size was relatively small, which led to considerable uncertainty in estimated trajectory patterns, as reflected by the wide confidence intervals of the trajectory curves. The small sample size may also have precluded us from identifying predictors that distinguished between *high decreasing* and *medium decreasing* trajectory groups. Thus, replication of our results in future studies is warranted. Asthma diagnosis was based on parental and child report and subject to recall bias. The prevalence of parent reported physician-diagnosed asthma has been found to be lower than the prevalence based on health administrative data (16% vs. 21%) in urban Canadian school children in cross-sectional setting [40]. However, validity of parent report of diagnosed asthma in longitudinal setting remains undetermined. There were some discrepancies in response regarding the child ever having asthma over the course of the NLSCY cycles suggesting that the

question asked may not have been perceived by the respondents the way they were intended. We excluded children with discrepant responses to obtain conservative estimates. We could not ascertain the exact age at asthma diagnosis because the question on ever having asthma was asked every two years and information on exact age or date of asthma diagnosis was not available. It is possible that children may have been younger than the age we considered to have asthma diagnosis. The recall period for asthma attack was 12 months prior to the interview, which may have resulted in underreporting of asthma attack requiring treatment, particularly of less severe events. As asthma attacks affect day-to-day lives of children and caregivers with or without necessitating medical care, parents likely reliably recalled severe asthma attack events. Nevertheless, we were unable to quantify asthma attack and ascertain severity because of a lack of this information. Children younger at NLSCY cycle 1 or asthma diagnosed at a younger age contributed more to the follow-up than children older at cycle 1 or asthma diagnosed at an older age. Different contribution to the follow-up by the children may have resulted in misclassification of trajectory group membership. We employed the traditional three-step method for identifying latent trajectories and their predictors, which does not take into account the uncertainty (classification error) in group allocation [28]. However, the odds of classification error for the trajectory groups in our final models exceeded the threshold and suggest fewer classification errors. We were unable to consider some potential predictors of the trajectory groups such as respiratory tract infection, objective markers of atopy and bronchial hyper-responsiveness, severity of asthma and asthma medication because of lack of information in the dataset [12]. Future studies should assess all potential predictors for trajectory group membership. Missing predictor values could bias the association between predictors and

trajectory group membership [41]. We performed sensitivity analysis after imputing missing predictor values and the results were similar.

In conclusion, our study suggests that children with asthma follow three distinct trajectories of asthma exacerbation. Membership in two of these trajectories was associated with two predictors at asthma diagnosis (number of siblings at home and age at asthma diagnosis), although the predictors were not able to distinguish between these two trajectories. Knowledge on the trajectories at the time of asthma diagnosis could help prognosticate the course and supplement the current paradigm of asthma management based on symptom control. Further studies on children with asthma in other settings, following children from birth through their entire childhood and using accurate measures of asthma and asthma attack, would provide further evidence on distinctive asthma exacerbation trajectories in children and enable comparison. Future studies are warranted to identify distinct predictors of the trajectory groups to predict individual child's exacerbation trajectory pattern. A comprehensive risk assessment model should be developed in the future, incorporating predictors from this study and future studies to aid prediction of distinct asthma exacerbation trajectory groups.

4.5. Supplementary Material

S Methods:

A 2-level hierarchical logistic regression model [19, 20] with repeated observations as level-1 units nested within individuals as level-2 units was performed to assess the overall pattern of asthma attack over time after asthma diagnosis and examine between-subject variability in trajectories. The combined level-1 and level-2 model included fixed effects for intercept and time since asthma diagnosis, and random effects for intercept and time since asthma diagnosis.

Level 1 model:

$$Logit\ \Pr(Asthma\ attack_{ti} = 1) = \beta_{oi} + \beta_{1i} Time\ since\ asthma\ diagnosis_{ti}$$

β_{0i} is the intercept and represents the log odds of having an asthma attack around the time of asthma diagnosis for a child *i*. β_{1i} represents the slope associated with time since asthma diagnosis for child *i* at time *t*.

Level 2 model:

For the intercept:

$$\beta_{0i} = \gamma_{00} + u_{oi}$$

For the slope:

$$\beta_{1i} = \gamma_{10} + u_{1i}$$

γ_{00} represents the log odds of having an asthma attack for a typical child, and u_{oi} is the level-2 error term representing a unique effect associated with child *i*. γ_{10} is the average effect of time since asthma diagnosis, and u_{1i} is the random effect for the slope associated with time since asthma diagnosis for child *i*.

Combined model:

$$Logit\ \Pr(Asthma\ attack_{ti} = 1) = \gamma_{00} + \gamma_{10} Time\ since\ asthma\ diagnosis_{ti} + u_{oi} + u_{1i}$$

Here, *i* = 1, 2,……, n individuals at time (survey cycle) *t* and *t* = 2,…..8 survey cycles. γ_{00} is the overall intercept and represents the log odds of having an asthma attack around the time of

asthma diagnosis for a child i , γ_{10} is the effect of time since asthma diagnosis, u_{oi} is the random intercept or child-level error, and u_{1i} is the random effect for the slope associated with time since asthma diagnosis for child *i*.

The intercept in a logistic regression model is the log odds of the dependent variable when all the independent variables are set to zero. Because we have one independent variable 'time since asthma diagnosis' in our hierarchical model, the intercept can be interpreted as the log odds of having an asthma attack around the time of asthma diagnosis. The fitted model was used to estimate time-specific probabilities of having an asthma attack, which were then plotted to depict the average trajectory of asthma attack following asthma diagnosis.

We used a logistic model for binary logit distribution in latent class growth modeling:[18] $\alpha_{it}^{j} = \frac{e^{\beta_0^j + \beta_1^j Time_{it} + \beta_2^j Time_{it}^2 + \beta_3^j Time_{it}^3}}{1 + e^{\beta_0^j + \beta_1^j Time_{it} + \beta_2^j Time_{it}^2 + \beta_3^j Time_{it}^3}}$ where α_{it}^{j} is the probability of the observed binary outcome $y_{it} = 1$ given membership in group *j*, $p^j(y_{it} = 1)$ with the assumption that the observed binary outcome $y_{it} = 1$ (individual *i* had asthma in time *t*) if the latent variable $y_{it}^{*} > 0$ and $y_{it} = 0$ (individual *i* did not have asthma in time *t*) if $y_{it}^{*} \leq 0$. Trajectory parameters were estimated using maximum likelihood with default start values. Identification of the trajectory groups involved a two-stage process [18]. In the first stage, the number of latent trajectory groups to include in the model was chosen. We tested five candidate models with cubic polynomial function in each model: the first model with one latent trajectory group, the second model with two latent trajectory groups, the third model with three latent trajectory groups, the fourth model with four latent trajectory groups and the fifth model with five latent trajectory groups (S Table 4.1). Among the five models tested, we chose the model with the lowest

Bayesian Information Criterion (BIC). BIC is a commonly used criterion for model selection and it is calculated as log (L) − 0.5k log (N) where L is the value of the model's maximized likelihood, N is the sample size and k is the number of parameters estimated by the model; the model with the lowest BIC is preferred [18, 22]. In the second stage, we chose the order of the polynomial defining the shape of each trajectory group in the model selected in the first stage. Including cubic polynomial function in the models in the first stage allowed for the possibility of cubic pattern of relationship between the logit of the probability of asthma attack and time since asthma diagnosis. Non-significant quadratic and cubic terms were removed but linear terms were retained in the model regardless of significance [11]. Thus, the final model included a linear term, depicting a straight-line trajectory pattern for each trajectory group. Adequacy of the final model was assessed by three diagnostics: average posterior probability of each group exceeded 0.70, odds of correct classification (OCC) for each group exceeded 5, and the model estimated probability of group membership differed <50% from the proportion assigned to a group based on largest posterior probability [18]. The OCC was calculated using the following formula:

$OCC_j = \frac{AvePP_j/1-AvePP_j}{\hat{\pi}_j/1-\hat{\pi}_j}$, where $AvePP_j$ denotes the average posterior probability of group $_j$ and $\hat{\pi}_j$ is the model-estimated probability of membership in group $_j$.

S Table 4. 1: Models tested in latent class growth modeling

No. of trajectory groups	BIC*	Sample size per group based on most likely group membership
All children (N=403)		
1	-1294.47	403
2	-1163.76	251/152
3	-1160.35	232/108/63
4	-1170.10	-†
5	-1182.41	-†
Children with asthma diagnosed after six years of age (N=177)		
1	-486.79	177
2	-438.52	99/78
3	-450.37	64/45/68
4	-461.57	-†
5	-475.74	-†

*BIC, Bayesian Information Criterion. Lowest BIC is preferable

†Indicates values not reportable because of small sample size (n<15) in one or more groups

S Table 4. 2: Latent trajectory groups of asthma attack in children with asthma, National Longitudinal Survey of Children and Youth, 1994/1995–2008/2009

Groups	Model estimated group membership, %	Assigned group membership using maximum probability rule, n (%)	Average posterior probability (AvePP)	Odds of correct classification	Parameter	Estimate (SE)*	t-statistic	BIC†
All children (N=403)								
Low increasing	21.3	104 (25.8)	0.72	9.48	Intercept	-3.36 (2.48)	-1.36	-1154.05
					Time to asthma diagnosis	0.14 (0.31)	0.46	
Medium decreasing	45.8	168 (41.7)	0.84	6.20	Intercept	0.69 (0.55)	1.26	
					Time to asthma diagnosis	-0.46 (0.12)	-3.95	
High decreasing	32.8	131 (32.5)	0.88	15.01	Intercept	2.21 (0.26)	8.59	
					Time to asthma diagnosis	-0.22 (0.04)	-5.89	
Children with asthma diagnosed after six years of age (N=177)								
Low decreasing	59.7	99 (55.9)	0.96	16.20	Intercept	-0.90 (0.25)	-3.60	-430.29
					Time to asthma diagnosis	-0.35 (0.08)	-4.21	

High decreasing	40.3	78 (44.1)	0.87	9.92	Intercept	1.97 (0.36)	5.47
					Time to asthma diagnosis	-0.27 (0.07)	-4.16

*SE, standard error, †BIC, Bayesian Information Criterion

4.6. References

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5. Chapter 5: The Effect of Gestational Diabetes Mellitus on the Risk of Asthma in the Offspring[3]

5.1. Introduction

Gestational diabetes mellitus (GDM) is diabetes that is "first diagnosed in the second or third trimester of pregnancy that is not clearly either preexisting type 1 or type 2 diabetes" [1]. The prevalence estimates of GDM varies from <1% to 28% worldwide [2, 3] and has increased significantly over the last few decades [4-8]. It is likely that the rising trend in GDM will continue with the increase in the prevalence of risk factors, such as older maternal age and obesity. GDM is associated with different short- and long-term consequences in mother (pre-eclampsia, caesarean section delivery, preterm delivery and future type 2 diabetes), fetus (fetal macrosomia, large for gestational age, fetal hypoxia, immune dysregulation, impaired surfactant production and delayed lung maturation) [9-12] and offspring (perinatal mortality, obesity and metabolic syndrome) [13]. Some of these consequences, notably cesarean section delivery [14-16], have also been implicated as risk factors for asthma. In addition, GDM could be increasing the risk of asthma in the offspring through other pathways. So, if indeed there is an effect of GDM on asthma in offspring, GDM can be contemplated to have not only an indirect component mediated by cesarean section delivery but also a direct component through other pathways independent of cesarean section delivery. Knowledge on both the total effect of GDM and direct effect beyond cesarean section delivery could help identify opportunities for interventions to reduce the risk of asthma in children. Previous studies have investigated the total effect of GDM on childhood asthma. However, results from these studies are inconclusive because some studies

[3] A version of this chapter is under review in a peer-reviewed journal.

suggested that GDM increased the risk of asthma in the offspring [17-22], while others suggested that GDM did not increase the risk of asthma [23]. The direct effect of GDM accounting for the mediating role of cesarean section delivery remains unknown.

In this study, we set to investigate the total effect of GDM on the risk of asthma in offspring and the controlled direct effect of GDM not mediated by cesarean section delivery by assuming a fixed value of cesarean section delivery. In addition, we assessed the joint effect of GDM and maternal smoking during pregnancy on the risk of asthma in the offspring given that maternal smoking in pregnancy is a known prenatal and intervenable risk factor for asthma in children [24, 25].

Methods

5.2.1. Data Source

Data from the National Longitudinal Survey of Children and Youth (NLSCY) were used for this study. Details of the NLSCY are available elsewhere [25]. Briefly, the NLSCY was a longitudinal population-based survey that collected information every two years from infancy to early adulthood. The first survey cycle of the NLSCY was conducted in 1994/1995 among 22,831 children aged 0–11 years living in 10 provinces of Canada using a multi-stage cluster sampling. In the longitudinal part of this survey, 15,405 children included in cycle 1 (1994/1995 original cohort) were followed every two years until the last cycle (cycle 8) in 2008/2009. A maximum of two children were included from each household. One person most knowledgeable (PMK) about the child was interviewed using questionnaire to collect information on socio-demographics, pregnancy with child and birth-related conditions for young children, and health professional-diagnosed chronic conditions in parents and children, children's physical development, learning, behavior, and social environment. Maternal pregnancy-related

information at enrollment was available for children aged 0–6 years. New cohorts of children aged 0–6 years, known as Early Childhood Development (ECD) cohorts, were added in each subsequent cycle to monitor early childhood development. The ECD cohort enrolled in cycle 2 of the 1994/1995 original NLSCY included younger siblings of the members of the original cohort. The ECD cohorts included one child per household except for twins. Same questionnaire was used for all ECD cohorts as in the original cohort.

5.2.2. Study Population

We pooled data from cohorts of children enrolled in NLSCY cycles 1–7 for this study (Supplementary Table, S Table 5.1). Children having a biological parent as the PMK, full information on the model variables and information on asthma in at least two survey cycles were included in this study. We excluded children with reported asthma defined as a positive response to the question "Has this child ever had asthma that was diagnosed by a health professional?" by the PMK at enrollment into the corresponding cohort (n=1,053). Children with prevalent asthma at enrollment were excluded because our study outcome was incident asthma. Children with reported asthma diagnosed during 0–2 years of age were also excluded as it is difficult to accurately diagnose asthma in young children (n=693) [27], and the majority of the children with wheezing before two years of age do not develop asthma later in childhood [28]. Some children with reported asthma had inconsistent asthma response on "ever diagnosed with asthma" during the follow-up ('no' response in a survey after 'yes' response in a previous survey) and were excluded (n=394). In households where more than one child was enrolled in the same or different cohorts, only one randomly selected child was retained and others were excluded (n=404). This led to an analytic sample of 19,933 children.

5.2.3. Study Outcome and Exposure

Incident asthma was the binary study outcome and defined as the first-time report of having health professional-diagnosed asthma. Children were followed until incident asthma, the end of the NLSCY survey follow-up, or loss to follow-up, whichever happened first. Loss to follow-up was defined as missing outcome data in two consecutive survey cycles.

Maternal gestational diabetes mellitus during pregnancy with the child was the binary exposure variable and was ascertained by a positive response to the question "During pregnancy with this child did you suffer from any of the following: Pregnancy diabetes?"

5.2.4. Covariates

The following characteristics of children and mothers relevant for our analyses were measured at NLSCY enrollment and included: the sex of the child, the birth weight of the child, maternal age at birth of the child, maternal asthma, maternal smoking during pregnancy, maternal high blood pressure in pregnancy, multiple gestation (e.g. twin, triplet or more), cesarean section delivery, preterm delivery, maternal race, maternal educational attainment, annual household income, and urban residence. Mothers were considered to have asthma if they were reported to have had health professional-diagnosed asthma. Maternal high blood pressure in pregnancy and maternal smoking in pregnancy were ascertained from an affirmative response to the questions "During the pregnancy with this child did you suffer from high blood pressure?" and "Did you smoke during your pregnancy with this child?" Cesarean section delivery was ascertained from response to the question "Was the delivery vaginal or cesarean?" Preterm delivery was ascertained from response to the following two questions: "Was this child born before, after or on his due date?" and "How many days or weeks before/after the due date was this child born?" Multiple gestation was ascertained from response to the question "Was this a single birth or twins, or triplets?"

Maternal age at birth and parity were represented as continuous variables. Maternal educational attainment was categorized into “less than secondary”, “secondary school graduation”, “some post-secondary” and “college or university degree (including trade)”. Annual household income was grouped into six categories: “$40,000 or more”, “$30,000 to $39,999”, “$20,000 to $29,999”, “$15,000 to $19,999”, “$10,000 to 14,999” and “less than $10,000”. Birth weight was categorized into three groups: “normal birth weight (2500 to 3900 g)”, “low birth weight (<2500 g)” and “high birth weight (≥4000 g)”. The remaining variables were represented as binary variables. Preterm delivery was categorized into “gestational age ≥259 days” and “gestational age ≤258 days”.

5.2.5. Statistical Analysis

Descriptive statistics for the child and maternal characteristics according to GDM status were computed and summarized by means (standard deviation, SD) or medians (interquartile range, IQR), depending on the distribution of the continuous variables and by percentages for categorical variables.

Total effect of GDM on asthma in offspring

In the counterfactual approach to causal inference, if an exposure is A with two levels ($a^* = 0$ and $a = 1$) and the outcome is Y, then the total effect can be defined as a measure of “how much the outcome would change overall for a change in the exposure from level $a^* = 0$ to $a = 1$” [29]. To estimate the total effect of GDM on the risk of asthma in offspring, we fitted pooled logistic regression model to emulate a Cox proportional hazards model [30-32]. First, we estimated the crude hazard ratio (HR) conditional on time since enrollment (hereafter time) and quadratic effect of time ($time^2$). Then we estimated the HR additionally adjusting for the confounders informed by the directed acyclic graph (DAG) drawn for the relationship between GDM and

asthma in the offspring using the web application DAGitty [33] (Figure 5.1). According to the DAG, we needed to adjust for the following potential confounders: sex of the child, maternal prepregnancy overweight/obesity, maternal age at birth of the child, maternal smoking during pregnancy, maternal high blood pressure in pregnancy, multiple gestation, maternal educational attainment, annual household income and urban residence. But we were unable to adjust for the unmeasured confounder maternal prepregnancy overweight/obesity. Thus, we conducted a sensitivity analysis to calculate bias-corrected estimates (described below). We also adjusted for the NLSCY cohort membership indicating the NLSCY survey cycle of enrollment.

Direct effect of GDM on asthma in offspring

The direct effect can be distinguished as controlled and natural direct effects in the counterfactual approach under certain no-confounding assumptions [29, 34]. If an exposure is A with two levels (a^*=0 and a=1), the outcome is Y and the mediator is M, then "The controlled direct effect (CDE(m)) expresses how much the outcome would change on average if the mediator were fixed at level m uniformly in the population but the treatment were changed from level a^* =0 to level a=1. The natural direct effect (NDE) expresses how much the outcome would change if the exposure were set at level a =1 versus level a^* =0 but for each individual the mediator were kept at the level it would have taken, for that individual, in the absence of the exposure. This NDE captures what the effect of the exposure on the outcome would remain if we were to disable the pathway from the exposure to the mediator" [29]. However, estimation of the NDE requires absence of exposure-induced confounders of mediator-outcome relationship in addition to the absence of confounding of the exposure-outcome, mediator-outcome and exposure-mediator relationships [29]. In our study, we had exposure-induced confounders of mediator-outcome relationship. According to the DAG, preterm delivery and birth weight were

GDM-induced confounders of cesarean section delivery-asthma in offspring relationship (Figure 5.1). So, we were only able to estimate the CDE that can be conceived as the effect of GDM on asthma in offspring with a fixed value of the mediator cesarean section delivery (here, in a hypothetical scenario, delivery not by cesarean section for all children).

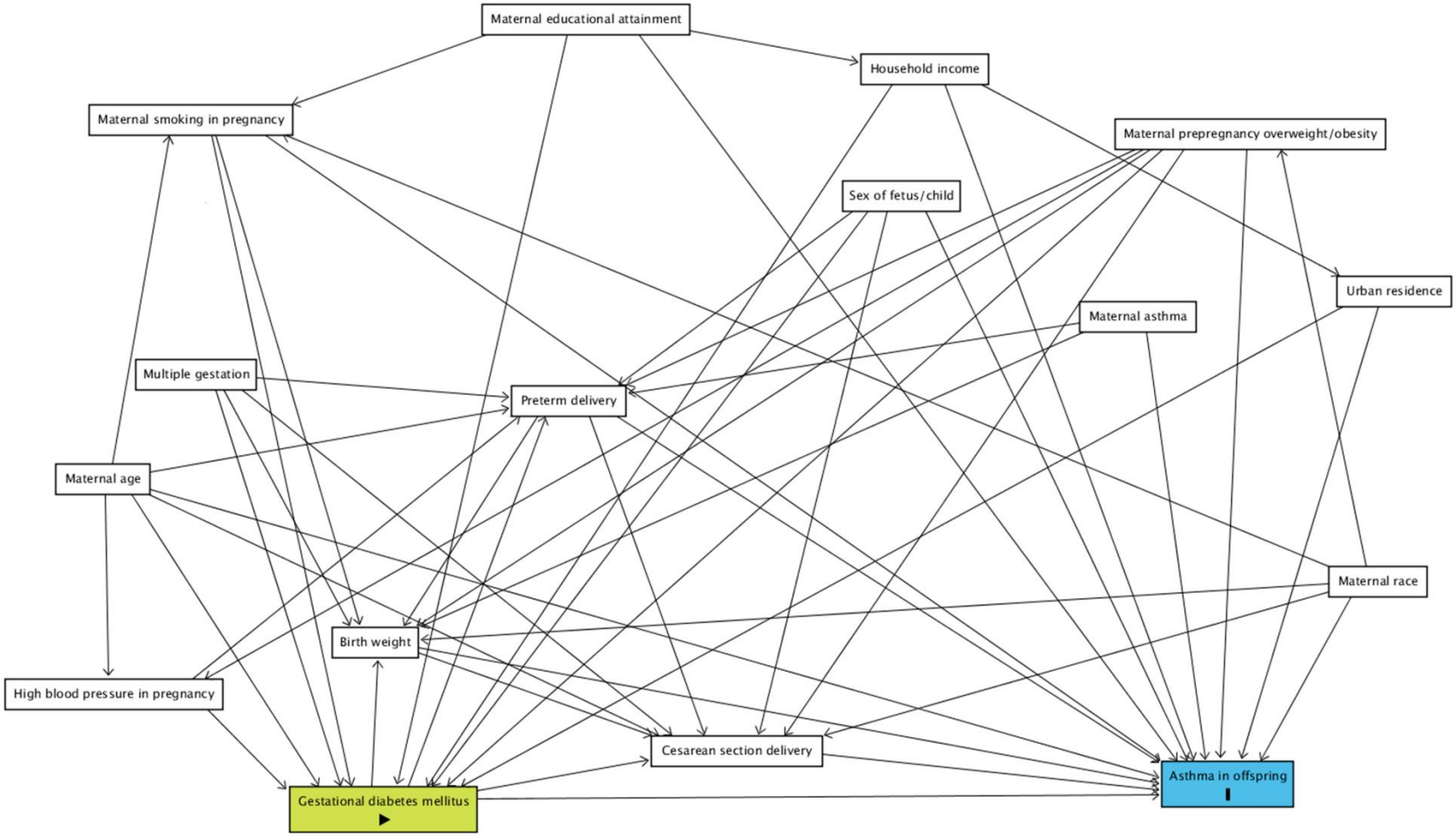

Figure 5. 1: Directed acyclic graph showing the paths between gestational diabetes mellitus and asthma in offspring

We fitted a pooled marginal structural logistic regression model with inverse probability weighting to estimate the controlled direct effect of GDM on the risk of asthma in offspring, not mediated by cesarean section delivery [29, 35]. Our model was a partial marginal structural model because it included covariates in addition to the exposure and mediator. For the inverse probability weighting, we calculated a weight for the mediator, cesarean section delivery for an observation at a time point. We fitted pooled logistic regression models to estimate the numerator and denominator inputs for the mediator weight. The numerator input was the probability of having the value of cesarean section delivery that a child actually had, conditional on having the exposure GDM the child actually had. The denominator input was the probabilities of having the value of the cesarean section delivery that a child actually had conditional on GDM (exposure), potential confounders of the GDM-asthma, GDM-cesarean section delivery and cesarean section delivery-asthma associations (i.e., sex of the child, maternal age at pregnancy, maternal asthma, maternal smoking in pregnancy, high blood pressure in pregnancy, multiple gestation, maternal race, maternal educational attainment, annual household income and urban residency), exposure-induced confounders of the mediator-outcome association (i.e., preterm delivery and birth weight), and NLSCY cohort membership, time, and time^2. The mean of the mediator weight was 1.00 (range= 2.46). To estimate the controlled direct effect of GDM on the risk of asthma in offspring, we fitted a weighted pooled logistic regression model with generalized estimating equations to estimate the parameters. The logit of incident asthma probability was regressed on GDM, cesarean section delivery, an interaction term between GDM and cesarean section delivery, the confounders of the GDM-asthma association (i.e., sex of the child, maternal age at pregnancy, maternal smoking during pregnancy, maternal high blood pressure during pregnancy, multiple gestation, maternal educational attainment, annual

household income, urban residency), NLSCY cohort membership, time and time^2 using the mediator weight.

Joint effect of GDM and maternal smoking during pregnancy on asthma in offspring

A multivariable pooled logistic regression model was fitted by regressing the logit of incident asthma probability on GDM, maternal smoking during pregnancy, an interaction term between GDM and maternal smoking during pregnancy, time, time^2 and NLSCY cohort membership, and the confounders sex of the child, maternal age at birth, maternal asthma, maternal educational attainment, maternal race, annual household income and urban residence. The interaction term between GDM and maternal smoking during pregnancy represented interaction on multiplicative scale. This is equivalent to: HR for exposure to both GDM and maternal smoking during pregnancy/[HR for exposure to GDM multiplied by HR for exposure to maternal smoking during pregnancy]. We also examined interaction on additive scale [36]. The additive interaction was assessed by estimating the relative excessive risk due to interaction (RERI) and synergy index [36-38]. The RERI is "the risk that is additional to the risk that is expected on the basis of the addition of the ORs under exposure, calculated as the difference between the expected risk and the observed risk" [37]. Synergy index is "the excess risk from exposure to both exposures when there is interaction relative to the risk from exposure without interaction" [37]. Synergy index was also calculated because RERI varies across strata defined by covariates and is not easy to interpret from models after including covariates to control for confounding. Synergy index does not vary across strata of covariates and is the measure of choice for additive interaction in multivariable models [37]. For calculation of RERI and synergy index, a new composite variable with four categories was computed: one category for joint exposure to both risk factors (+ +), a category for exposure to one of the risk factors only (+ - or - +), and a joint reference category

for no exposure (background risk or - -). A pooled logistic regression model was then fitted to estimate the HRs using the new indicator variable adjusting for the variables included in the pooled logistic regression model for multiplicative interaction. RERI was calculated using the following formula: RERI = $HR_{++} - HR_{+-} - HR_{-+} + 1$ and synergy index was calculated using the following formula: $[HR_{++} - 1] / [(HR_{+-} - 1) + (HR_{-+} - 1)]$. A RERI value of "0" and synergy index of "1" indicates no interaction effect. We also calculated the attributable proportion due to interaction (AP), which is "the proportion of disease or mortality that is due to interaction among persons with both exposures". AP was calculated using the following formula: AP = $RERI/HR_{++}$ and an AP value of '0' indicates no interaction [37]. The results of the interaction are reported according to the recommended guidelines [36].

Sensitivity analyses for unmeasured confounding for the total effect

To assess the effect of a possible unmeasured binary confounding factor maternal prepregnancy overweight/obesity on the estimates of the total effect of GDM on the risk of asthma in offspring, we performed a sensitivity analysis under a range of potential bias conditions [29]. The estimated prevalence of overweight and/or obesity in pregnant women in general varies between 10% and 60% globally [39, 40] and in women with GDM varies between 35% and 71% [41-43]. In the sensitivity analyses, we allowed the prevalence of maternal prepregnancy overweight/obesity to vary between 10% and 60% among mothers without GDM and between 35% and 75% among mothers with GDM, and the association between maternal prepregnancy overweight/obesity and asthma in offspring to vary between HR of 2.0 and 10.0. The following bias factor formula was used [29]: $B_{mult}(c) = \frac{1+(\gamma-1)P(U=1|a,c)}{1+(\gamma-1)P(U=1|a^*,c)}$ where γ is the effect of the unmeasured confounder U on the outcome Y conditional on the exposure (A=a if exposed and A=a^* if unexposed) and

measured confounders (C=c). Bias corrected HR was estimated by dividing the estimated HR with the calculated bias factor.

We also estimated the minimum strength of association on the hazard ratio scale that an unmeasured confounder would need to have with both the exposure GDM and the outcome incident asthma in offspring to fully explain away (i.e., nullify) the observed GDM-asthma in offspring association conditional on the measured confounders. This is known as the "E-value" and was calculated using the following formula [44, 45]: $HR + \text{sqrt}\{HR \times (HR - 1)\}$.

SAS software v 9.4 (SAS Institute Inc., Cary, North Carolina) was used in all analyses.

5.2. Results

Among the 19,933 children, a total of 1,178 children (5.9%) had mothers with GDM. A higher proportion of mothers with GDM smoked during pregnancy and had high blood pressure during pregnancy compared with mothers without GDM (Table 5.1). As expected, a higher proportion of children whose mothers had GDM had high birth weight, were delivered by cesarean section and were born preterm compared with children whose mothers did not have GDM. Maternal race was black in 227 (1%) children. The frequencies of maternal race according to the GDM status are not reportable because of small sample size (n<15) among mothers with GDM. The median follow-up was 4 years (IQR: 4). A total of 1,639 children in the cohort reported incident asthma during the follow-up, and 119 of them had mothers with GDM.

Table 5. 1: Characteristics of children and mothers, National Longitudinal Survey of Children and Youth, 1994/1995–2008/2009

Characteristic	Mothers did not have GDM*, frequency (%) N=18,755	Mothers had GDM*, frequency (%) N=1,178
Sex of the child, male	9,415(50)	591 (50)
Birth weight		
Normal (2500 to 3900 g)	15,193 (81)	899 (76)
Low birth weight (<2500 g)	922 (5)	76 (6)
High birth weight ((≥4000 g)	2,640 (14)	203 (17)
Maternal age at birth in years, mean (SD†)	29 (5.2)	30 (5.4)
Maternal asthma	1,160 (6)	84 (7)
Maternal smoking during pregnancy	3,390 (18)	260 (22)
Maternal high blood pressure in pregnancy	2,004 (11)	241 (20)
Multiple gestation	345 (2)	26 (2)
Cesarean section delivery	4,004 (21)	362 (31)
Preterm delivery (gestational age ≤258 days)	1,750 (9)	183 (16)
Maternal educational attainment		
Less than secondary school graduation	2,040 (11)	148 (13)
Secondary school graduation	3,081 (16)	222 (19)
Some post-secondary	4,042 (22)	277 (24)
College or university degree	9,592 (51)	531 (45)
Annual household income		
<$10,000	328 (2)	20 (2)
$10,000–$14,999	895 (5)	73 (6)
$15,000–$19,999	827 (4)	74 (6)
$20,000–$29,999	1,862 (10)	141 (12)
$30,000–$39,999	2,437 (13)	157 (13)
≥$40,000	12,406 (66)	713 (61)

Urban residence	14,887 (79)	925 (79)
NLSCY[‡] cohort membership		
Cycle 1	1,047 (6)	56 (5)
Cycle 2	2,707 (14)	200 (17)
Cycle 3	5,212 (28)	351 (30)
Cycle 4	1,761 (9)	109 (9)
Cycle 5	1,887 (10)	122 (10)
Cycle 6	3,029 (16)	160 (14)
Cycle 7	3,115 (17)	180 (15)

[*] GDM, gestational diabetes mellitus
[†] SD, standard deviation
[‡] NLSCY, National Longitudinal Survey of Children and Youth

In the unadjusted time-conditional model, the HR for the total effect of GDM was 1.27 (95% CI: 1.05, 1.54). After adjusting for the potential confounders, the association attenuated slightly (HR: 1.25, 95% CI: 1.03, 1.51), suggesting that there may not have been material confounding by the controlled-for characteristics in our study (Table 5.2). When estimating the controlled direct effect of GDM on incident asthma in offspring by adjusting for the cesarean section delivery, the HR was 1.17 (95% CI: 0.91, 1.49) (Table 5.3).

Table 5. 2: Total effect of gestational diabetes mellitus on asthma in the offspring, National Longitudinal Survey of Children and Youth, 1994/1995–2008/2009

Variables	HR (95% CI)*	P-value
Gestational diabetes mellitus	1.25 (1.03, 1.51)	0.03
Sex of the child, male	1.47 (1.33, 1.62)	<0.0001
Maternal age at birth in years	0.99 (0.98, 1.00)	0.18
Maternal smoking during pregnancy	1.08 (0.95, 1.23)	0.26
Maternal high blood pressure in pregnancy	1.19 (1.03, 1.38)	0.02
Multiple gestation	1.45 (1.04, 2.03)	0.03
Maternal educational attainment		
Less than secondary school graduation	1.03 (0.86, 1.23)	0.73
Secondary school graduation	1.01 (0.87, 1.17)	0.91
Some post-secondary	1.09 (0.96, 1.24)	0.17
College or university degree	Reference	
Annual household income		
<$10,000	1.62 (1.17, 2.23)	0.004
$10,000–$14,999	1.57 (1.26, 1.95)	<0.0001
$15,000–$19,999	1.35 (1.07, 1.70)	0.01
$20,000–$29,999	1.23 (1.04, 1.45)	0.01
$30,000–$39,999	1.14 (0.98, 1.33)	0.09
≥$40,000	Reference	
Urban residence	1.14 (1.01, 1.30)	0.04
Time since enrollment	1.64 (1.53, 1.76)	<0.0001
Time since enrollement^2	0.97 (0.96, 0.97)	<0.0001
NLSCY† cohort membership	1.09 (1.06, 1.13)	<0.0001

*Adjusted for maternal age at birth of the child, maternal smoking during pregnancy, maternal educational attainment, sex of the child, annual household income, urban residency, time since enrollment, time since enrollment^2 and NLSCY cohort membership

† National Longitudinal Survey of Children and Youth

Table 5. 3: Controlled direct effect of gestational diabetes mellitus on asthma in the offspring, National Longitudinal Survey of Children and Youth, 1994/1995–2008/2009

Variables	HR (95% CI)*	P-value
Gestational diabetes mellitus	1.17 (0.91, 1.49)	0.22
Cesarean section delivery	1.17 (1.03, 1.33)	0.02
Gestational diabetes mellitus*Cesarean section delivery interaction	1.17 (0.77, 1.77)	0.46
Sex of the child, male	1.44 (1.30, 1.60)	<0.0001
Maternal age at birth in years	0.99 (0.98, 1.00)	0.10
Maternal smoking during pregnancy	1.08 (0.95, 1.23)	0.25
Maternal high blood pressure in pregnancy	1.20 (1.03, 1.40)	0.02
Multiple gestation	1.48 (1.01, 2.18)	0.04
Maternal educational attainment		
Less than secondary school graduation	1.03 (0.86, 1.23)	0.75
Secondary school graduation	1.01 (0.87, 1.18)	0.86
Some post-secondary	1.08 (0.95, 1.23)	0.23
College or university degree	Reference	
Annual household income		
<$10,000	1.63 (1.18, 2.25)	0.003
$10,000–$14,999	1.64 (1.31, 2.04)	<0.0001
$15,000–$19,999	1.29 (1.02, 1.64)	0.03
$20,000–$29,999	1.24 (1.05, 1.47)	0.01
$30,000–$39,999	1.13 (0.97, 1.33)	0.11
≥$40,000	Reference	
Urban residence	1.14 (1.00, 1.29)	0.05
Time since enrollment	1.67 (1.54, 1.81)	<0.0001
Time since enrollement^2	0.96 (0.96, 0.97)	<0.0001
NLSCY† cohort membership	1.09 (1.05, 1.12)	<0.0001

* The controlled direct effect of gestational diabetes mellitus (GDM) not mediated by cesarean section delivery using marginal structural model with inverse probability weights. The model included GDM, cesarean section delivery, an interaction term between GDM and cesarean

section delivery, confounders of GDM-asthma relationship (i.e., sex of the child, maternal age at pregnancy, maternal smoking during pregnancy, maternal high blood pressure during pregnancy, multiple gestation, maternal educational attainment, annual household income, urban residency), NLSCY cohort membership, time since enrollment and time since enrollment^2 and applying the mediator weight

† National Longitudinal Survey of Children and Youth

The measure of interaction between GDM and maternal smoking during pregnancy on the multiplicative scale, the ratio of the HR for both exposure and the product of the HRs for the two exposures individually), was 1.23 (95% CI: 0.79, 1.90; $P = 0.35$), meaning that the estimated joint effect on the HR scale of GDM and maternal smoking during pregnancy was greater than the product of the estimated effects of GDM alone and maternal smoking during pregnancy alone so suggesting a positive multiplicative-scale interaction. The estimated RERI was 0.30 (95% CI: −0.32, 0.93), meaning that on the additive scale, the estimated joint effect of GDM and maternal smoking during pregnancy was greater than the sum of the estimated effects of GDM alone and maternal smoking during pregnancy alone, suggesting a positive additive-scale interaction (Table 5.4). The synergy index was 2.15, meaning that there was excess risk from exposure to both GDM and maternal smoking during pregnancy when there is interaction relative to the risk from exposure without interaction suggesting a positive interaction on the additive scale. The attributable proportion due to interaction was 0.19 meaning that 19% of asthma in offspring is due to interaction among children with both GDM and maternal smoking in pregnancy.

Table 5. 4: Interaction between maternal gestational diabetes mellitus and maternal smoking during pregnancy on the risk of asthma in the offspring

	Maternal smoking during pregnancy				HR (95% CI) for maternal smoking during pregnancy within strata of GDM
	Mother did not smoke		Mother smoked		
	N asthma/no asthma	HR (95% CI)	N asthma/no asthma	HR (95% CI)	
Mother did not have GDM	1211/33509	1.0	309/7452	1.06 (0.92, 1.21); *P* = 0.42	1.07 (0.93, 1.22); *P* = 0.35
Mother had GDM	86/1974	1.20 (0.96, 1.51); *P* = 0.11	33/530	1.56 (1.09, 2.25); *P* = 0.02	1.24 (0.80, 1.95); *P* = 0.34
HRs (95% CI) for GDM within strata of maternal smoking during pregnancy		1.21 (0.97, 1.52); *P* = 0.09		1.44 (0.99, 2.10); *P* = 0.06	

Measure of interaction on additive scale: RERI (95% CI) = 0.30 (−0.32, 0.93)

Measure of interaction on multiplicative scale: ratio of HRs (95% CI) = 1.23 (0.79, 1.90)

HRs are adjusted for sex of the fetus/child, maternal age at birth of the child, maternal educational attainment, maternal asthma, maternal race, annual household income, and urban residence, time since enrollment, time since enrollment^2 and NLSCY cohort membership

Sensitivity analyses across the range of potential bias conditions demonstrated that in scenarios where the prevalence of prepregnancy overweight/obesity was higher in mothers with GDM than in mothers without GDM, the HR for the association between GDM and incident asthma in offspring decreased with increasing prevalence of prepregnancy overweight/obesity in mothers with GDM and with increasing effect size of prepregnancy overweight/obesity on asthma in the offspring. Thus, the bias-corrected HR estimates suggest that the HR for incident asthma would be overestimated in these scenarios. However, the HR for the association between GDM and incident asthma in offspring would be underestimated in scenarios where the prevalence of prepregnancy overweight/obesity among mothers without GDM is higher than the prevalence among mothers with GDM (Table 5.5). The E-value for the estimated total effect of GDM suggests that the observed HR of 1.25 could be explained away by an unmeasured confounder that was associated with both GDM and asthma in offspring by an HR of 1.81-fold each, above and beyond the measured confounders (and other potential sources of error), but a weaker confounding could not do so. The E-value for the lower 95% limit of the total effect was 1.21.

Table 5. 5: Bias-corrected hazard ratios for quantifying the total effect of GDM on asthma, considering unmeasured confounder maternal prepregnancy overweight/obesity with a range of determinants of bias

Prevalence of unmeasured confounder maternal prepregnancy overweight/obesity		Bias-Corrected Hazard Ratio				
No GDM (%)	GDM (%)	The effect size of the unmeasured maternal prepregnancy overweight/obesity in Hazard Ratio				
		2.0	4.0	6.0	8.0	10.0
10	35	1.02	0.79	0.68	0.62	0.57
10	40	0.98	0.74	0.63	0.56	0.52
10	45	0.95	0.69	0.58	0.51	0.47
10	50	0.92	0.65	0.54	0.47	0.43
10	55	0.89	0.61	0.50	0.44	0.40
10	60	0.86	0.58	0.47	0.41	0.37
10	65	0.83	0.55	0.44	0.38	0.35
10	70	0.81	0.52	0.42	0.36	0.33
10	75	0.79	0.50	0.39	0.34	0.31
20	35	1.11	0.98	0.91	0.87	0.84
20	40	1.07	0.91	0.83	0.79	0.76
20	45	1.03	0.85	0.77	0.72	0.69
20	50	1.00	0.80	0.71	0.67	0.64
20	55	0.97	0.75	0.67	0.62	0.59
20	60	0.94	0.71	0.63	0.58	0.55
20	65	0.91	0.68	0.59	0.54	0.51
20	70	0.88	0.65	0.56	0.51	0.48
20	75	0.86	0.62	0.53	0.48	0.45
30	35	1.20	1.16	1.14	1.12	1.11
30	40	1.16	1.08	1.04	1.02	1.01
30	45	1.12	1.01	0.96	0.93	0.92
30	50	1.08	0.95	0.89	0.86	0.84
30	55	1.05	0.90	0.83	0.80	0.78
30	60	1.02	0.85	0.78	0.75	0.72
30	65	0.98	0.81	0.74	0.70	0.68
30	70	0.96	0.77	0.69	0.66	0.63
30	75	0.93	0.73	0.66	0.62	0.60
40	35	1.30	1.34	1.36	1.38	1.39
40	40	1.25	1.25	1.25	1.25	1.25
40	45	1.21	1.17	1.15	1.14	1.14
40	50	1.17	1.10	1.07	1.06	1.05
40	55	1.13	1.04	1.00	0.98	0.97
40	60	1.09	0.98	0.94	0.91	0.90

40	65	1.06	0.93	0.88	0.86	0.84
40	70	1.03	0.89	0.83	0.81	0.79
40	75	1.00	0.85	0.79	0.76	0.74
50	35	1.39	1.52	1.59	1.63	1.66
50	40	1.34	1.42	1.46	1.48	1.49
50	45	1.29	1.33	1.35	1.36	1.36
50	50	1.25	1.25	1.25	1.25	1.25
50	55	1.21	1.18	1.17	1.16	1.16
50	60	1.17	1.12	1.09	1.08	1.07
50	65	1.14	1.06	1.03	1.01	1.00
50	70	1.10	1.01	0.97	0.95	0.94
50	75	1.07	0.96	0.92	0.90	0.89
60	35	1.48	1.71	1.82	1.88	1.93
60	40	1.43	1.59	1.67	1.71	1.74
60	45	1.38	1.49	1.54	1.57	1.58
60	50	1.33	1.40	1.43	1.44	1.45
60	55	1.29	1.32	1.33	1.34	1.34
60	60	1.25	1.25	1.25	1.25	1.25
60	65	1.21	1.19	1.18	1.17	1.17
60	70	1.18	1.13	1.11	1.10	1.10
60	75	1.14	1.08	1.05	1.04	1.03

5.3. Discussion

In this study, we estimated the total effect of maternal GDM on the risk of asthma in the offspring using data from a large Canadian population-based longitudinal study. We also examined the controlled direct effect of GDM not mediated by cesarean section delivery and the joint effect of GDM and maternal smoking during pregnancy on the risk of asthma in the offspring. Our findings suggest that maternal GDM increases the risk of asthma in the offspring. Similar to our findings, maternal diabetes was associated with around 20% higher odds of asthma in children followed from 2 years of age in two studies using proxy measures for asthma (i.e. hospitalization for asthma and asthma medication) [19, 20]. Another study reported a higher association between maternal diabetes and asthma (OR 1.95, 95% CI: 0.98, 3.86) in children at 7-8 years of age [21]. That study, however, did not adjust for important confounders such as sex, gestational age and birth weight of the child as well as maternal age and socioeconomic status, which may have resulted in the stronger association compared with our study. In yet another study, the HR for the association between maternal GDM and asthma was 1.09 ($p<0.0001$) among children followed from 5 years of age; and when compared with children having mothers without GDM, the HR for the association was 1.15 ($p<0.0001$) for children whose mothers required antidiabetic medication for GDM during pregnancy and the HR for the association was 1.06 ($p=0.01$) for children whose mothers did not use medication for GDM during pregnancy [18]. But unfortunately, that study has not been published in a journal yet and cannot be judged based on limited information provided in the abstract. One study reported a decreased rate of asthma-associated hospitalization in children having mothers with diet-treated GDM (HR 0.93, 95% CI: 0.82, 1.06) and pharmacologically-treated GDM (HR 0.94, 95% CI: 0.61, 1.42) compared with children having mothers without GDM [23]. Nonetheless, the HR ranging from a

39% reduction to a 42% increase, a substantial positive association for pharmacologically-treated GDM was also compatible with their data reflected by the 95% confidence interval.

If indeed GDM is a risk factor for asthma, approaches to prevent GDM might help in prevention of asthma in the offspring. Different lifestyle modification strategies, dietary supplementation, and pharmacological and non-pharmacological approaches have been evaluated as potential GDM prevention strategies. Among these interventions, healthy eating alone, healthy eating with physical activity, myoinositol (a vitamin B complex) supplementation and probiotic treatment have shown some promising results in high-risk women in reducing GDM but require replication [46, 47]. Identification of effective measures to prevent GDM, particularly in women at risk of developing GDM would be the first step in this regard followed by evaluating effectiveness in preventing outcomes in offspring, including asthma.

When considering the controlled direct effect of GDM on the risk of asthma not mediated by cesarean section delivery, GDM appeared to increase the risk of asthma in the offspring. The point estimate suggests that in this hypothetical scenario where cesarean section delivery was not practiced (i.e., none of the children delivered by cesarean section), GDM would still have retained much of its effect on the risk of asthma in the offspring on the population level. However, the effect estimate was imprecise considering the width of the 95% confidence intervals. This could further suggest that there are other intermediaries in the pathway between GDM and asthma in the offspring or the effect of GDM on asthma in the offspring varies according to the duration, severity and control of hyperglycemia or both. Future studies should examine the direct effect of GDM according to GDM severity or treatment status and aim to identify other intervenable mediators to effectively reduce the risk of developing asthma in

children whose mothers had GDM, considering the absence of confirmed effective GDM prevention strategies.

The estimated joint effect of GDM and maternal smoking during pregnancy on asthma in offspring supports some positive interaction between GDM and maternal smoking during pregnancy on both multiplicative and additive scales. However, the evidence is weak as reflected by the 95% confidence intervals that were also compatible with negative interaction. Hence, further studies are warranted to generate additional evidence in this regard.

This study has some strengths. First, the use of data from a national population-based large longitudinal study enabled us to follow children up to 16 years of age. Second, we were able to adjust for relevant potential confounders except for maternal prepregnancy overweight or obesity. Third, we had longitudinal data and we used longitudinal data analysis, particularly pooled logistic regression to emulate a Cox proportional hazards model to estimate the effect of GDM on the risk of asthma in the offspring. Fourth, we sought further explanation beyond the total effect of GDM by examining the controlled direct effect accounting for the mediating role of cesarean section delivery. Last, we also examined the joint effect of GDM and maternal smoking during pregnancy on the risk of asthma in the offspring that has not been assessed before. We assessed interaction on both multiplicative and additive scales.

The results of this study need to be interpreted in light of some limitations. First, information on asthma was based on reported physician-diagnosed asthma and therefore, subject to misclassification of asthma status. Parent-reported physician-diagnosed asthma had 59% to 89% sensitivity and 81% to 96% specificity when validated against medical records, health claims diagnosis or pediatric allergist diagnosis of asthma in previous studies [21, 48-50].

Because NLSCY was not an asthma-focused study, misclassifications are expected to be non-differential with regard to maternal GDM status. As a result, the non-differential misclassification of asthma will bias associations toward the null. Second, we were unable to differentiate between pregestational and gestational diabetes mellitus of mothers reporting diabetes during pregnancy with the child, as mothers were not asked if they had diabetes before pregnancy. However, most of the diabetes mellitus during pregnancy are likely to be GDM [51]. Third, there may have been inaccuracies in reporting of pregnancy- and birth-related information, including the exposure, GDM. Nevertheless, studies have suggested high reproducibility and accuracy of maternal recall of pregnancy and birth-related events occurring even ≥30 years ago [52, 53]. As a result, we believe that misclassification of exposure and pregnancy- and birth-related confounders was relatively minor and consequently was not a major source of bias. Fourth, there may also have been errors in reporting of the socio-demographic confounders resulting in residual confounding. Moreover, we did not have information on a potential confounder maternal prepregnancy overweight/obesity, which has not been considered in previous studies. We conducted sensitivity analysis across a range of scenarios of unmeasured confounding by maternal prepregnancy overweight/obesity to estimate bias corrected total effect, which suggested that in plausible scenarios, the association is likely overestimated. We also estimated the E-value, the minimum strength of association required by an unmeasured confounder with both GDM and asthma in offspring to explain away the observed estimated total effect of GDM on the risk of asthma. While the sensitivity analyses for unmeasured confounder maternal prepregnancy overweight/obesity or any confounder suggest overestimation of the effect measure or the potential for explaining away the observed effect, non-differential misclassification of the outcome could bias the estimate towards the null. As such, the net effect

of unmeasured confounders and nondifferential misclassification of exposure remains unknown. Future studies should collect data on maternal prepregnancy anthropometric and metabolic status and consider it as a potential confounder when examining the association between GDM and asthma in offspring. This, together with accurate diagnosis of asthma in children, would help estimate relative unbiased effect of GDM on asthma in the offspring. Last, despite a relatively large sample size, our estimates of additive and multiplicative interaction were imprecise, likely because of low prevalence of GDM and low incidence of asthma in our study.

In conclusion, the findings from our study suggest, albeit weakly, that GDM increases the risk of asthma in the offspring overall and directly beyond the mediating role of cesarean section delivery, and there may be an interaction between GDM and maternal smoking in pregnancy. Joint interventions on preventing GDM and smoking in pregnancy or identification of intervenable intermediaries (other than cesarean section delivery) in the pathway between GDM and asthma in the offspring could provide opportunities for prevention of asthma.

5.4. Supplementary Table

S Table 5. 1: Different cohorts of children in the study population and their participation in survey cycles of the National Longitudinal Survey of Children and Youth, 1994/1995–2008/2009

Cohort	Enrollment survey cycle(year)	Age at enrollment (years)	Surveyed cycles							
			Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8
1994/1995 Original cohort	Cycle 1 (1994/1995)	0–1	√	√	√	√	√	√	√	√
ECD* 1996	Cycle 2 (1996/1997)	0–1		√	√	√				
ECD* 1998	Cycle 3 (1998/1999)	0–1			√	√	√		√	
ECD* 2000	Cycle 4 (2000/2001)	0–2				√	√	√	√	
ECD* 2002	Cycle 5 (2002/2003)	0–2					√	√	√	√
ECD* 2004	Cycle 6 (2004/2005)	0–6						√	√	√
ECD* 2006	Cycle 7 (2006/2007	0–5							√	√

* ECD, early childhood development

5.5. References

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6. Chapter 6: Integrated Discussion

6.1. Introduction

The overall goal of this research was to further our understanding on three aspects of asthma epidemiology: trends in asthma burden in adults, course of asthma in children with asthma and the role of prenatal factor maternal gestational diabetes mellitus in the risk of asthma in the offspring. The overarching theme across these topics ultimately relates to the control of asthma morbidity and mortality.

This chapter summarizes the findings with regard to existing literature and discusses their potential implications, strengths and limitations of this research, and provides suggestions for future research.

6.2. Summary of Key Findings vis-à-vis Previous Findings

6.2.1. Objective One

This study examined the age, period and cohort effects on the prevalence of asthma, including active asthma (defined as diagnosed asthma, and asthma symptoms and/or intake of asthma medication), among Canadian adults for 16 years from 1994 through 2011 using age, period and cohort effect theoretical and analytic framework.

Among Canadian adults, the prevalence of asthma had a curvilinear relationship with age (age effect): it was highest during early adulthood (12% in 20-year-olds), was half of the prevalence in young adults in adults aged 50–60 years (6%) and in between the prevalence in young and late adulthood in 80-year-olds (8%). The prevalence of active asthma was highest during early adulthood (8% in 20-year-olds), lower in adults aged 50–60 years (5%) and slightly higher in old age (6% in 80-year-olds). Our empirical finding of age effect on asthma prevalence

is in line with the non-model-based estimates that did not use formal age, period, cohort framework demonstrating age effect on asthma prevalence, including active asthma prevalence among Canadians during 1996–2015 using administrative data [1-3].

The prevalence of asthma and active asthma increased over time during our study period (period effect): asthma prevalence increased from 5% in 1994/1995 to 11% in 2010/2011 and active asthma prevalence increased from 4.5% in 1994/1995 to 8% in 2010/2011 independent of age and sociodemographic and lifestyle factors. An increasing temporal trend of age-standardized asthma prevalence was also observed in prior studies applying non-model-based and non-age-period-cohort analytic approaches in Canada during 1996–2012 [1, 3]. Contrary to our finding, the prevalence of age-standardized active asthma prevalence was reported to decrease slightly in Canadians from 2.8% in 2000/2001 to 2.3% in 2011/2012 in the CCDSS (1). The active asthma definition in the CCDSS comprised of at least one physician claim in the first diagnostic field or at least one hospitalization for asthma in any diagnostic field in a given fiscal year. As a result, the decline in active asthma prevalence observed in the CCDSS may be indicative of improved asthma management and control that required less health care utilization. Our definition of active asthma (having asthma symptoms or taking asthma medication) was able to capture milder cases, cases that were under control by taking medication not necessitating medical care or cases that did not seek medical care. This may have led to the finding of increasing prevalence of active asthma in our study.

In our study, the period effect on asthma prevalence was different among individuals of different age between 1994/1995 and 2002/2003, and between 2002/2003 and 2010/2011 (cohort effect): the steepest increase in prevalence was in individuals aged 20 years and least increase was in individuals aged 80 years. An increase in prevalence of asthma over time varying by age

from 2000/2001 to 2011/2012 was reported in the CCDSS [1]. For active asthma prevalence in our study, the steepest increase was in individuals aged 20 years and was least steep in individuals aged 80 years.

6.2.2. Objective Two

This study examined the overall trajectory and groups of trajectories of asthma exacerbation in children with incident asthma and identified the predictors of trajectory groups.

The median age of asthma diagnosis was six years. The overall trajectory of asthma attack probability decreased from 0.63 at asthma diagnosis to 0.11 at 12 years after asthma diagnosis, and asthma attack probability at diagnosis and asthma attack probabilities across time since asthma diagnosis varied across children.

Three distinct trajectories were identified in children with incident asthma regardless of age at asthma diagnosis: *low increasing* (21.3% of children), *medium decreasing* (45.8% of children) and *high decreasing* (32.8% of children). The asthma attack probability estimates in the *low increasing* group increased gradually from the initial low level after diagnosis and remained higher than the asthma attack probability estimates in the *medium decreasing* group from around seven years after asthma diagnosis. The asthma attack probability estimates in the *medium decreasing* group decreased from moderate level after diagnosis to almost zero probability at the end of follow-up. The asthma attack probability estimates in the *high decreasing* group decreased after diagnosis but remained higher than other two groups at 12 years after diagnosis. Overall, children belonging to the *medium decreasing* trajectory group had better long-term prognosis than children belonging to the other two trajectory groups. Among children in the *low increasing* trajectory group, more than half of the children (54.8%) had asthma diagnosed after

six years of age, while more than half of the children in the *medium decreasing* (58.9%) and *high decreasing* (61.1%) trajectory groups had asthma diagnosed before six years of age. Some studies have examined the trajectories of wheezing, cough, atopy or asthma prevalence in children followed from birth. However, the stark differences between these studies and our study in terms of study population (all children regardless of asthma status vs. children with diagnosed asthma), outcome (trajectories of wheezing, cough, atopy or asthma prevalence vs. trajectories of asthma exacerbation), onset of follow-up (birth vs. asthma diagnosis) and time axis for outcome pattern (age of child vs. time since asthma diagnosis) precluded us from making any meaningful comparison.

With regard to the determinants, two predictors were independently associated with trajectory group membership in our study: number of siblings at home and age at asthma diagnosis. In our study, children having more siblings at home were more likely to belong to the *medium decreasing* and *high decreasing* trajectory groups than the *low increasing* trajectory group; children older at asthma diagnosis were less likely to belong to the *medium decreasing* and *high decreasing* trajectory groups than the *low increasing* trajectory group. Asthma exacerbation patterns in the *medium decreasing* and *high decreasing* trajectory groups reflect more frequent asthma attacks in these two trajectory groups compared with the *low increasing* trajectory group. Our study is novel in examining the course of asthma in terms of trajectory groups. Thus, there are no previous studies using the outcome 'trajectory group'. Still, studies on severe asthma or asthma exacerbation somehow relate to our findings on the predictors. Studies examining the relationship between sibship and severe asthma in children reported a positive association between larger sibship and severe asthma symptom [4]. Younger age is a known risk factor for asthma attack [5] and a predictor of severe asthma exacerbation in children [6].

6.2.3. Objective Three

This study examined the association between maternal GDM and the risk of asthma in the offspring and the joint effect of maternal GDM and maternal smoking during pregnancy on the risk of asthma in the offspring.

Among 19,933 children, the prevalence of maternal GDM was 5.9% and a total of 1,639 children reported incident asthma during the follow-up. Maternal GDM was positively associated with incident asthma in the offspring (HR 1.25, 95% CI: 1.03, 1.51). This is comparable to the findings from most of the previous studies [7-10]. However, there are also other studies that suggested a decreased risk of asthma-associated hospitalization in children having mothers with diet-treated GDM and pharmacologically-treated GDM compared to children having mothers without GDM, although a 42% increase in the risk for pharmacologically-treated GDM was also compatible with their data [11].

After accounting for the mediating role of cesarean section delivery and adjusting for the confounders, the HR for the association between GDM and incident asthma in the offspring was 1.17 (95% CI: 0.91, 1.49). Thus, the evidence supporting the controlled direct effect of GDM on the risk of asthma in the offspring is weak. We were unable to identify any literature examining the controlled direct effect of GDM not mediated by cesarean section delivery.

There was some evidence of positive interaction on the multiplicative scale (HR 1.23, 95% CI: 0.79, 1.90; $P = 0.35$) because the joint effect of GDM and maternal smoking during pregnancy on the HR scale was greater than the product of the estimated effects of GDM alone and maternal smoking during pregnancy alone. On the additive-scale, the estimated joint effect of GDM and maternal smoking during pregnancy was greater than the sum of the estimated

effects of GDM alone and maternal smoking during pregnancy alone on the basis of risk differences suggesting a positive additive-scale interaction (RERI 0.30, 95% CI: −0.32, 0.93). However, the evidence of interaction in our study is weak because our data is also compatible with negative interaction as reflected from the lower limits of the 95% confidence intervals. Previous studies have not examined the joint effect of maternal GDM and maternal smoking during pregnancy on the risk of asthma in the offspring.

6.3. Potential Implications

6.3.1. Theoretical Implications

The first implication of the findings from this study primarily relates to enhancing theoretical understanding by addressing the gaps in knowledge with respect to three particular aspects of asthma. This study provides further understanding of the overall trends in asthma prevalence, the age groups with higher prevalence and the rates of prevalence increase in Canadian population employing the age, period and cohort effect theoretical and analytic framework for the first time. The differential asthma prevalence across adult life in our study indicates the groups with higher asthma burden in Canadian population. Even the relatively lower prevalence of asthma in older adults compared to younger adults reflected from the age effect would translate into substantial burden in the aging population.

The three distinct trajectories of asthma exacerbation in children at the time of asthma diagnosis and the two predictors of the trajectory group membership identified in this study is a first step in looking at asthma course in children in terms of longitudinal pattern of exacerbation from a group-based trajectory perspective beyond individual trajectory. These findings will add to the existing knowledge base on asthma course and pave the way to future studies on asthma course employing trajectory group perspective.

Our finding of the association between maternal GDM and the increased risk of asthma in the offspring increases understanding the etiology of asthma and mechanisms of the effect. This also adds to the growing body of evidence for GDM as a possible risk factor for asthma. The evidence of a joint effect of maternal GDM and maternal smoking during pregnancy also adds knowledge in this regard.

6.3.2. Future Research and Public Health Implications

The findings from this research have implications related to future research agenda and public health perspective. Different contemporary analytic methods employed in this research will encourage researchers to use these methods in future research.

Future studies need to examine if the increasing prevalence of asthma, including active asthma in adults over the study period observed in this study continues into the foreseeable future. This will help to compare trends at different time periods examined in different studies and in understanding the long-term trends in asthma burden in Canadian population. The trends over the recent past observed in our study will also help policy makers to some extent gauge health care needs and resource allocation for the population. There are likely underlying driving factors other than the sociodemographic and lifestyle factors accounted for in our study for the observed temporal trend of asthma prevalence. Considering the considerable improvement in air quality and decreased prevalence of smoking over the last few decades, future studies could explore other environmental factors alone or together with epigenetic changes to shed light into the underlying causes.

Future studies should replicate our study on asthma exacerbation trajectory and their predictors and seek to identify additional predictors to differentiate different trajectories. The

ultimate goal of future research would be to develop a risk assessment tool including all predictors to help physicians better prognosticate the long-term course of asthma in children and supplement the current paradigm of asthma management based on symptom control. Such approach to aid asthma management through prognostication of asthma course would help in secondary prevention of asthma in children.

The findings from the third study in this dissertation have implications related to the primary prevention of asthma in children. None of the different dietary, pharmacological, immunotherapy, allergen or surgical interventions tested alone or in combination for prevention of asthma has provided adequate evidence to move forward with implementation in clinical or public health practices. As such, primary prevention of asthma in children remains elusive and alternative or novel approaches are being sought. Our finding of the association between maternal GDM and the increased risk of asthma in the offspring places GDM as a potential unique out of the box candidate for asthma prevention and opens avenues to facilitate the development, evaluation and improvement of novel preventive measures to reduce asthma occurrence in children.

6.4. Strengths and Limitations

6.4.1. Strengths of Research

This doctoral research addressed three domains of asthma, a chronic disease with substantial public health burden, and has several notable strengths. First, the use of two national longitudinal surveys allowed us to expand the knowledge base on three epidemiological aspects of asthma, including distribution, course and determinants of occurrence. The NLSCY and NPHS provide a unique source of sociodemographic and health related data collected from individuals across Canada followed for more than a decade. Population-based nature of these two longitudinal

surveys enabled us to include more asthma cases as asthma cases not seeking medical care or medical care delivered by physicians outside fee-for-service were captured by these surveys. We were also able to take into account different socioeconomic and lifestyle factors necessary to address our objectives.

Second, to our knowledge, this is the first study to examine the age, period and cohort effects on asthma prevalence in Canadians using age, period and cohort theoretical and analytic framework, including epidemiological conceptualization of the cohort effect. The use of data from the NPHS, a population-based longitudinal survey gave us the opportunity to assess the effects of age, period and cohort over a period of 16 years. Model-based standardization allowed us to visualize population-wide effect of age and period, and the difference in period effect across different ages on asthma prevalence using population standardized prevalence.

Third, there is a dearth of literature on the course of asthma in children in terms of exacerbation following asthma diagnosis. To the best of our knowledge, this is the first study to identify trajectories of exacerbation in children following incident asthma diagnosis considering the dynamic nature of asthma course. The trajectories of asthma manifestation and their determinants in individuals with diagnosed asthma will add knowledge to this understudied area. Use of population-based data from the NLSCY enabled us to follow children for up to 12 years after asthma diagnosis. We considered factors readily available to the physicians, specifically in primary care setting as predictors of the trajectory groups bearing in mind the practicality of our findings.

Fourth, our study contributes to the evidence on and help fill in the knowledge gap on the effect of maternal GDM on the risk of asthma in the offspring. We also looked at the direct effect

of GDM on the risk of asthma after accounting for the mediating effect of cesarean section delivery and considering the intricate relationships among the exposure, mediator, outcome and confounders. We also examined the joint effect of maternal GDM and maternal smoking during pregnancy on the risk of asthma in the offspring that could suggest additional avenues for prevention of asthma in children.

Last, this research employed state-of-the-art analytic methods to address the knowledge gaps. Model-based standardization was conducted to better depict the effects of age, period and cohort on asthma prevalence. Hierarchical logistic regression was performed to examine the overall asthma course and latent class growth modeling was performed to identify group-based asthma course in children. Pooled logistic regression to emulate Cox proportional hazards model and marginal structural models with inverse probability weight were performed to examine the total effect of maternal GDM and the controlled direct effect of maternal GDM after accounting for the mediating role of cesarean section on the risk of asthma in the offspring, respectively. We used directed acyclic graph to inform and guide us in selecting pertinent confounders and the analytic approach to estimate the controlled direct effect. We have examined both multiplicative and additive interactions to assess the joint effect of maternal GDM and smoking during pregnancy on the risk of asthma in the offspring.

6.4.2. Limitations of Research

Misclassification

Information on health professional-diagnosed asthma, asthma symptoms/attack and medication were based on self- or parent-report and may have resulted in misclassification of asthma status.

In the study addressing objective one, respondents with milder symptoms or longer symptom-free periods may have underreported asthma status compared with the respondents with frequent or severe symptoms resulting in an underestimation of the prevalence of asthma or active asthma in adults. However, a study reviewing literature on asthma assessed by questionnaires in adults found on average 68% estimated sensitivity (range 48–100%) and 94% estimated specificity (range 78–100%) of reported physician-diagnosed asthma when validated against clinical diagnosis of asthma in adults [12].

There is a potential for misclassification of asthma status in the study addressing objective two. Parent-reported physician-diagnosed asthma had 59% to 89% estimated sensitivity and 81% to 96% estimated specificity when validated against medical records, health claims diagnosis or pediatric allergist diagnosis of asthma [10, 13-15]. Furthermore, the recall period for asthma attack in children was 12 months prior to the interview and could have led to misreporting of asthma attack because parents of children with mid attacks may forget to report asthma attack.

There is also the potential for misclassification of asthma status in our study addressing objective three. As the NLSCY was not an asthma-focused study, misclassifications are expected to be non-differential with regard to maternal GDM. As a result, the non-differential misclassification of asthma will bias associations toward the null. There may have also been errors in the reporting of pregnancy and birthrelated information, including the exposure, GDM. However, maternal recall of pregnancy-related events occurring even ≥30 years ago is known to have high reproducibility and accuracy [16, 17]. As a result, we believe that misclassification of exposure and pregnancy- and birth-related confounders was relatively minor and consequently was not a major source of bias. We were not able to differentiate between pregestational and

gestational diabetes mellitus of mothers reporting diabetes during pregnancy. Nevertheless, most of the diabetes mellitus during pregnancy are likely to be GDM [18].

Residual and unmeasured confounding

In the study addressing objective three, there may have been errors in reporting of socio-demographic confounders leading to misclassification and resulting in residual confounding. However, we believe that the misclassification would be nondifferential across the exposure groups as the NLSCY was not an asthma-focused study and information on GDM was collected along with other pregnancy- and birth-related information from all young children. We could not adjust for the unmeasured confounder maternal prepregnancy overweight/obesity. However, we conducted sensitivity analyses to estimate bias corrected association between GDM and asthma in the offspring across a range of scenarios of the unmeasured confounder.

Sample size and precision of estimates

In the study addressing objective two, our sample size for the identification of asthma exacerbation trajectories in children was relatively small because we applied certain exclusion criteria to best address our study objective and to apply the statistical tool. The small sample size led to considerable uncertainty in estimated trajectory patterns and may also have precluded us from identifying predictors that distinguished between *high decreasing* and *medium decreasing* trajectory groups. Thus, replication of our results in future studies is warranted.

In the study addressing objective three, despite having a relatively large sample size, our results on the joint effect of maternal GDM and smoking during pregnancy on the risk of asthma in the offspring were imprecise for additive and multiplicative interactions likely because of the low prevalence of exposure, GDM and low incidence of outcome, incident asthma in our study.

Lack of information

In the study addressing objective two, we were unable to consider some potential predictors of the trajectory groups such as respiratory tract infection, objective markers of atopy and bronchial hyper-responsiveness, severity of asthma and asthma medication because of lack of information in the dataset [19]. Future studies should assess all potential predictors for trajectory group membership.

6.5. Future Research Directions

This research addressed some of the gaps in knowledge on three epidemiological aspects of asthma. However, the findings from this research indicate areas of future research to aid in the prevention and control of asthma. Firstly, future research using age, period and cohort effect theoretical and analytical framework is warranted to see whether the age effect on asthma prevalence, the rising temporal trend along with the variation in asthma prevalence by age continues beyond our study period in Canadian population to guide public health policy in resource allocation for asthma management. These studies should also seek to explain the underlying causes of the effects. Secondly, future studies on identifying trajectories of asthma exacerbation in children with asthma in other settings and using accurate measures of asthma and asthma attack are needed to provide further evidence on distinctive asthma exacerbation trajectories in children and to enable comparison with the findings from our study. Future studies should assess all potential predictors for trajectory group membership, including respiratory tract infection, objective markers of atopy and bronchial hyper-responsiveness, severity of asthma and asthma medication to identify distinct predictors of the trajectory groups to predict individual child's exacerbation trajectory pattern. Ultimately, a comprehensive risk assessment model should be developed incorporating predictors from our study and future studies to aid prediction

of distinct asthma exacerbation trajectory groups. Finally, future studies are warranted to identify effective GDM preventive interventions, particularly in women at risk of developing GDM and if found effective should evaluate effectiveness in preventing outcomes in offspring, including asthma. Studies should also seek to identify intervenable mediators in the pathway between GDM.

6.6. Conclusions

This dissertation contributes towards providing insights on asthma burden in adults, the course of asthma in children and the role of a novel exposure maternal GDM in the risk of asthma in the offspring. The theoretical contributions could potentially help in future studies towards prevention and control of asthma. We have demonstrated that asthma prevalence in Canadian adults is higher in young adults and older adults compared to middle-aged adults and increased over time in all age groups although at different rates in increase and suggests substantial health burden for Canadian adults. Children with asthma followed three distinct trajectories that require replication and corroboration in future studies and warrants identification of additional predictors of trajectories and development of a comprehensive risk assessment model to aid physician's prognosticate asthma course. Maternal GDM could be a potential novel candidate for targeting interventions to prevent asthma in children and requires further evaluation in future studies.

6.7. References

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Appendices

Appendix A: The table of contents of the National Population Health Survey, household component, cycle 9 (2010/2011)

National Population Health Survey

Household Component
Cycle 9 (2010-2011)

Questionnaire

Statistics Canada

May 2011

Statistics Canada Statistique Canada

Canada

Table of Contents

Appendix B: The table of contents of the National Longitudinal Survey of Children and Youth, cycle 8 (2008/2009)

National Longitudinal Survey of Children and Youth

Cycle 8 Survey Instruments, 2008/2009
Book 1
Contact, Household and Exit, Parent, Child and Youth Components

Statistics Canada
Human Resources and Skills Development Canada

Statistique Canada
Ressources humaines et Développement des compétences Canada

Canada

BOOK 1 – TABLE OF CONTENTS

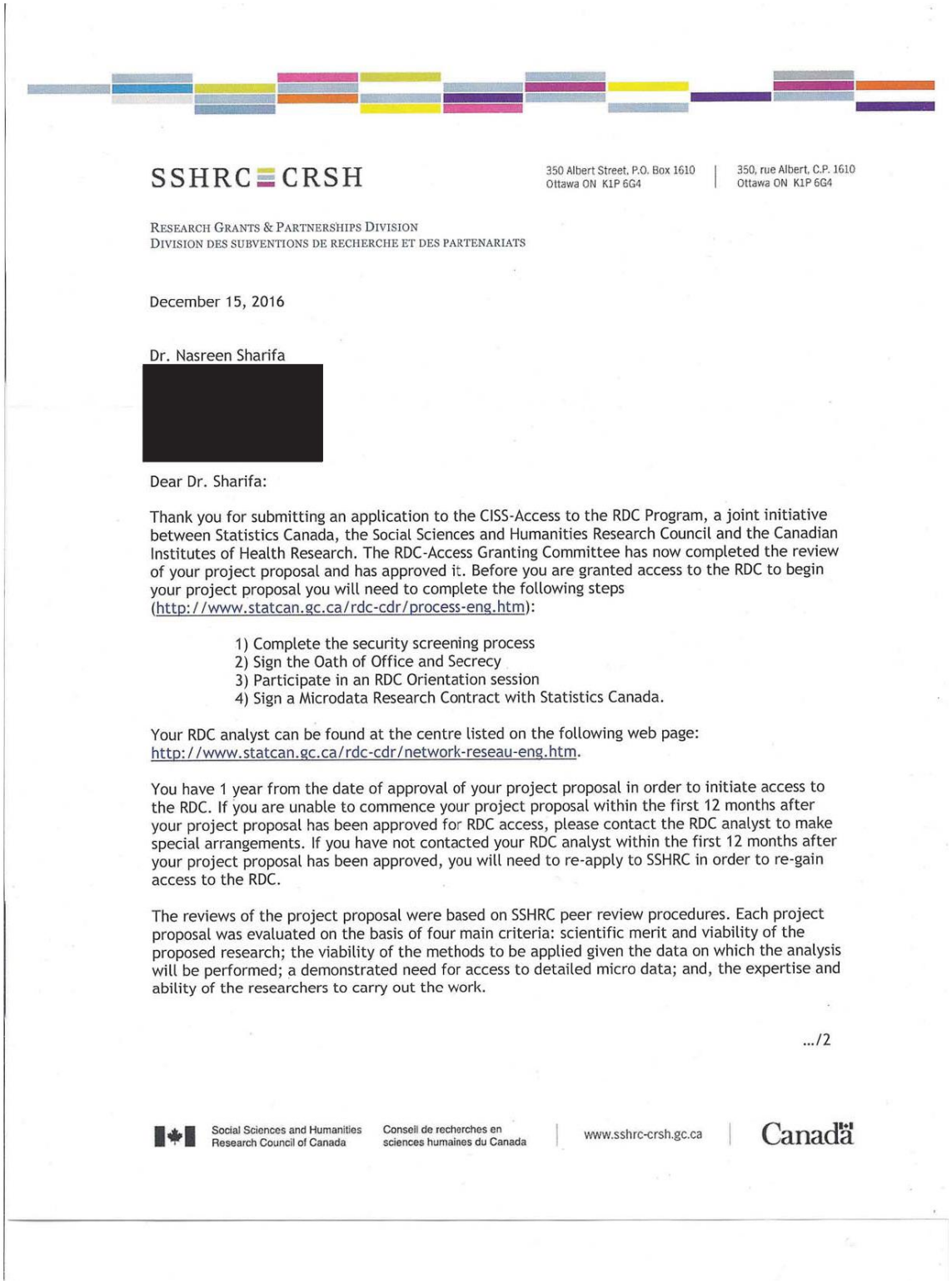
Appendix C: Child level response at data collection in the National Longitudinal Survey of Children and Youth, 1994/1995 – 2008/2009

Sampling type	Sampling cohort	Survey cycle	Age group in years	Sample size		Sample reduction		Out-of-scope Dropped from previous cycle		Non-respondents Dropped from previous cycle		In-scope		Respondents		In-scope rate (%)	Response rate (%)
				hhs	child	hhs	child	hhs	child	hhs	child	hhs	child	hhs	child	hhs	child
1994 Original cohort	1	1	0-11	43,751	..	..	..	..	..	..	..	15,502	26,409	13,439	22,831	35.4	86.5
		2	2-13	11,188	16,903	25,588	..	5,345	..	1,677	..	11,140	16,816	10,216	15,391	99.6	91.5
		3	4-15	11,032	16,718	0	0	38	71	73	114	10,937	16,563	9,801	14,777	99.1	89.2
		4	6-17	10,449	15,632	0	0	65	106	618	980	10,418	15,588	8,834	13,176	99.7	84.5
		5	8-19	10,355	15,163	0	0	24	32	286	437	10,320	15,113	8,582	12,280	99.7	81.3
		6	10-21	9,881	13,657	0	0	0	0	878	1,506	9,816	13,572	8,201	11,178	99.3	82.4
		7	12-23	10,522	13,709	0	0	7	11	406	602	10,454	13,616	8,561	10,966	99.4	80.5
		8	14-25	12,021	15,056	0	0	13	17	28	39	11,981	15,007	8,468	10,208	99.7	68.0
1996 ECD & NB Buy-in	2	2	0-1	5,592	..	..	..	..	..	..	..	4,929	5,087	4,496	4,634	88.1	91.1
		3	2-3	3,992	4,046	558	..	598	..	444	..	3,950	4,004	3,592	3,640	98.9	90.9
		4	4-5	3,577	3,610	520	540	25	25	34	35	3,552	3,585	3,023	3,052	99.3	85.1
1998 ECD & 5 top-up	3	3	0-1 & 5	16,812	..	..	..	..	..	..	..	15,929	16,263	13,256	13,546	94.7	83.3
		4	2-3	7,941	8,118	6,935	..	516	..	1,420	..	7,896	8,070	6,956	7,111	99.4	88.1
		5	4-5	6,960	7,115	0	22	41	41	940	940	6,919	7,073	6,208	6,340	99.4	89.6
		7	8-9	6,016	6,016	..	..	..	..	..	..	5,988	5,988	5,321	5,321	99.5	88.9
2000 ECD & 5 top-up	4	4	0-1 & 5	9,439	..	..	..	..	..	..	..	9,116	9,192	6,908	6,961	96.6	75.7
		5	2-3	3,788	3,841	4,405	..	125	..	1,121	..	3,776	3,829	3,281	3,324	99.7	86.8
		6	4-5	3,280	3,323	0	10	11	11	497	497	3,270	3,313	2,931	2,964	99.7	89.5
		7	6-7	3,231	3,231	0	43	3	3	46	46	3,217	3,217	2,882	2,882	99.5	89.6
2002 ECD	5	5	0-1	4,492	4,492	..	..	..	..	..	..	4,394	4,394	3,252	3,252	97.8	74.0
		6	2-3	3,252	3,252	0	0	98	98	1,142	1,142	3,233	3,233	2,866	2,866	99.4	88.6
		7	4-5	3,215	3,215	0	0	4	4	33	33	3,189	3,189	2,740	2,740	99.2	85.9
		8	6-7	3,214	3,214	0	0	26	26	3	3	3,205	3,205	2,580	2,580	99.7	80.5
2004 ECD & 2-5 top-up	6	6	0-5	5,795	5,795	..	..	..	..	..	..	5,763	5,763	4,684	4,684	99.4	81.3
		7	2-7	5,631	5,631	0	0	21	21	143	143	5,600	5,600	4,650	4,650	99.4	83.0
		8	4-7	5,039	5,039	0	0	31	31	688	688	5,006	5,006	3,852	3,852	99.3	76.9
2006 ECD & 2-5 top-up	7	7	0-5	5,843	5,843	..	..	..	..	..	..	5,808	5,808	4,691	4,691	99.3	80.8
		8	2-7	5,797	5,797	0	0	35	35	11	11	5,769	5,769	4,561	4,561	99.5	79.1
2008 ECD & 2-5 top-up	8	8	0-5	6,685	6,685	..	..	..	..	..	..	6,666	6,666	5,065	5,065	99.7	76.0

Notes:
.. Not available
hhs stands for "household", child stands for "respondent children".
Source: Statistics Canada, National Longitudinal Survey of Children and Youth.

Source: Microdata User Guide, National Longitudinal Survey of Child and Youth, Cycle 8

Appendix D: Approval Letter of research proposal from the Social Sciences and Humanities Research Council (For Secondary Data Source Access)



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RESEARCH GRANTS & PARTNERSHIPS DIVISION
DIVISION DES SUBVENTIONS DE RECHERCHE ET DES PARTENARIATS

December 15, 2016

Dr. Nasreen Sharifa
[redacted]

Dear Dr. Sharifa:

Thank you for submitting an application to the CISS-Access to the RDC Program, a joint initiative between Statistics Canada, the Social Sciences and Humanities Research Council and the Canadian Institutes of Health Research. The RDC-Access Granting Committee has now completed the review of your project proposal and has approved it. Before you are granted access to the RDC to begin your project proposal you will need to complete the following steps (http://www.statcan.gc.ca/rdc-cdr/process-eng.htm):

1) Complete the security screening process
2) Sign the Oath of Office and Secrecy
3) Participate in an RDC Orientation session
4) Sign a Microdata Research Contract with Statistics Canada.

Your RDC analyst can be found at the centre listed on the following web page: http://www.statcan.gc.ca/rdc-cdr/network-reseau-eng.htm.

You have 1 year from the date of approval of your project proposal in order to initiate access to the RDC. If you are unable to commence your project proposal within the first 12 months after your project proposal has been approved for RDC access, please contact the RDC analyst to make special arrangements. If you have not contacted your RDC analyst within the first 12 months after your project proposal has been approved, you will need to re-apply to SSHRC in order to re-gain access to the RDC.

The reviews of the project proposal were based on SSHRC peer review procedures. Each project proposal was evaluated on the basis of four main criteria: scientific merit and viability of the proposed research; the viability of the methods to be applied given the data on which the analysis will be performed; a demonstrated need for access to detailed micro data; and, the expertise and ability of the researchers to carry out the work.

.../2

Social Sciences and Humanities Research Council of Canada | Conseil de recherches en sciences humaines du Canada | www.sshrc-crsh.gc.ca | Canada

Enclosed is a copy of the evaluation results from the SSHRC peer review procedures for your information. If you need to discuss these results please contact your RDC analyst.

SSHRC encourages you to comply with the Open Access policy implemented by the Tri-Agencies in 2015. For more information, please see the entire policy here: http://www.sshrc-crsh.gc.ca/about-au_sujet/policies-politiques/open_access-libre_acces/index-eng.aspx

Should you have further questions, please feel free to contact the officer responsible for the administration of the CISS-Access to the RDC Program, Mika Oehling, at (613) 992-4227 or by email at mika.oehling@sshrc-crsh.gc.ca.

Sincerely,

[redacted]

Tim Wilson, PhD.
Executive Director

cc: Pamela Moren, Research Data Centres Headquarters Operations

Encl. 1

Applicant: Sharifa, Nasreen
Project title: Asthma in Canadian children and adults: trends in occurrence, asthma course trajectories and etiologic role of gestational diabetes mellitus

Data Access

Can the information required for the project be obtained from public sources such as public use of micro data files or existing publications? ○ Yes ◉ No ○ Unable to assess

Data Requirements

Does the researcher provide sufficient information and an adequate justification for access to confidential data file(s) requested? ◉ Yes ○ No

Is the population of interest described adequately in the proposal? ◉ Yes ○ No

Is there sufficient sample size to support the research on this population of interest when you consider the specified level of geography? ◉ Yes ○ No

Can the data support the proposed analysis for the population of interest? ◉ Yes ○ No

Are the variables to be used clearly described? ◉ Yes ○ No

Are the variables available in the data file requested? ◉ Yes ○ No

Does the level of the proposed geography ensure sufficient sample for analysis? ◉ Yes ○ No

Yes

Is a record linkage required to conduct the analysis? ○ Yes ◉ No

Legal Requirements

Does a share file agreement exist for these data? ◉ Yes ○ No

Are there respondents on the analytical file who have refused to share their information with the sharing (sponsoring) partner? ◉ Yes ○ No

Yes, with ESDC formerly HRSDC

If there is a sharing agreement, is the share file for these data distinctly different from the full master file? ○ Yes ◉ No

Does this project have any federal partners or funding partners (identified on the application form) who have a sharing agreement for the data requested? ○ Yes ◉ No

Conflict of Interest

Is the project funded by a private corporation/enterprise? ○ Yes ◉ No

Do you feel that this research poses a potential conflict of interest? ○ Yes ◉ No

Suitability of Mode of Data Access

Can these analysis be obtained through custom tabulation in your division? ○ Yes ◉ No

Overall Assessment

Based on the above data criteria, should the applicant and team members (if applicable) be granted access to a RDC? If No, please summarise reasons for rejection. ◉ Yes ○ No ○ Resubmit

If resubmission is advised, outline your concerns and recommendations (i.e. alternate dataset).

General Comments

Include any general comments you wish to pass along to the researcher.

Warnings

[X] Sample size or detailed tabular output may limit the release of the results. Consult you RDC analyst about the relevant disclosure rules.

[ ] Census profile data is required for the analysis. The Public Use Microdata Files (PUMF) must be obtained from the Data Liberation Initiative (DLI) services provided by the university. Ask your RDC analyst for more details.

Appendix E: Permission to Use the Published Papers from the Copyright Holder

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ELSEVIER

Title: Asthma exacerbation trajectories and their predictors in children with incident asthma

Author: Sharifa Nasreen,Piotr Wilk,Tara Mullowney,Igor Karp

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Age, period and cohort effects on asthma prevalence in Canadian adults, 1994–2011

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Asthma exacerbation trajectories and their predictors in children with incident asthma

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ABSTRACT

Background: Asthma exacerbation trajectories in children after incident asthma diagnosis are understudied.
Objective: To identify trajectories of asthma exacerbation and predictors of these trajectories in children with incident asthma.
Methods: Children from the National Longitudinal Survey of Children and Youth, Canada, with incident asthma were followed-up for up to 12 years during childhood. Latent class growth modeling was used to identify distinct asthma exacerbation trajectory groups. Multinomial logistic regression was performed to identify predictors of trajectory group membership.
Results: The mean age at asthma diagnosis among 403 children was 5.9 years. Three distinct trajectories were identified: low increasing (21.3% of children), medium decreasing (45.8% of children), and high decreasing (32.8% of children). Asthma attack probability increased gradually after diagnosis in low increasing group, decreased from moderate level after diagnosis to almost zero probability at the end of follow-up in the medium decreasing group, and decreased after diagnosis but remained higher in the high decreasing group than the other 2 groups at 12 years after diagnosis. Children having more siblings at home were more likely to belong to the medium decreasing and high decreasing trajectory groups, whereas children older at asthma diagnosis were less likely to belong to the medium decreasing and high decreasing trajectory groups than the low increasing trajectory group.
Conclusion: Our results suggest that children with incident asthma follow 3 distinct trajectories of asthma exacerbations after asthma diagnosis. The trajectory group with initial moderate exacerbation probability has better long-term prognosis.

Introduction

Asthma, a chronic disease characterized by periodic exacerbations and remissions, accounts for substantial medical and economic burden in children. Asthma exacerbations cause considerable suffering in children and can result in unscheduled emergency department visits, outpatient visits, hospitalizations, and even death.[1] Furthermore, asthma exacerbations can have extra-medical consequences such as school absenteeism and loss of parental or caregiver's productivity.[2,3] Much of the clinical-epidemiological literature on asthma has focused on the trajectories of wheezing to identify wheeze phenotypes and their subsequent association with asthma development in children,[4–6] and a few studies followed-up children since birth and attempted to identify trajectories of asthma prevalence according to age.[7–9] However, none have examined the trajectories of asthma course in children using time since asthma diagnosis as the time scale to inform the course after diagnosis.

The trajectories of asthma course in terms of exacerbations in children remain understudied. Qualitatively distinct groups of asthma exacerbation trajectories are possible among children with incident asthma. Identifying the trajectory groups and their predictors could enhance physicians' ability to better prognosticate the

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course of asthma. The objectives of this study were to identify trajectories of exacerbation in children with incident asthma and to identify the predictors of these trajectories at the time of asthma diagnosis.

Methods

Data Source

Ethical approval was not needed, because the study relied on anonymous and "secondary" data from Statistics Canada. The data source for this study was the National Longitudinal Survey of Children and Youth (NLSCY), Canada. Details of the NLSCY are available elsewhere.[10] Briefly, the NLSCY used a multi-stage cluster sampling to select households in 10 Canadian provinces in 1994 to 1995 (cycle 1) with children aged 0 to 11 years. Of the 22,831 children surveyed in cycle 1, 15,405 children were followed-up for 14 years and surveyed every 2 years through the final survey (cycle 8) in 2008 to 2009, when they were 14 to 25 years old. A maximum of 2 children (siblings) were selected from each household. One person most knowledgeable about a child (aged 0-15 years) and older children (>15 years) responded to survey questionnaires administered to collect sociodemographic and lifestyle, environment, and health-related data.

Study Sample

An affirmative response to the question "Has this child ever had asthma that was diagnosed by a health professional?" asked to the person most knowledgeable for children aged 0 to 15 years in survey cycles indicated the presence of asthma. An affirmative response to the question "Have you ever had asthma that was diagnosed by a health professional?" asked to children aged older than 15 years in survey cycles 4 to 5 indicated the presence of asthma. The first-time report of asthma during survey cycles 2 through 8 indicated incident asthma diagnosed at some point during the 2 years before the survey. Children meeting the following criteria were included in our study: having a biological parent as the person most knowledgeable (parent hereafter), no asthma at survey cycle 1, and reported asthma diagnosed by a health professional during follow-up. Children with the following conditions were excluded from the study: not having a parent as the person most knowledgeable (parent hereafter) (n = 958); asthma at survey cycle 1 (n = 1530), missing asthma information at survey cycle 1 (n = 178); no health professional–diagnosed asthma during the follow-up (n = 10,617); information on asthma at less than 4 survey cycles (to be able to assess cubic pattern of the trajectories)[11] (n = 1538); and inconsistent response ("no" after "yes") on "ever diagnosed with asthma" question between surveys (n = 161). Another 20 children were excluded because of missing asthma information between surveys with a "no" and a "yes" response on asthma, which precluded identification of time of incident asthma; older child from households with 2 children to allow longer follow-up of the younger child, and children whose reported sex changed between surveys before asthma diagnosis. A total of 403 children diagnosed with incident asthma were retained for the analysis to identify trajectories during childhood. Follow-up of a child for our study started at asthma diagnosis and lasted for 6 to 12 years (up to 17 years of age), depending on the age at survey cycle 1 and the age at asthma diagnosis.

Description of Variables

"Asthma attack" was considered as the measure of asthma exacerbation. An affirmative response to the question "Has he/she had an attack of asthma in the last 12 months?" asked to parents of 0- to 15-year-old children with asthma at each survey cycle, or "Have you had an attack of asthma in the last 12 months?" asked to 16- to 17-year-old children with asthma in survey cycles 4 or 5 was considered as having an asthma attack. The following baseline variables measured at or before incident asthma diagnosis were considered as potential predictors for trajectory group membership based on review of literature on prognostic factors in asthma[12–17] and available information in the NLSCY: sex of the child, child having health professional–diagnosed allergy as a proxy for allergen sensitization or atopy of the child, at least 1 biological parent with a history of health professional–diagnosed asthma or allergy, smoking habit of parent or spouse as a proxy for exposure to environmental tobacco smoke at home, number of siblings at home, and age at asthma diagnosis. Except age at asthma diagnosis, predictor information from the survey cycle before asthma diagnosis was used, considering a 12-month recall period for asthma attack and because predictors should be established at the time of asthma diagnosis (ie, at the beginning of period of trajectory).[18] Available information from a prior survey cycle was used to replace missing predictor data, assuming the condition remained the same at the survey cycle before asthma diagnosis. Age at asthma diagnosis and number of siblings were treated as continuous variables, and the other predictors were represented by binary variables.

Statistical Analysis

At first, a hierarchical logistic regression model was used to assess the overall pattern of asthma attack after diagnosis.[19,20] Latent class growth modeling, a semi-parametric approach, was then used to identify distinct groups of children with similar patterns of asthma exacerbations over time.[18,21] Latent class growth modeling attempts to identify trajectory groups in the population even if these trajectory groups are latent ("not identifiable ex ante on the basis of measured characteristics")[18] and thus unobservable. We first attempted to identify the number of latent trajectory groups by testing models with up to 5 latent trajectory groups. Each model included the linear, quadratic, and cubic polynomial terms for time since asthma diagnosis, to allow for the possibility of an S-shaped pattern of the relation between the logit of the probability of asthma attack and time since asthma diagnosis. Among these, the model having the lowest Bayesian Information Criterion was selected (eTable 1).[18,22] Examination of the results of statistical-significance testing of the 3 polynomial terms for time since asthma diagnosis revealed that the quadratic and cubic terms were not statistically significant. Thus, these terms were dropped from the model,[11,18] so the final model only included a linear term, suggesting a straight-line (rather than parabolic or S-shaped) pattern of the relation between the logit of the probability of asthma attack and time since asthma diagnosis. We used time since asthma diagnosis as the time axis in both hierarchical modeling and group-based trajectory modeling. Details of these analytic methods are provided in eMethods. Finally, multinomial logistic regression modeling was performed to identify the predictors of trajectory group membership. Data on parental history of asthma or allergies and exposure to environmental tobacco smoking at home were missing in 7% and 1% of children, respectively. We first performed a complete-case analysis, restricted to children having information on all predictors. We also performed sensitivity analysis after conducting 10 imputations for the missing risk factor values employing multivariate imputation using chained equations.[23]

We conducted a secondary analysis to identify asthma exacerbation trajectories restricted to children with asthma diagnosed after 6 years of age, because some preschool children with diagnosed asthma may outgrow their asthma after 6 years of age.[24,25] To identify predictors of trajectory group membership, we fitted logistic regression models. We performed a complete-case and

sensitivity analyses, which involved conducting 15 imputations for missing risk factors using multivariate imputation using chained equations.

Hierarchical logistic regression modeling was performed using SAS's PROC GLIMMIX procedure with Laplace estimation to obtain maximum likelihood estimation of the parameters (SAS Institute, Inc., Cary, NC).[26] Latent class growth modeling was performed using the PROC TRAJ procedure and multinomial logistic regression in SAS.[27] Sensitivity analysis was performed using Stata software (StataCorp LP, College Station TX). All statistical-significance tests were carried out at the alpha level of 0.05 (2-sided).

Results

We report findings on the trajectories and predictors following the recommended guidelines for reporting on latent trajectory studies, including studies using latent class growth modeling.[28]

Characteristics of Children at Asthma Diagnosis

Among 403 children retained in the analysis, the mean age at asthma diagnosis was 5.9 years; most children (61%) were male, and one fifth (20%) of the children had allergies at or before asthma diagnosis (Table 1). The mean duration of follow-up was 8 years; 170 (42%) children contributed data for 6 years, 104 (26%) children contributed data for 8 years, 79 (20%) children contributed data for 10 years, and the remaining 50 (12%) children contributed data for 12 years of follow-up. Of the 403 children, 177 (44%) were aged older than 6 years at asthma diagnosis. Among these 177 children, 136 (77%) contributed data for 6 years, and 41 (23%) contributed data for 8 years of follow-up.

Average Asthma Trajectory from Hierarchical Modeling

Table 2 presents the parameter estimates from the hierarchical logistic regression model. The fixed-effects parameter estimate for the intercept was 0.68, implying that the estimated probability of asthma attack was 0.66 at asthma diagnosis. The fixed-effects parameter estimate for time since asthma diagnosis was −0.358, implying that the odds of having had asthma attack decreased by 30% with each year increase in time since asthma diagnosis. The random-effects parameter estimates for between-child variance in both the intercept and "growth" rate of asthma attack over time since asthma diagnosis were statistically significant (Table 2, random effects) suggesting that asthma attack probability at diagnosis and asthma attack probabilities across time since asthma diagnosis vary across children. The overall trajectory of asthma attack plotted from the fitted model suggested that the probability of asthma attack decreased with time after asthma diagnosis, from 0.63 at asthma diagnosis to 0.11 at 12 years after diagnosis (Fig 1).

Table 1
Characteristics of Children at Asthma Diagnosis, National Longitudinal Survey of Children and Youth (NLSCY), 1994/1995–2008/2009

Characteristics	Frequency (%) (n = 403)
Sex, male	246 (61)
Child has allergy	82 (20)
Parent has asthma or allergy	114 (34)
Exposure to environmental tobacco smoke at home	192 (48)
Number of siblings at home, mean (SD)	1.02 (0.83)
Age of child at asthma diagnosis in years, mean (SD)	5.90 (2.55)

SD, standard deviation.

Table 2
Parameter Estimates from the Hierarchical Logistic Regression Model, National Longitudinal Survey of Children and Youth (NLSCY), 1994/1995–2008/2009

Parameter	Estimate (SE)	*P*
Fixed effects		
Intercept	0.68 (0.14)	<.0001
Time[a]	−0.36 (0.03)	<.0001
Random effects		
Between-child variance in intercepts	2.91 (0.49)	<.0001
Between-child variance in "growth" rate of asthma attack over time[a]	0.04 (0.02)	.003
Fit statistics		
BIC	2291.93	
−2 Log likelihood	2267.94	

SE, standard error; BIC, Bayesian information criterion.
[a]Time since asthma diagnosis.

Trajectory Groups of Asthma Attack from Latent Class Growth Modeling

Asthma attack over time was best fitted by a 3-group model. Figure 2A presents the trajectories of each of the 3 groups, and eTable 2 presents the estimates of the trajectory parameters and model adequacy information. The first trajectory group (*low increasing*) comprised 21.3% of children who had an initial low level of asthma attack probability that gradually increased after diagnosis and remained higher than the asthma attack probability for the second trajectory group from approximately 7 years after asthma diagnosis (Fig 2A). The second trajectory group (*medium decreasing*) comprised 45.8% of children having a moderate level of initial asthma attack probability with initial steep decrease followed by gradual decrease with almost zero asthma attack probability at the end of the 12-year follow-up. The third trajectory group (*high decreasing*) comprised 32.8% of children having very high initial asthma attack probability that decreased gradually and had a higher level of asthma attack probability than *low increasing* and *medium decreasing* trajectory groups at 12 years after asthma diagnosis. The predicted and observed trajectories for the 3 trajectory groups suggested good fit (Fig 2B). Among 104 children in the *low increasing* trajectory group, the mean age of asthma diagnosis was 6.5 (standard deviation [SD], 2.4) years, and 57 (54.8%) children had asthma diagnosed after 6 years of age; among 168 children in the *medium decreasing* trajectory group, the mean age at asthma diagnosis was 5.9 (SD 2.4) years, and 99 (58.9%) children had asthma diagnosed before 6 years of age; and among 131 children in the *high decreasing* trajectory group, the mean age at

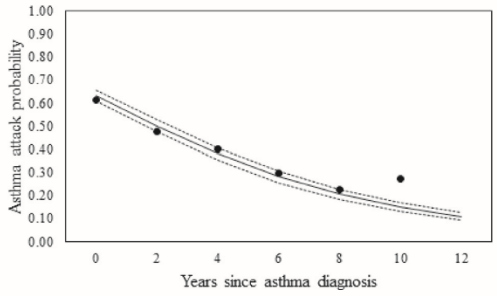

Figure 1. Overall trajectory of estimated probability of asthma attack, hierarchical logistic regression model, National Longitudinal Survey of Children and Youth, Canada, 1994/1995–2008/2009. Solid line represents the point estimate of the probability, and dashed lines represent the 95% confidence interval estimates. Black circles represent observed proportion of asthma attack. Proportion at 12 years since asthma diagnosis is not reportable because of a small sample size (n < 15) in this subpopulation.

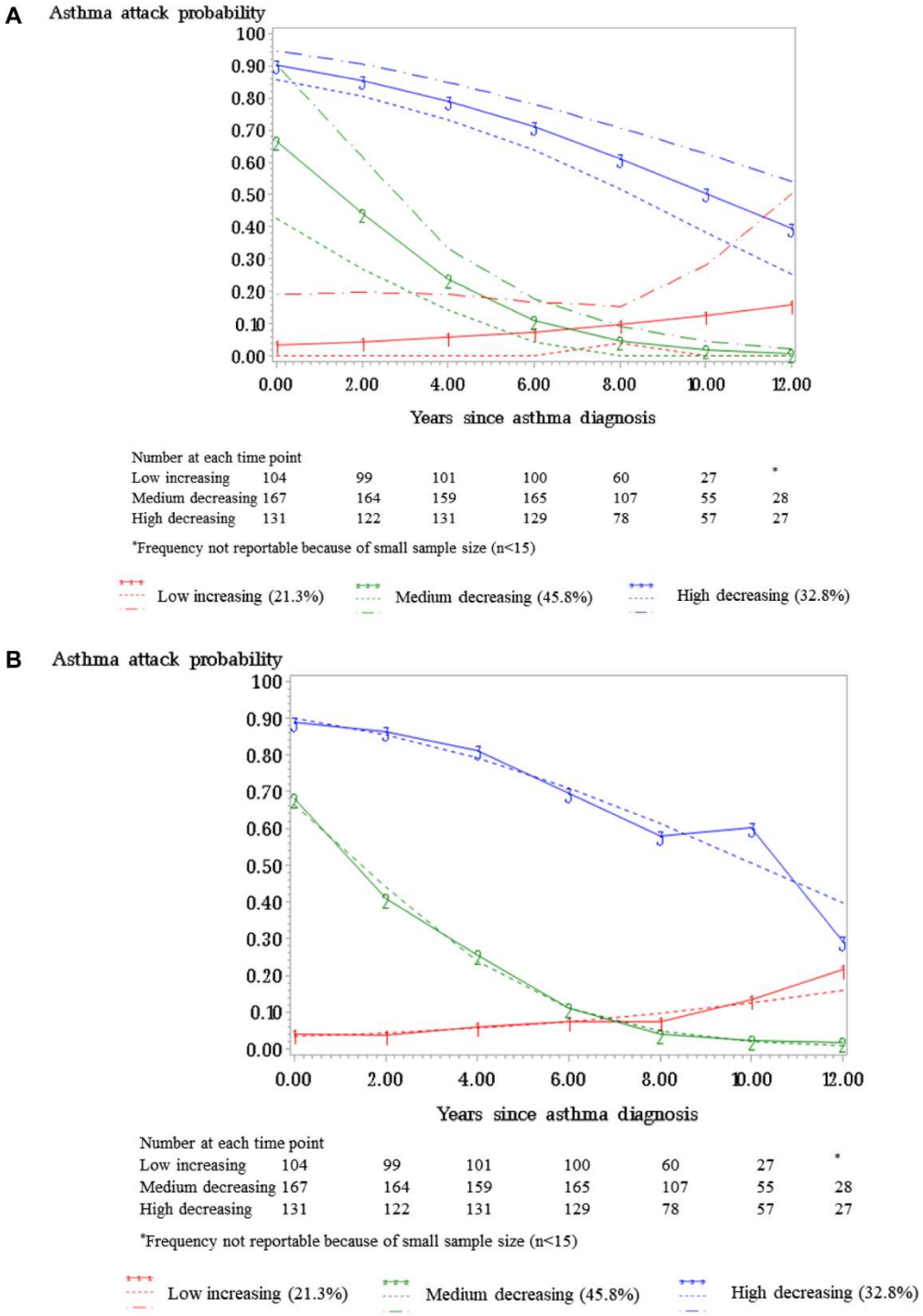

Figure 2. Trajectories of asthma attack, latent class growth modeling, National Longitudinal Survey of Children and Youth, Canada, 1994/1995–2008/2009. **A,** Solid line depicts predicted trajectory and dashed line 95% confidence interval. **B,** Solid line depicts observed trajectory and dashed line the predicted trajectory.

asthma diagnosis was 5.4 (SD 2.8) years, and 80 (61.1%) children had asthma diagnosed before 6 years of age.

Predictors of Trajectory Groups

A total of 371 children had information on all potential predictors. According to the multivariable model, children having more siblings at home were more likely to belong to the *medium decreasing* and *high decreasing* trajectory groups, and children older at asthma diagnosis were less likely to belong to the *medium decreasing* and *high decreasing* trajectory groups than *low increasing* trajectory group (Table 3). The magnitude of the estimated association was largest for having more siblings. Male children were less likely to belong to the *medium decreasing* and *high decreasing* trajectory groups compared with the *low increasing* group, but the 95% confidence intervals were wide to allow meaningful interpretation. Similarly, imprecise results were obtained for children having allergy and exposure to environmental tobacco smoke at home, although there were positive associations with the probability of belonging to the *medium decreasing* and *high decreasing* trajectory groups. The association between having parents with asthma or allergy and trajectory group membership was ambiguous: children having parents with asthma or allergy were less likely to belong to the *medium decreasing* trajectory group but more likely to belong to the *high decreasing* trajectory group. Sensitivity analysis with imputed data for missing predictors yielded similar results (Table 3).

Asthma Attack Trajectory Groups and Predictors in Children with Asthma Diagnosed after Six Years of Age

Among 177 children with asthma diagnosed after 6 years of age, the pattern of asthma attack over time was best represented by a 2-group model. Figure 3A depicts the trajectories of these two groups, and eTable 2 depicts the estimates of the trajectory parameters and model adequacy statistics. The first trajectory group (*low decreasing*) comprised 59.7% of children having a low level of asthma attack probability that gradually decreased during the follow-up (Fig 3A). The second trajectory group (*high decreasing*) comprised 40.3% of children having very high initial asthma attack probability that decreased gradually over the 8 years of follow-up and had a higher level of asthma attack probability than the *low decreasing* trajectory group throughout the follow-up. The predicted and observed trajectories for the 2 trajectory groups suggested good fit (Fig 3B).

In the complete-case analysis (N = 160), male children were less likely to belong to the *high decreasing* trajectory group, whereas children having allergy, having parents with asthma or allergy, with exposure to tobacco smoke at home, having more siblings at home, and being older at asthma diagnosis were more likely to belong to the *high decreasing* trajectory group compared with the *low stable* trajectory group (Table 3). Similar results were obtained with imputed data.

Discussion

Using data from a population-based longitudinal survey, we identified 3 distinct trajectories of asthma attack in children for a period of up to 12 years after incident asthma diagnosis: *low increasing, medium decreasing,* and *high decreasing.* We also identified 2 predictors of the trajectory group membership: number of siblings at home and age at asthma diagnosis. Knowledge on the trajectories could help physicians foresee disease course at the time of asthma diagnosis.

Although one fifth of the children belonged to the *low increasing* trajectory group, most of the children belonged to the *medium decreasing* and *high decreasing* trajectory groups, with substantially high probabilities of asthma attack during the initial phase of follow-up immediately after asthma diagnosis. The mean age of

Table 3
Predictors of Trajectory Groups of Asthma Attack in Children with Asthma, National Longitudinal Survey of Children and Youth, 1994/1995–2008/2009

Group	Predictor	Odds ratio (95% confidence interval)			
		Complete case analysis (N = 371)		Sensitivity analysis (N = 403)	
		Bivariate	Multivariable	Bivariate	Multivariable
All children[a]					
Medium decreasing	Sex of the child, male	0.76 (0.45-1.33)	0.74 (0.42-1.29)	0.94 (0.57-1.56)	0.91 (0.54-1.53)
	Child has allergy	1.07 (0.57-2.02)	1.19 (0.62-2.30)	1.26 (0.68-2.34)	1.38 (0.73-2.60)
	Parent has asthma/allergy	0.69 (0.39-1.23)	0.67 (0.37-1.24)	0.69 (0.39-1.21)	0.64 (0.36-1.16)
	Exposure to environmental tobacco smoke at home	1.33 (0.79-2.24)	1.28 (0.75-2.18)	1.21 (0.74-1.99)	1.15 (0.69-1.91)
	Siblings at home	1.37 (0.99-1.90)	1.60 (1.11-2.30)	1.36 (0.99-1.86)	1.53 (1.08-2.16)
	Age at asthma diagnosis (years)	0.92 (0.83-1.02)	0.87 (0.78-0.98)	0.44 (0.84-1.02)	0.88 (0.79-0.98)
High decreasing	Sex of the child, male	0.83 (0.47-1.46)	0.70 (0.39-1.26)	1.01 (0.60-1.72)	0.87 (0.50-1.50)
	Child has allergy	1.02 (0.53-1.99)	1.11 (0.55-2.22)	1.11 (0.57-2.14)	1.14 (0.58-2.26)
	Parent has asthma/allergy	1.45 (0.82-2.56)	1.36 (0.75-2.49)	1.47 (0.83-2.58)	1.36 (0.76-2.44)
	Exposure to environmental tobacco smoke at home	1.41 (0.82-2.42)	1.21 (0.69-2.13)	1.27 (0.75-2.15)	1.11 (0.64-1.92)
	Siblings at home	1.26 (0.90-1.78)	1.59 (1.09-2.33)	1.34 (0.96-1.86)	1.62 (1.13-2.32)
	Age at asthma diagnosis (years)	0.83 (0.74-0.93)	0.80 (0.71-0.90)	0.85 (0.77-0.94)	0.82 (0.74-0.92)
		Complete case analysis (N = 160)		Sensitivity analysis (N = 177)	
		Bivariate	Multivariable	Bivariate	Multivariable
Children with asthma diagnosed after 6 years of age[b]					
High decreasing	Sex of the child, male	0.83 (0.44-1.56)	0.69 (0.35-1.38)	0.89 (0.49-1.61)	0.75 (0.40-1.43)
	Child has allergy	1.72 (0.85-3.50)	1.71 (0.81-3.61)	1.55 (0.78-3.08)	1.53 (0.75-3.15)
	Parent has asthma/allergy	1.28 (0.65-2.54)	1.31 (0.62-2.79)	1.26 (0.64-2.48)	1.27 (0.60-269)
	Exposure to environmental tobacco smoke at home	1.57 (0.83-2.98)	1.79 (0.92-3.51)	1.52 (0.83-2.79)	1.70 (0.91-3.20)
	Siblings at home	1.57 (1.03-2.41)	1.54 (0.99-2.39)	1.45 (0.97-2.17)	1.44 (0.95-2.18)
	Age at asthma diagnosis (years)	1.22 (0.94-1.59)	1.23 (0.93-1.62)	1.18 (0.93-1.49)	1.20 (0.93-1.53)

[a]Multinomial logistic regression, low increasing trajectory is the comparison group.
[b]Logistic regression, low decreasing trajectory is the comparison group.

asthma diagnosis in children was 5.9 years. Virus-induced wheezing is prevalent in the preschool years, and symptoms may abate soon afterward.[24,29,30] We would expect *low increasing* trajectory group with low exacerbation rate to have predominance of children with asthma diagnosed at a younger age. However, the mean age at asthma diagnosis was higher in children in the *low increasing* trajectory group compared with the mean age at asthma diagnosis in children in the *medium decreasing* and *high decreasing* trajectory groups, contrary to our expectation. Our finding of children with asthma diagnosed before 6 years of age belonging to the *medium decreasing* and *high decreasing* trajectory groups are comparable to the findings from previous studies that an earlier age at asthma onset may lead to persistent asthma in childhood.[29,31] The reason for the low level of exacerbation probability in children in the *low increasing* trajectory group warrants exploration in future studies. Children belonging to the *low increasing* group may require attention several years after asthma diagnosis to decrease the increasing probabilities of asthma attacks, and children belonging to the *medium decreasing* and *high decreasing* trajectory groups could particularly benefit from reduction in exacerbation frequency during the initial period after diagnosis. Overall, children belonging to the *medium decreasing* trajectory group have better long-term prognosis than children belonging to the other 2 trajectory groups. Lack of similar studies on individuals with diagnosed asthma and with follow-up beginning right after asthma diagnosis in children or adults precluded us comparing exacerbation trajectories identified in our study.

Having more siblings at home was positively associated with membership in the *medium decreasing* and *high decreasing* trajectory groups compared with the *low increasing* trajectory group. Having more siblings at home may have increased exposure to respiratory infections via contact with the siblings resulting in more asthma exacerbation immediately after asthma diagnosis. Our finding is similar to the finding that larger sibship was associated with severe asthma symptoms in children aged 6 to 7 years and 13 to 14 years in a worldwide study.[32] Nevertheless, our finding seems contrary to the finding from a study reporting that exposure to older siblings was associated with an increased rate of asthma remission in childhood.[33] Assessing a factor for asthma remission measured at a particular age or time does not provide information on the role of the factor over the course of asthma. In our study, children older at asthma diagnosis experienced milder asthma course, because they were less likely to belong to the *medium decreasing* and *high decreasing* trajectory groups that had higher probabilities of asthma attack. In other studies, younger age was found to be a risk factor for asthma attack[34] and a predictor of severe asthma exacerbation in children.[35] These findings are consistent with the results from our study. However, age at asthma diagnosis was only weakly associated with frequent episodic asthma in children in another study.[36]

Exposure to environmental tobacco smoke is known to be positively associated with asthma severity and hospitalization with asthma exacerbation[37,38] and negatively associated with asthma remission.[14] In our study, the estimated association between exposure to environmental tobacco smoke at home and trajectory group membership in our study was imprecise. Nevertheless, a study reported that exposure to second-hand smoke was "not associated" with frequent episodic asthma compared with infrequent asthma in children.[36] Although exposure to environmental tobacco smoke is time-varying and can change during the course of asthma, we considered exposure to environmental tobacco smoke before asthma diagnosis as a predictor to be able to predict trajectory group membership at the time of asthma diagnosis. An imprecise association was also found between allergy in child and trajectory group membership. Parent-reported allergy in a child may have led to inaccurate documentation of child's allergy status, potentially resulting in an underestimation of the association. The point estimates suggested that allergy in a child was a weak predictor, but the upper limits of the 95% confidence interval indicated that our data are compatible with relatively strong associations too. In addition, strong predictors of asthma course may not necessarily be strong predictors of our outcome, "trajectory group." Among children with asthma diagnosed after 6 years of age, nearly three-fifths of the children belonged to the *low decreasing* trajectory group with better prognosis compared with the two-fifths of the children belonging to the *high decreasing* trajectory group. Our results weakly support the association between exposure to environmental tobacco smoke at home, siblings at home, and age at asthma diagnosis, with high decreasing trajectory group membership.

This study has several strengths. To our knowledge, this is the first study to identify trajectories of exacerbation in children after incident asthma diagnosis using a group-based trajectory method that takes into account the dynamic nature of asthma course. Use of population-based data enabled us to follow-up with children up to 12 years after asthma diagnosis. We were able to capture less severe asthma attacks that may not have necessitated urgent medical care and would have been excluded if administrative data were used. Asthma attacks managed at home, not seeking medical care, or medical care received from non–fee-for-service physicians who do not remit service information are not captured in administrative data.[39] Information on the predictors of the trajectory groups identified in this study would be readily available to the physicians even at a primary care setting.

The findings of this study need to be interpreted in light of some limitations. Our sample size was relatively small, which led to considerable uncertainty in estimated trajectory patterns, as

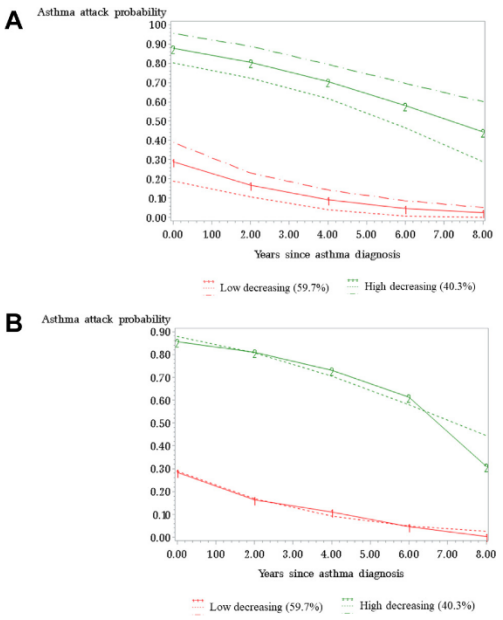

Figure 3. Trajectories of asthma attack in children with asthma diagnosed after 6 years of age, latent class growth modeling, National Longitudinal Survey of Children and Youth, Canada, 1994/1995–2008/2009. **A,** Solid line depicts predicted trajectory and dashed line 95% confidence interval. **B,** Solid line depicts observed trajectory and dashed line the predicted trajectory.

reflected by the wide confidence intervals of the trajectory curves. The small sample size also may have precluded us from identifying predictors that distinguished between *high decreasing* and *medium decreasing* trajectory groups. Thus, replication of our results in future studies is warranted. Asthma diagnosis was based on parental and child report and subject to recall bias. The prevalence of parent-reported physician-diagnosed asthma has been found to be lower than the prevalence based on health administrative data (16% vs 21%) in urban Canadian school children in cross-sectional setting.[40] However, validity of parent report of diagnosed asthma in longitudinal setting remains undetermined. Some discrepancies in response regarding the child ever having asthma over the course of the NLSCY cycles was seen, suggesting that the questions asked may not have been perceived by the respondents in the way they were intended. We excluded children with discrepant responses to obtain conservative estimates. We could not ascertain the exact age at asthma diagnosis because the question on ever having asthma was asked every 2 years, and information on exact age or date of asthma diagnosis was not available. Possibly children may have been younger than the age we considered to have asthma diagnosis. The recall period for asthma attack was 12 months before the interview, which has the potential for recall bias. Because asthma attacks affect day-to-day lives of children and caregivers with or without necessitating medical care, parents likely reliably recalled any asthma attack event. Nevertheless, we were unable to quantify asthma attack and ascertain severity because of a lack of this information. Children younger at NLSCY cycle 1 or asthma diagnosed at a younger age contributed more to the follow-up than children older at cycle 1 or asthma diagnosed at an older age. Different contribution to the follow-up by the children may have resulted in misclassification of trajectory group membership. We employed the traditional 3-step method for identifying latent trajectories and their predictors, which does not take into account the uncertainty (classification error) in group allocation.[28] However, the odds of classification error for the trajectory groups in our final models exceeded the threshold and suggest fewer classification errors. We were unable to consider some potential baseline predictors of the trajectory groups, such as respiratory tract infection, objective markers of atopy and bronchial hyperresponsiveness, severity of asthma, and asthma medication because of lack of information in the dataset.[12] Future studies should assess all potential predictors for trajectory group membership. Missing predictor values could bias the association between predictors and trajectory group membership.[41] We performed sensitivity analysis after imputing missing predictor values, and the results were similar.

In conclusion, our study suggests that children with asthma follow 3 distinct trajectories of asthma exacerbation. Membership in 2 of these trajectories was associated with 2 predictors at asthma diagnosis (number of siblings at home and age at asthma diagnosis), although the predictors were not able to distinguish between these 2 trajectories. Knowledge on the trajectories at the time of asthma diagnosis could help prognosticate the course and supplement the current paradigm of asthma management based on symptom control. Further studies on children with asthma in other settings, following children from birth through their entire childhood and using accurate measures of asthma and asthma attack, would provide further evidence on distinctive asthma exacerbation trajectories in children and enable comparison. Future studies are warranted to identify distinct predictors of the trajectory groups to predict an individual child's exacerbation trajectory pattern. A comprehensive risk assessment model should be developed in the future, incorporating predictors from this study and future studies to aid prediction of distinct asthma exacerbation trajectory groups.

Supplementary Data

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.anai.2019.05.013.

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eMethods

A 2-level hierarchical logistic regression model[19,20] with repeated observations as level 1 units nested within individuals as level 2 units was performed to assess the overall pattern of asthma attack over time after asthma diagnosis and examine between-subject variability in trajectories. The combined level 1 and level 2 model included fixed effects for intercept and time since asthma diagnosis, and random effects for intercept and time since asthma diagnosis. The intercept in a logistic regression model is the log odds of the dependent variable when all of the independent variables are set to zero. Because we have 1 independent variable, "time since asthma diagnosis," in our hierarchical model, the intercept can be interpreted as the log odds of having an asthma attack around the time of asthma diagnosis. The fitted model was used to estimate time-specific probabilities of having an asthma attack, which were then plotted to depict the average trajectory of asthma attack after asthma diagnosis.

We used a logistic model for binary logit distribution in latent class growth modeling[18]: $\alpha_{it}^{j} = \frac{e^{\beta_0^j + \beta_1^j Time_{it} + \beta_2^j Time_{it}^2 + \beta_3^j Time_{it}^3}}{1+e^{\beta_0^j + \beta_1^j Time_{it} + \beta_2^j Time_{it}^2 + \beta_3^j Time_{it}^3}}$ where α_{it}^{j} is the probability of the observed binary outcome $y_{it} = 1$ given membership in group j, $p^j(y_{it} = 1)$ with the assumption that the observed binary outcome $y_{it} = 1$ (individual i had asthma in time t) if the latent variable $y_{it}^{*} > 0$ and $y_{it} = 0$ (individual i did not have asthma in time t) if $y_{it}^{*} \leq 0$. Trajectory parameters were estimated using maximum likelihood with default start values. Identification of the trajectory groups involved a 2-stage process.[18] In the first stage, the number of latent trajectory groups to include in the model was chosen. We tested 5 candidate models with cubic polynomial function in each model: the first model with 1 latent trajectory group, the second model with 2 latent trajectory groups, the third model with 3 latent trajectory groups, the fourth model with 4 latent trajectory groups, and the fifth model with 5 latent trajectory groups (eTable 1). Among the 5 models tested, we chose the model with the lowest Bayesian Information Criterion (BIC). The BIC is a commonly used criterion for model selection, and it is calculated as $\log(L) - 0.5k \log(N)$, where L is the value of the model's maximized likelihood, N is the sample size, and k is the number of parameters estimated by the model; the model with the lowest BIC is preferred.[18,22] In the second stage, we chose the order of the polynomial defining the shape of each trajectory group in the model selected in the first stage. Including cubic polynomial function in the models in the first stage allowed for the possibility of an S-shaped pattern of relationship between the logit of the probability of asthma attack and time since asthma diagnosis. Nonsignificant quadratic and cubic terms were removed but linear terms were retained in the model regardless of significance.[11] Thus, the final model included a linear term, depicting a straight-line trajectory pattern for each trajectory group. Adequacy of the final model was assessed by 3 diagnostics: average posterior probability of each group exceeded 0.70, odds of correct classification exceeded 5, and the model estimated probability of group membership differed by less than 50% from the proportion assigned to a group based on largest posterior probability.

eTable 1
Models Tested in Latent Class Growth Modeling

No. of trajectory groups	BIC[a]	Sample size per group based on most likely group membership
All children (N = 403)		
1	−1294.47	403
2	−1163.76	251/152
3	−1160.35	232/108/63
4	−1170.10	—[b]
5	−1182.41	—[b]
Children with asthma diagnosed after 6 years of age (N = 177)		
1	−486.79	177
2	−438.52	99/78
3	−450.37	64/45/68
4	−461.57	—[b]
5	−475.74	—[b]

BIC, Bayesian information criterion.
[a]Lowest BIC is preferable.
[b]Indicates values not reportable because of small sample size (n < 15) in 1 or more groups.

eTable 2
Latent Trajectory Groups of Asthma Attack in Children with Asthma, National Longitudinal Survey of Children and Youth, 1994/1995–2008/2009

Groups	Model estimated group membership, %	Assigned group membership using maximum probability rule, n(%)	Average posterior probability (AvePP)	Odds of correct classification	Parameter	Estimate (SE)	*t* statistic	BIC
All children (N = 403)								
Low increasing	21.3	104 (25.8)	0.72	9.48	Intercept	−3.36 (2.48)	−1.36	−1154.05
					Time to asthma diagnosis	0.14 (0.31)	0.46	
Medium decreasing	45.8	168 (41.7)	0.84	6.20	Intercept	0.69 (0.55)	1.26	
					Time to asthma diagnosis	−0.46 (0.12)	−3.95	
High decreasing	32.8	131 (32.5)	0.88	15.01	Intercept	2.21 (0.26)	8.59	
					Time to asthma diagnosis	−0.22 (0.04)	−5.89	
Children with asthma diagnosed after 6 years of age (n = 177)								
Low decreasing	59.7	99 (55.9)	0.96	16.20	Intercept	−0.90 (0.25)	−3.60	−430.29
					Time to asthma diagnosis	−0.35 (0.08)	−4.21	
High decreasing	40.3	78 (44.1)	0.87	9.92	Intercept	1.97 (0.36)	5.47	
					Time to asthma diagnosis	−0.27 (0.07)	−4.16	

BIC, Bayesian information criterion; SE, standard error.

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