LONGITUDINAL STUDIES OF DISEASE PROGRESSION, HEALTH CARE COSTS AND HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH ASTHMA

by

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(Pharmaceutical Sciences)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

September 2016

Abstract

This thesis examines the burden of asthma and its determinants though a series of longitudinal observational studies. **Objectives**: 1) To quantify the natural history of severe asthma and the impact of early risk factors; 2) To examine the influence of socioeconomic status (SES) on excess direct medical costs of moderate-to-severe asthma and guideline-based asthma care; 3) To estimate excess costs of asthma and the economic implications of comorbidities; 4) To assess the joint influences of asthma control and comorbidity on health-related quality of life. **Methods:** For the first three objectives, administrative health data (for the period of 1997-2013) were obtained from British Columbia (BC) Ministry of Health, and for the last objective data were obtained from the Economic Burden of Asthma (EBA) study in BC. Various models for longitudinal data were applied for each objective. **Findings:** 1) Most patients (83%) with incident severe asthma transitioned to milder states after 10 years. Low SES and comorbidity at disease onset led to worse long-term prognosis. 2) Across both individual- and neighborhood-levels, there was evidence that low-SES asthma patients and/or their care providers did not follow guideline-based asthma care and subsequently incurred substantially greater excess costs of asthma. 3) Excess costs in patients with asthma were $1187/year (95%CI $1130–$1243) overall, with comorbidity-attributable costs five times higher than asthma-attributable costs, all of which greatly increased with age. 4) Changes in asthma control had a greater effect on disease-specific (AQ5D) than generic (EQ5D) utilities, whereas changes in comorbidity burden had a larger impact on EQ5D than AQ5D utilities. **Conclusions:** With several novel methodology techniques, this thesis provided evidence for the first-time on the long-term trajectory and burden of asthma. Projection of cost and effectiveness of decisions and policies in

asthma care requires a robust understanding of the natural history of asthma, effect of risk factors on this trajectory, and estimates of costs and health-related quality of life associated with asthma. This thesis provides new evidence on all such parameters. These findings have direct relevance to estimating cost-effectiveness of health technologies in asthma and can result in more informed decision-making in health policy and clinical practice.

Preface

This thesis comprises four research essays initiated and developed by Wenjia Chen. The author defined the research questions, designed the studies, developed the analytical frameworks, cleaned and prepared data, performed statistical analyses and wrote the four thesis-based manuscripts. The co-authors, including several members of Wenjia Chen's thesis committee, provided methodological guidance and clinical judgment throughout the thesis work and were involved in the acquisition of data.

Manuscripts related to this thesis:

(1) Wenjia Chen, Carlo A Marra, Larry D Lynd, J Mark FitzGerald, Zafar Zafari, Mohsen Sadatsafavi. The natural history of severe asthma and influences of early risk factors: a population based study. Thorax. 2016 Mar;71(3):267-75. [published, related to Chapter 2]

(2) Wenjia Chen, Larry D Lynd, J Mark FitzGerald, Mohsen Sadatsafavi. Influences of Socioeconomic Status on Costs of Asthma under Universal Health Coverage. Med Care. 2016 Aug;54(8):789-95. [published, related to Chapter 3]

(3) Wenjia Chen, Larry D Lynd, J Mark FitzGerald, Carlo A Marra, Robert Balshaw, Teresa To, Mohsen Sadatsafavi. Excess medical costs of asthma and the role of comorbidity. Eur Respir J. 2016. In press. [published, related to Chapter 4]

(4) Wenjia Chen, Larry D Lynd, J Mark FitzGerald, Carlo A Marra, Roxanne Rousseau, Mohsen Sadatsafavi. The added effect of comorbidity on health-related quality of life in patients with asthma. Qual Life Res. 2015 Oct;24(10):2507-17. [published, related to Chapter 5]

Ethics approvals were acquired for the data used in this thesis

(1) For retrieving and using data from the administrative health databases of British Columbia (BC) Ministry of Health: University of British Columbia Human Ethics Certificate H08-01287

(2) For collecting and analyzing data of the Economic Burden of Asthma (EBA) study: University of British Columbia Human Ethics Board H10-01542

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95% CI, 95% Confidence Interval;

AQLQ, Asthma Quality of Life Questionnaire;

BC, British Columbia

CCI, Charlson Comorbidity Index

COPD, Chronic Obstructive Pulmonary Disease;

EPR3, National Asthma Education and Prevention Program, Third Expert Panel;

EQ5D, EuroQol-5D;

GEE, Generalized Estimating Equations;

GINA, the Global Initiative for Asthma

GLM, Generalized Linear Model

HRQoL, Health-related Quality of Life;

HUI-3, Health Utility Index Mark 3;

ICD, International Classification of Diseases;

ICS, inhaled corticosteroids;

LABA, long-acting β2-agonists;

LTRA, leukotriene receptor antagonists;

OLS, Ordinal least Square;

OR, odds ratio;

PDC, proportion of days covered;

PY, person-year;

QALYs, Quality-adjusted Life Years

SABA, short-acting β2-agonists;

SCQ, Self-administered Comorbidity Questionnaire;

SD, standard deviation;

SES, socioeconomic status;

SF-3, Short Form 6D;

US, United States.

Acknowledgements

I would like to express my sincere gratitude to my supervisors, Prof. Larry Lynd and Prof. Mohsen Sadatsafavi, for their generous supports of my Ph.D research. They guided me to establish the overall direction of the research, encouraged and advised me to pursue in-depth investigations and seek for innovative methodologies, provided me with thoughtful insights into the research questions, designs and findings, and supported me in every way to stay focused to achieve my goal.

I offer my sincere gratitude to the rest of my thesis committee: Prof. Carlo Marra, Prof. Mark FitzGerald, and Dr. Robert Balshaw, for their insightful comments, encouragement, clinical and statistical inputs, as well as mentorship which ultimately helped me broaden my research into a variety of different research questions and methods yet keep the objectives coherent and synergistic. Special thanks to Prof. Carlo Marra, as my former supervisor, for helping me start my Ph.D study in the University of British Columbia and providing guidance toward shaping this thesis during the first two years of my candidature.

I thank my fellow colleagues, especially Dr. Hamid Tavakoli, Natalie McCormick, and Dr. Zafar Zafari, for the stimulating discussions, great team works, intuitive suggestions as well as all the friendship I have had in the past four years.

Last but not least, special thanks are owed to my husband and son, parents and parent-in-laws, for their love, patience, understanding and support which allowed me to dedicate most of the time on this thesis. Without their wholeheartedly support I would not have been able to finish this thesis.

Dedication

To my beloved late grandparents.

Chapter 1: Introduction

1.1 Asthma pathophysiology

Asthma is a common chronic disease of the airways. Patients with asthma frequently experience recurrent, reversible symptoms of coughing, wheezing, shortness of breath, tightness of the chest and various degrees of airflow obstruction.[1,2] The underlying disease process is characterized by airway inflammation and airway hyperresponsivenes.[3] Depending on the extent and interaction of these features, clinical manifestation, disease severity and the responsiveness to treatments vary across patients and over time.[4]

Phenotypically, asthma is often categorized, based on the overall disease trajectory, into intermittent, persistent, and severe asthma. However, regardless of these phenotypes, airway inflammation plays a consistent central role in the pathophysiology of asthma.[5] The process of airway inflammation involves interaction of multiple cell types and cellular elements within the airways, such as mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells.[6] This process results in inflammation and airway limitation (obstruction), which eventually lead to recurrent episodes of wheezing, shortness of breath, and coughing in susceptible individuals.[6]

In acute exacerbations of asthma, the airway quickly narrows in response to exposure to a variety of stimuli, including allergens, irritants, aspirin and other nonsteroidal anti-inflammatory drugs, stress and others, which subsequently interferes with airflow.[6] With the persistence of asthma and progression of inflammation, airflow can be further restricted by other factors such as edema and mucus hypersecretion.[6] Additionally, the airway response to stimuli can become

exaggerated – referred to as airway hyperresponsiveness – with ongoing allergen exposure. While several components of such pathophysiology are reversible, for a subset of asthma patients, permanent alterations can occur in the airway structure.[7] This process, termed as airway remodeling, usually leads to worsened airflow obstruction and airway responsiveness, and makes the patient less responsive to therapy.

The terms "severe asthma", or "difficult-to-treat asthma", generally refer to patients who are treatment-resistant and/or require high-intensity treatment despite optimization of standard care and elimination of environmental allergens.[3] Sometimes it also describes patients whose process of asthma management is difficult because of external reasons such as poor adherence, comorbidities, ongoing exposure to environmental risk factors, who may in fact have uncontrolled asthma.[3] Thus, severe asthma is often defined as asthma with frequent and severe manifestations which do not respond to, or only respond to, high-dose therapy of anti-inflammatory and other controller medications.[8] These characteristics make severe asthma a frustrating disease to care for and with subjects prone to severe exacerbations.

1.2 Asthma epidemiology

As one of the most prevalent chronic diseases worldwide, asthma affects roughly 300 million people, with the prevalence increasing by 50% every decade.[9] In particular, severe asthma affects approximately 5% to 10% of the asthma population.[10] The prevalence of asthma varies across the world, with higher prevalence among English-speaking countries than Asia-Pacific, Indian Subcontinent and Eastern Europe.[11,12] Asthma is also more prevalent in childhood as compared to adulthood.[9] Globally, approximately 14.0% of children and 8.6% of young

adults (18 to 45 years of age) experience asthma symptoms.[9] In Canada, about 15.6% of children and 7.9% of adolescents and young adults suffer from asthma.[13,14] In older age groups (over 45 years of age), a large proportion of patients present with features of both asthma and chronic obstructive pulmonary disease (COPD).[15] This group of patients is described as having asthma – COPD overlap syndrome (ACOS). Thus, it is more difficult to distinguish between asthma, COPD and ACOS in older patients[15] and there are fewer studies on asthma prevalence in this age group.[9] Additionally the prevalence of asthma varies by gender. In childhood, boys have a higher risk of asthma or wheezing compared to girls.[16] In adolescence and adulthood, asthma becomes more prevalent in females than males.[16,17] As of 2014, asthma is prevalent in approximately 9.2% of female and 7.0% of male Canadians.[18]

1.3 Asthma control, severity and natural history

1.3.1 Asthma control

A primary goal of modern asthma management is to achieve and maintain optimal control of asthma over time.[1,2,4] Asthma control is defined by the extent to which the clinical manifestations of asthma are completely controlled or reduced by treatment.[2–4] As consistently described in international guidelines[2] and particularly emphasized in the National Asthma Education and Prevention Program, Third Expert Panel (EPR3),[4] asthma control should be assessed in two domains: current impairment (frequency and intensity of current symptoms and functional limitations) and future risk (risk of asthma exacerbations, progressive lung function decline, adverse drug effects). Earlier guidelines predominately focused on optimally controlled asthma, defined as eliminated or minimized symptoms with minimal or no need for use of rescue inhaled short-acting β_2-agonists (SABA), no night-time or early morning symptoms, no life

disruptions, and minimal airway obstruction.[19] Since 2006, the Global Initiative for Asthma (GINA) guidelines formalized the classification of asthma control based on asthma symptoms, exacerbations and other risk factors for future poor outcomes, and lung function measures.[2] In the 2015 GINA guidelines, the symptomatic control of asthma is categorized into 3 levels: "Well controlled", where within the past 4 weeks, the patient has asthma symptoms and reliever use no more than twice per week, no night waking, no activity limitation due to asthma; "partly controlled" where one or two of these individual features are present within the past 4 weeks; and "uncontrolled" where any three or four of these are present within the past 4 weeks (Table 1.1).[2]

Asthma control can be achieved in the majority of patients with guideline-based treatments,[2] whereby anti-inflammatory drugs are used to reverse the process of airway inflammation.[20,21] The recommended first-line controller therapy for patients with persistent asthma symptoms is inhaled corticosteroids (ICS).[1,2] In addition to the optimization of inhaled corticosteroids and other controller medications, guideline-based treatment also emphasizes that SABA, which temporarily relieves airflow obstruction but do not control the inflammation, should be used only as rescue medication for the quick relief of asthma symptoms.[2]

Table 1.1 2015 GINA criteria for asthma symptom control.[2]

In the past 4 weeks, has the patient had:			Well controlled	Partly controlled	Uncontrolled
Daytime symptoms more than twice/week?	Yes	No	None of these	1-2 of these	3-4 of these
Any night waking due to asthma?	Yes	No			
Reliever needed for more than twice/week?	Yes	No			
Any activity limitation due to asthma	Yes	No			

1.3.2 Asthma severity

Asthma severity refers to the activity of the underlying disease pre-treatment, as indicated by symptoms and lung function metrics at initial presentation of asthma, before a standardized approach to therapy.[4] Recently, the EPR3[4] and GINA[2] guidelines suggested a dual definition of asthma severity. For clinical practice, these guidelines recommend that severity be defined based on clinical features off-treatment. [22] In the real world, however, such a definition has important limitations because many patients already receive certain forms of therapy at the time of initial assessment.[23] In addition, Cockcroft and Swystun also argue that clinical metrics such as symptoms and lung function, measured at a patient's untreated state, can as well be indicators for suboptimal control instead of reflecting the true severity.[19] For use in population-based evaluations, Taylor and colleagues recommend asthma severity be assessed as the lowest intensity of treatment required to maintain control after optimal therapy has been established.[3] This is of particular relevance to studies based on health administrative data, an important source of evidence and population-based information on the real-world utilization of health services and technologies. A variety of algorithms have been developed for the classification of asthma severity using health administrative data, but most are focused solely on treatment intensity without considering whether optimal treatment has been established to minimize the risk of asthma exacerbations.[22,24,25] Using dispensed medications and medical services records, in 2007 Firoozi and colleagues developed a database index of severity based on definitions in the Canadian Asthma Consensus Guideline.[26,27] Once the treatment has been initiated, this algorithm classified severity into mild, moderate and severe based on the intensity of ICS and other controller medications (indicating the level of medication intensity to control current impairment), in combination with markers of asthma-related adverse events such as the use of

SABA and presence of moderate-to-severe exacerbations ,.[23,26,27] This algorithm has been validated against lung function measures. In addition, the levels of severity measured from these resource-use records were found to correlate well with the risk of asthma-related hospitalisations and fatal exacerbations.[27,28]

In a traditional approach for chronic diseases, treatment decisions are made depending on whether initial treatment effectively controls the disease process and clinical manifestations.[3] However, the situation is more complex in asthma management because disease course is heterogeneous, characterized by varied signs and symptoms across different individuals and within the same individual over time.[3,4,29] The clinical manifestations of asthma vary quickly in response to changes in environmental exposures, treatment adherence and the responsiveness to treatment.[4] Even when patients achieve optimal control of their asthma symptoms, asthma severity can vary over time.[4] In line with this concept, the 2015 GINA guideline recommends a stepwise approach to asthma treatment: first initiate regular daily controller treatment as soon as the diagnosis of asthma; then adjust asthma treatment on a regular basis in a continuous cycle of assessing diagnosis, asthma control and adherence; and adjust treatment.[2] The management process is closely related both to asthma control and also asthma severity, each of which varies over time.

Of note, the definition of asthma severity should be distinguished from asthma control, with the former emphasizing on the intensity of treatment required to maintain good control of asthma.[19] This concept is particularly relevant to severe asthma in the real-world asthma management. Although severe asthma only affects a small proportion of the asthma population, it contributes disproportionately to the overall morbidity, mortality and health-related resource

uses in asthma.[10] However, even in the case of severe asthma, the underlying disease process may change in intensity over time, either intrinsically or in response to external factors. Therefore, effective management of severe asthma involves regular assessment of asthma severity in patients who initially developed severe asthma, with down-titration of treatment when possible to establish minimally effective treatment that maintains good control.[2]

1.3.3 Natural history of asthma

The natural history of asthma refers to the clinical course of asthma over time, with variations such as remission or increase in severity.[6] Like other chronic diseases, the natural history of asthma begins with a prodromal stage in which people are susceptible of developing asthma but do not have the disease yet. After initial onset in response to certain triggers, asthma can progress persistently, or the prognosis can be improved with disease-modifying strategies.[30] Thus, a clinically relevant question is which risk factors and treatment strategies applied early in the course of the disease improve long-term asthma prognosis and prevent airway remodelling.

Asthma is a heterogeneous condition and it is not yet clear whether it represents a single disease entity or is a common label of several disease phenotypes.[30] Differences in the genetic, developmental and environmental factors that predispose to asthma can lead to variations in age of onset, disease severity and clinical course.[30] The influences of various risk factors on the long-term impairment of lung function have been investigated frequently.[31–33] However, changes in lung function are not always closely related to the clinical manifestation of asthma and its severity.[6] In fact, previous studies have found that longitudinal changes in lung function in asthma substantially varies between young children, older children, adolescents and adults, suggesting that variation in lung function is more likely to be associated with age than with

asthma symptoms.[4] Moreover, it is unclear whether and to what extent the progressive decline in lung function is clinically significant, or whether it is related to airway remodeling and permanent airflow obstruction.[4]

Despite the fact that asthma is generally reversible and milder cases can be effectively controlled, patients with severe asthma often suffer from poor outcomes that are not responsive to conventional therapies.[10] Several observational studies which focused on lung function metrics suggest that the pattern of lung function decline is different in people with severe versus non-severe asthma.[31–33] However, findings on lung function trajectories can hardly provide the much needed evidence on the real-life long-term trajectory of asthma, such as changes in the intensity of therapy over time and the risk of future exacerbations. Few studies have evaluated the long-term natural history of asthma in terms of clinically relevant outcomes. Ernst and colleagues used a large population-based cohort to examine changes in the intensity of drug therapy in people with asthma for a period of three continuous years.[28] Their findings suggested a non-progressive course of severe asthma, as patient's who initially received high-intensity asthma medications, indicating the presence of severe asthma, often had their treatment intensity wane over time. However, because patients were censored once changes in the intensity of their prescribed therapies suggested non-severe asthma, this study did not consider the possible subsequent events – especially relapse to severe asthma. To date, the long-term trajectory of asthma (in terms of dynamic transitions in asthma severity) remains largely unknown.

In the current literature, age is found to be a significant risk factor for the prognosis of asthma in general[28,34] whereas there are barely sex-related effects.[28,35] However, it is unclear whether age and sex affect severe asthma in the same way as they affect general asthma, nor do

we know whether the clinical course of severe asthma is also affected by other more directly modifiable risk factors. For instance, while socioeconomic status (SES) and asthma comorbidities are both associated with greater asthma severity and worse asthma control,[36–38] the extent of their influences on the long-term prognosis of severe asthma remains unclear.

1.4 Economic and humanistic burden of asthma

1.4.1 Economic burden of asthma

1.4.1.1 Direct and indirect costs of asthma and risk factors

The overall economic burden of a chronic disease includes both direct and indirect costs.[39] Direct costs refer to costs related to direct health care resource utilization, such as outpatient services, hospitalizations, emergency room visits, prescription medications, alternative treatment or medications, diagnostic procedures, ambulance and other transportations. Indirect costs refer to the disease-attributed loss in work productivity.[39] Productivity loss is generally divided into absenteeism (absent from work), "presenteeism" (present at work with insufficiency due to impairment), or loss of opportunities for work or education because of the disease.[39]

The economic burden of diseases are usually measured in terms of either excess costs or attributable costs.[39,40] Excess costs refer to the differences between the costs incurred by people with the disease versus those incurred by the general population who do not have the disease.[39] In this way, excess costs are able to capture the overall picture of disease costs by considering both costs of the disease and its related comorbid conditions. However, precise estimation of excess costs requires careful analysis that controls for the confounding and systematic differences between the diseased and comparison cohorts (such as age, sex, baseline comorbidity

status and so forth).[39] On the other hand, attributable costs refer to costs that can be directly attributed to the disease, for instance, costs of a hospitalization of which the disease is a major reason for admission.[39] Attributable costs are often estimated in a rather straightforward way by summing all costs linked with the diagnosis code of the disease. However, misclassification bias arises when the diagnostic codes associated with health records are incorrectly assigned or when the diagnosis itself is wrong.[39,40]

As a major chronic disease worldwide, asthma is responsible for tremendous economic burden. In the United States (US), the total excess costs to the society in people with asthma were estimated at $56 billion in 2007 (in 2009 US dollars), with 11% being direct costs.[41] In Europe, the asthma-attributable costs were estimated at €19.3 billion among Europeans aged from 15 to 64 years in 2011 (in 2011 Euros), of which 27% was direct costs.[42] In Canada, the asthma-attributable costs were estimated at $604 million per year in 1990.[43] Within direct costs, medications and inpatient care contributed the most in both excess and asthma-attributable costs. Prescribed medication for maintenance management is required for the majority of asthma patients. Asthma-attributable inpatient costs, including costs of emergency room visits, is related to adverse asthma outcomes such as exacerbations and indicates severe asthma or uncontrolled asthma. In the past, hospital costs were the largest component of the asthma-attributable costs. [10] However, with the advent of new guidelines aiming at improvement in asthma management and more expensive drugs over the past decade,[2] patterns of asthma-related resource use and costs have changed over time. Over a ten-year period in the US, hospital costs were the largest component of direct asthma-attributable costs in 1985 whereas medication became the largest one in 1994.[44] In a recent large-scale study of attributable costs, medications accounted for

68.2% of the total direct costs of asthma in British Columbia (BC), Canada, while hospital costs accounted for 16.0% of the costs.[45] Between 2002 and 2007, total medication costs attributable to asthma increased by 38.7%, whereas the attributable costs of hospitalizations decreased by 239.8%.[45] Another major component of direct costs is outpatient services provided in a physician's office (general practitioner's office or a specialty clinic) or by other health care providers in an outpatient setting.[10]

Both severe asthma and poor asthma control are associated with higher costs of asthma.[10] Attributable costs associated with a patient with severe asthma was estimated to be 1.3 to 3 times higher than those of a patient with moderate asthma and 1.7 to 12 times higher than that of mild asthma.[10] In a recent population-based study in BC, the annual attributable costs per patient for uncontrolled asthma were 2.2 times, 1.0 times and 2.8 times higher than that of controlled asthma in patients with mild, moderate, and severe asthma, respectively.[46] In addition, disability status, comorbid medical conditions, and demographic characteristics such as age and sex have also been found to be associated with the total costs of asthma.[10]

1.4.1.2 Socioeconomic gradient in the economic burden of asthma

Evidence is strong in support of the attainability of asthma control in the majority of the population with available and accessible treatments,[2] and in support of the link between controlled asthma and lower costs.[46] Together, these indicate that uncontrolled asthma represents a care gap and a preventable source of economic burden. As such, investigation factors which cause disparity in the economic burden of asthma can identify targets for improving patient care. One of the strongest and most consistent source of inequality in health is a person's SES.[47] The association between low SES and poor health and health outcomes has been well demonstrated,

including higher rates of disease-specific morbidity and mortality, poorer physiological indicators of health and worse psychological characteristics in adulthood.[48] SES is a complex, multidimensional construct which is commonly conceptualized as the standing or class of an individual or group in a society.[49] SES is often measured by indictors of prestige within society, such as education and occupation, or by indicators of resource use such as income and savings.[50] Numerous studies have found that low SES is associated with lack of access to good-quality health care, lack of knowledge on self-management, risk-promoting behaviors, presence of risk factors in work environments, and worse mental health.[51–55] Beyond this, SES also affects health at an aggregate-level through deprived living environment, supplies of healthy food and recreational facility, social capital, health care services and other factors in the neighborhood.[56]

Access to care is commonly perceived as a major pathway for social gradients in health.[57] In private health care settings such as US and Brazil, low-SES populations can barely afford expensive health insurance and good-quality health care.[58] Consequently, the disadvantaged populations end up using fewer routine medical check-ups and prevention screenings[58] but experience more expensive emergency room visits and hospitalizations.[59] Such patterns of health care indicate great unmet needs for good-quality health care. Theoretically, a single-payer, publicly administered health care system should be able to remove the economic barrier to good-quality health care and thus reduce these inequalities. Canada provides universal health care coverage of inpatient and outpatient services for all legal residents. BC in specific provides drug coverage for individuals receiving social assistance; since 2003, income-based drug coverage has been implemented for non-recipients of social resistance.[60] However, while universal health care tends to ameliorate the socioeconomic gap in mortality in Canada,[61] the corresponding gap in

self-perceived health has widened over time.[62] To what extent socioeconomic disparities exist within the domain of discrete medical conditions remains an understudied area. Given its ambulatory nature and tremendous economic burden,[10] asthma can serve as a good case study for the efficacy of an existing universal care system in mitigating the barriers to good-quality health care.

1.4.1.3 Comorbidity as a potential driver of the costs of asthma

Poor asthma control can be due to multiple causes, including undiagnosed asthma, under-treatment due to either a physician's under-assessment of disease severity or poor compliance with therapy, ongoing exposure to environmental triggers, severe asthma with unresponsive disease process, or various comorbid conditions that contribute to the treatment unresponsiveness.[38] In a large cohort study based on a Canadian population, asthma was associated with a significantly higher risk of all major chronic comorbidities except cancer.[63]Among others, rhinosinustis, gastro-oesophageal reflux disease, psychological disorders, respiratory infections and obstructive sleep apnoea were the most prevalent comorbidities in asthma patients.[38] In addition, adult patients with active asthma are up to 12 times more likely to develop COPD, a highly debilitating respiratory condition, than their counterparts without active asthma.[64] These comorbidities contribute to asthma severity, make asthma difficult to control, and also complicate its treatment regimen.[38]

Although the potentially substantial effect of comorbidities on the overall burden of asthma should not be ignored, few studies to date have investigated it. A recent study used administrative data to confirm that the rates of hospitalizations, emergency department visits, and the use of ambulatory care for major comorbid conditions are much higher in an asthma

population compared to a non-asthma population in Canada.[65] In another US-based administrative data analysis, hemiplegia, neurological disorders, psychosis, and acquired immune deficiency syndrome were the major components in the excess costs of the asthma cohort.[66] However, this study only estimated one-year costs (May 1997 to April 1998). There is a paucity of knowledge regarding how comorbidity-attributable health care costs changes over the course of asthma. It is likely that comorbidity-attributable costs in asthma patients would vary over the course of asthma, given the demonstrated impact of age on asthma costs and the potential influences of asthma itself on comorbidities.

1.4.2 Humanistic burden of asthma

1.4.2.1 Generic and disease-specific health-related quality of life

With advancements in medical technology and public health interventions that lead to better treatment and delayed mortality, public concerns about health have extended from saving lives to improving the quality of life.[67] Health-related quality of life (HRQoL), defined as an individual's satisfaction with domains of life that are affected by their health, is a multidimensional construct with physical, mental, and social domains.[68] In general, the domains of life include physical, social/role, psychological/emotional, cognitive functioning, symptoms for disease-specific HRQoL, health perceptions, and overall quality of life.[69] Focusing on HRQoL allows health agencies to address broader-scale public health issues with a diverse group of stakeholders around a common theme bridging boundaries between different disciplines and between medical, mental and social services.[67,70] HRQoL measurement helps determine the burden of diseases, provides new insights into the impact of risk factors, and identifies vulnerable populations (especially the elderly). It is also a central public health tool for

evaluation of the needs for health policies, such as guiding development plan and resource allocation decisions, and assessing the effectiveness of medical technologies and public health interventions.[67] Currently recommended asthma management strategies emphasize the improvement in HRQoL as an ultimate goal of asthma management.[2]

Utility instruments measure HRQoL and generate a single-index utility value, which integrates different domains of health and represents the health state by an index anchored between 0 for death and 1 for perfect health (with negative values being worse than death). The utility value for a particular health state can be integrated over the length of time in that state to calculate the quality-adjusted life years (QALYs), one of the two key metrics of cost-utility analysis.[71] The gold standard utility instruments, such as the standard gamble and the time-tradeoff are generally cumbersome to administer in clinical research or clinical care settings.[72,73] As a result, survey instruments have been developed to estimate HRQoL. These instruments are, in general, developed to be applicable to any health condition (referred to as generic HRQoL instruments) or to specific diseases of interest (disease-specific HRQoL).[69] Examples of the former include EuroQol-5D (EQ5D),[74–76] Health Utility Index Mark 3 (HUI-3)[77] and the Short Form 6D (SF-6D).[78] Examples of disease-specific HRQoL instruments for respiratory diseases include Asthma Quality of Life Questionnaire (AQLQ).[79] The responses of AQLQ can be converted to a preference-based utility value, namely AQ5D, though validated algorithms.[80] Generic and disease-specific utility instruments have their distinct advantages and disadvantages. Generic instrument allow cross-disease comparisons, but they might not have enough sensitivity to capture the subtle changes in quality of life that occurs due to changes in disease status. On the other hand, disease-specific measures are designed to be more capable of detecting minor

changes in disease status but do not allow comparison between changes in HRQoL for health technologies associated with different diseases.[65]

1.4.2.2 HRQoL and its determinants in patients with asthma

Asthma is associated with substantial humanistic burden.[81] As one would expect, both generic and asthma-specific HRQoL progressively decline with increased asthma severity.[82,83] Since current asthma guidelines have a primary focus on achieving asthma control, researchers have been interested in examining the impact of asthma control, the central component of asthma management, on HRQoL. Epidemiological studies from different countries consistently demonstrated a significant association between poor asthma control and worse HRQoL.[82,84–86] The ability of HRQoL instruments to distinguish between levels of asthma control and severity reflects the construct validity of these instruments. This ability significantly varies across different instruments, and the published results are generally inconsistent in terms of which instrument performs better in different contexts. For instance, Pickard and colleagues consider EQ5D a valid and reliable instrument for asthma studies.[87] However, McTaggart-Cowan and colleagues compared the validity of HRQoL instruments in asthma,[65] and found only AQLQ able to discriminate between adjacent levels of self-reported asthma control and severity while the generic preference-based instruments (including EQ5D) could, in general, only discriminate between the extreme levels. The responsiveness of AQLQ to changes in asthma severity and control has also been demonstrated in other studies.[83]

In addition to asthma itself, the presence of comorbidity affects HRQoL of asthma patients.[81,82,88,89] Compared to asthma patients with no other chronic disease, HRQoL is lower among those with one or more chronic diseases irrespective of the choice of HRQoL

instruments.[65] In particular, Wijnhoven and colleagues shows that the presence of comorbidity is associated with an increased risk of worsening asthma-specific HRQoL (OR 2.08; 95% CI).[89] When the entire constellation of asthma and its comorbid conditions are targeted for disease management, generic HRQL instruments might be of particular relevance as their scope is beyond that of asthma itself. The interaction between asthma control and severity, comorbid conditions, and generic and diseases-specific HRQL measures is yet to be explored.

1.5 Current knowledge gap that inspired this thesis

This thesis encompasses a coherent set of studies that together address several important knowledge gaps about the burden of asthma and its determinants.

Little is known about the natural course of severe asthma, despite the fact that this subgroup contributes disproportionately to the overall burden of the disease.[90] Whether severe asthma remains stable over time because of the disease phenotype or whether it improves over time is unclear. Understanding the course of severe asthma will improve evidence-based clinical practice and asthma research, especially cost-effectiveness analyses of health interventions, as such studies should properly simulate the longitudinal course of the disease, so that the impact of programs and interventions on this course can be evaluated. If severe asthma is observed to improve over time, researchers should modify assumptions regarding treatment intensity and asthma severity in the contemporary economic models. Also, this information will provide better evidence to determine the optimal treatment required to maintain control over time. I hypothesized that, given its "difficult-to-treat" nature, severe asthma will tend to persist over time, especially in patients with lower SES and poorer overall health.

Asthma imposes substantial economic burden on the individuals and the society both worldwide and in Canada,[9] despite the fact that the latter provides universal access to health care. Asthma can serve as a good case study for the efficacy of Canada's universal health care system, because it is particularly prevalent in the poor population, and it can be effectively controlled with guideline-based asthma management. A policy-relevant question is thus how well this universal health care system operate, to ensure guideline-based care and to reduce unnecessary social gradients in the economic burden of asthma. The answers will convey important policy implications for countries with universal health care or for those planning expanded coverage and will provide insights into potential areas for improvement in the management of asthma and possibly other chronic diseases. To date, few studies have sought to understand the extent and trend of socioeconomic disparities in direct costs of asthma as well as the use of asthma controller therapies and rescue medications in such a system. It is hypothesized that the socioeconomic disparities in the costs of asthma are minimal, and that guideline-based asthma care is provided to all asthma patients regardless of their SES.

Patients with asthma also frequently suffer from other comorbidities.[63] Asthma comorbidities like depression and digestive disorders are also associated with greater health care use, worse asthma control[65,81] and can potentially complicate overall treatment strategies. Thus, management of these comorbidities may have profound economic impacts on the burden of asthma. For this reason, valid and current evidence on the burden of asthma that considers both asthma and asthma-associated comorbidities will convey important implications for fully informed evidence-based policies and guidelines. However, currently available evidence on the health care costs of asthma focuses mainly on costs that are directly attributable to asthma (e.g.,

hospitalizations with asthma as the main diagnosis code)[10] whereas costs attributable to asthma comorbidities have received much less attention. In addition, with most studies focusing on cross-sectional designs,[10] we know very little about how health care costs changes over time. I hypothesized that the economic burden of asthma comorbidities is substantial and will increase with age.

Finally, asthma comorbidities also influence the HRQoL of asthma patients. However, quality of life studies in asthma are predominantly focused on asthma control,[82,84–86] and the few studies with a focus on the burden of asthma comorbidities often disregarded asthma control.[89,91,92] To date, the concurrent impacts of asthma and comorbidities in determining HRQoL remain unclear. In particular, few studies have evaluated the responsiveness of general and asthma-specific HRQoL instruments to the presence and extent of comorbid conditions in asthma when asthma control is considered. This is an important gap in evidence because interventions and strategies which aim at reducing the burden of asthma can vary in scope, ranging from active treatments targeted at reducing asthma symptoms to broader-scope approaches (e.g., smoking cessation, weight reduction) that improve both asthma outcomes and overall health. Establishing the cost-effectiveness profiles of these different interventions requires accurate quantification of their impacts on HRQoL, which should be evaluated and compared using valid instruments that are sensitive to the targeted changes of outcomes. I hypothesized that both asthma control and comorbidities significantly influence the quality of life of asthma patients, but that generic and asthma-specific HRQoL instruments differentially capture their respective impacts.

1.6 Content of the thesis

Using population-based samples of people with asthma in BC, Canada, this thesis aimed to address the above-mentioned gaps. A unifying theme of this thesis was to identify modifiable risk factors and to estimate their independent effects on the long-term asthma outcomes.

Chapter 1, the current chapter, provided background knowledge on the longitudinal trajectory of asthma and asthma outcomes along with a review of the literature. The research components, starting from Chapter 2, consist of four studies. First, to understand the natural history of severe asthma and risk factors in the early course of the disease, a novel statistical framework was constructed and applied to estimate transitions between states of asthma severity following incident episode of severe asthma. This rigorous approach allowed for the quantification of a ten-year trajectory of severe asthma and the exploration of the independent effects of risk factors at diagnosis on the later disease trajectory.

In Chapter 3, I investigated inequalities in the economic burden of asthma in a universal health care setting, which included the extent and trend of SES effects on the long-term excess costs in people with moderate to severe asthma. This is done using 16 years population-based administrative data of BC. The social gradients in the differential utilization of asthma medications were also evaluated. SES-related inequalities were estimated using a novel regression model that appropriately adjusted for censored data, zero-inflated costs, and high costs prior to death.

Using the same data source as in Chapters 2 and 3, I assessed the excess economic burden of asthma and the respective shares of burden attributable to asthma and comorbidities in

Chapter 4. This study adopted a matched cohort design and provided key estimates of the long-term health care demands in patients with asthma. I further examined the trend of these burdens across age groups and over the clinical course of asthma.

Finally, based on the data of a random cohort of adult asthma patients in BC, in Chapter 5 I characterized the changes in HRQoL over one year, and examined the validity of generic and disease-specific instruments in terms of their ability to simultaneously discriminate against changes in asthma control and comorbidity status. This work had a specific focus on the empirical measurement properties of generic and disease-specific instruments and their applicability to assessing HRQoL outcomes and comparing intervention options in asthma.

The discussion, Chapter 6, connects the four studies and provides a comprehensive picture of the longitudinal profiles of disease progression, health care costs and quality of life in people with asthma. I discuss clinical and policy implications of the findings of the studies presented in this dissertation. In particular, I discuss how the findings can significantly impact the design of studies evaluating the long-term costs, effectiveness, and cost-effectiveness of health technologies for the prevention and management of asthma.

Chapter 2: The natural history of severe asthma and influences of risk factors in the early disease course*

2.1 Synopsis

Severe asthma is characterized by frequent and severe symptoms and exacerbations which do not respond to, or only poorly respond to, high dose of anti-inflammatory and other controller medications.[8] Affecting only 5% to 10% of the asthma population, severe asthma remains a frustrating disease to care for and prone to severe exacerbations; as such, patients with severe asthma contribute disproportionately high to the overall morbidity and costs of asthma.[10]

Little is known about the clinical course of severe asthma and its risk factors. Previous longitudinal studies of the natural history of severe asthma drew samples from specialty clinics and were focused primarily on lung function.[31–33] While lung function decline likely indicates more severe asthma, its clinical relevance in terms of asthma outcomes is not established.[6] Physiological measures can hardly provide much needed evidence on the real-life outcomes of asthma such as risk of exacerbations over time. For population-based evaluations, asthma severity can be assessed by the intensity of treatment after a standardized approach to therapy.[23,26] Levels of severity can be calculated based on the amount of medications required to maintain acceptable control, in combination with the markers of asthma-related adverse events, in health administrative data[27]. The levels of severity measured from these resource use records

* A version of this chapter has been published:

Chen W, Marra CA, Lynd LD, FitzGerald JM, Zafari Z, Sadatsafavi M. The natural history of severe asthma and influences of early risk factors: a population-based cohort study. Thorax. 2016 Mar;71(3):267-75.

has been found to correlate well with lung function measures, risk of asthma exacerbations resulting in hospitalizations and death.[27,28]

In a prior longitudinal study based on claims data, the majority of patients with initially aggressive treatment intensity, indicating severe asthma, were found to use less medications over time.[28] However, this study used survival analysis as the main statistical approach, which censored patients at the first instance of not having indicators of severe asthma. Thus, this study did not follow the severe patients to assess the relapse of severe asthma. In addition, this study only explored the effects of age and sex over a three-year period of observation. We still know little about the long-term trajectory of severe asthma, whether these patients quickly or slowly transitioned back to severe states, or whether they mitigated to even milder asthma. In addition, it is yet to be studied whether other factors such as asthma treatments, comorbiditites, or socioeconomic status can influence the later course of severe asthma.

The current knowledge gap has triggered my interest to examine the long-term natural history of severe asthma and identify potentially modifiable risk factors early in the course of severe asthma. In this chapter, I have developed and fitted a transition (Markov) model, which utilizes all available longitudinal data to estimate the dynamic transitions across severity states and the influences of various risk factors at initial presentation of severe asthma. Using a special causal inference approach, I further projected a ten-year disease trajectory of severe asthma and quantified the effects of early risk factors on the disease trajectory.

2.2 Methods

2.2.1 Data source

A provincial health insurance program provides universal health care coverage to all legal residents of BC, Canada, one of Canada's larger provinces which represents 13% of the Canadian population (4.4 million as of 2011).[93] The administrative demands of this program have resulted in the creation of centralized databases that capture resource use records for all legal residents, regardless of their third-party insurance coverage or any co-payment. I had access to registration files,[94] vital statistics,[95] Discharge Abstract Databases (capturing all instances of hospitalization),[96] Medical Services Plan (capturing outpatient services records)[97] and PharmaNET (capturing all medications dispensed outside of a hospital setting).[98] Previous analyses have shown low prevalence of missing data, under-reporting, and misclassification in these databases.[99,100] All databases are linked at the individual level with unique but anonymous identifiers and access permission was granted by the BC Ministry of Health. All inferences, opinions, and conclusions drawn in this research are those of the authors, and do not reflect the opinions or policies of the Data Steward(s). The study period was from January 1, 1997 to December 31, 2012.

2.2.2 Study sample

Using a validated case definition,[45,101] patients with asthma between 14 and 55 years of age were identified from the BC health administrative data between January 1, 1997 and December 31, 2012. This definition was based on meeting at least one of the following three criteria in any 12-month window within the study period: one or more asthma-related hospitalizations (codes of the International Classification of Diseases, 9th edition (ICD-9): 493.x, 10th edition (ICD-10): J45,

J46); two or more physician visits with diagnostic ICD codes of asthma; or filling three or more prescriptions for asthma-related medications such as ICS (see Appendix A for the detailed medication list).

From this initial cohort, this study identified patients with a new onset of severe asthma by including those who met a validated definition of severe asthma in any calendar year after at least 2 years of being classified as having non-severe asthma or not having any asthma (see Section 2.2.3, *classification of asthma severity*). The index year was defined as the first calendar year in which the patient was identified as having severe asthma. Of note, patients in the final sample did not have to be diagnosed with asthma before the new onset of severe asthma, because the first date in a 12-month window when they met the asthma case definition could be the same date they were identified as having severe asthma. All included patients were followed until death, last date of registration with the program, or the end of available data (December 31st, 2012), whichever came first. The unit of observation was the patient-year. For each patient-year of data, I assessed the level of severity as well as whether the patient died during that year. To reliably evaluate severity, patient-years were purposefully removed if the patient was registered with the provincial health insurance program for fewer than 300 days, (except in the year in which they died).

2.2.3 Classification of asthma severity

Using a validated algorithm,[27] from the index year onward, every calendar year for each patient was categorized into 3 severity states (mild, moderate, or severe) based on a combination of variables representing the intensity of controller therapy, use of rescue medications, and markers of moderate-to-severe exacerbations (i.e., a filled prescription for oral corticosteroids, an

emergency department visit and/or hospital admission for asthma). This algorithm has been developed using Canadian databases and validated against the Canadian Asthma Consensus Guidelines[26]. In each calendar year, severe asthma was defined by either an average daily dose of at least 1000 µg/day of ICS in beclomethasone-chlorofluorocarbon equivalent, or more than 10 doses per week of SABA on average while still experiencing moderate-to-severe exacerbations. On the other hand, mild asthma corresponded to low ICS doses (0-250 µg/day if receiving additional controller therapy, otherwise 0-500 µg/day) while, at the same time, no occurrence of moderate-to-severe exacerbation nor SABA uses for more than three doses per week. If a patient-year did not meet the criteria for either severe or mild asthma, it was classified as moderate asthma. In addition, a fourth state representing death was assigned to all patient-years in which death occurred.

2.2.4 Assessment of risk factors and covariates

This study considered age, sex, SES, comorbidity, and proportion of days (PDC) covered by controller medications as risk factors that could potentially affect the course of severe asthma. All these variables were ascertained in the index year, i.e., the first calendar year when a patient was identified as having severe asthma. SES was categorised into 3 levels (low, middle, high) based on the median neighbourhood household income quintile, with low SES defined as being in the lowest 2 quintiles, middle SES as the 3rd quintile and high SES as the highest 2 quintiles. Neighbourhood household income is frequently used to study the effects of SES on health and health care expenditures and correlates well with individual-level SES.[102] Comorbidity was assessed using the Charlson comorbidity index (CCI), excluding asthma from the score).[103] Based on commonly used cut-off points in previous studies,[104] comorbidity burden was classified

into 4 ordinal levels: level 1, CCI score =0; level 2, score=1; level 3, score=2; level 4, score≥3, with higher levels corresponding to greater comorbidity. PDC was calculated as the proportion of days covered by any of the following commonly prescribed controller medications in the index year: systemic corticosteroids, ICS, or ICS/long acting β2 agonists or leukotriene receptor antagonists (Appendix A). PDC was classified in to 3 levels: level 1, PDC<50%; level 2, 50%≤ PDC<80%; level 3, PDC≥80%.[105]

2.2.5 Statistical analysis

2.2.5.1 Overview

A Markov model was developed to model the longitudinal pattern of transitions among severity states over time. A similar approach has been used to model changes in asthma control over time.[106,107] In particular, this model estimated severity in the future year based on severity history (current and past two years), covariates of interest (age, sex, SES, comorbidity and PDC, all measured in the index year), and the calendar year of the index year.

The dependent variable, asthma severity in the future year, was treated as ordinal because it has 4 possible states (mild, moderate, severe, and death). The effects of each independent variable were estimated in terms of the three odds ratios (OR) for transition to a given severity state in the next year: transition to moderate/severe/death versus transition to mild, to severe/death versus to mild/moderate, and to death versus to mild/moderate/severe. For each independent variable, these three ORs could be the same or different, depending on whether it satisfied the proportional odds assumption, i.e., where the independent variable has the same effect across different thresholds of the dependent variable. This partial proportional odds model was fitted using a

Generalized Linear Model (GLM), with Generalized Estimating Equations (GEE) to account for the correlations among the longitudinal observations of patient-years within individuals[108].

To assess model fit, I compared the observed versus predicted population-averaged trajectories of severity after incident severe asthma over the entire study period. The disease trajectory was defined as the probability of being in a particular severity state at a given follow-up year over the next ten years. Once the model fit was assured, I estimated the trajectories of severe asthma as a function of a given baseline risk factor, while adjusting for all other risk factors.

All statistical analyses were performed using SAS (Version 9.3, SAS Institute Inc, Carey, North Carolina, United States). A two-tailed p-value of less than 0.05 was used to determine statistical significance.

2.2.5.2 Theoretical model

Let $Y_{i,t}$ be asthma severity or death in year t from the beginning of follow-up for the ith patient in the cohort, where i=1, 2 ,…, n and t=-2,-1, 0 ,1,…, n_i . $Y_{i,t}$ is classified in to 4 possible states: mild ($Y_{i,t}$ =0), moderate ($Y_{i,t}$ =1), severe ($Y_{i,t}$ =2) and death ($Y_{i,t}$ =3). The negative time indices indicate the years prior to the index year.

The reason for including asthma history in the model was to capture the auto-correlated nature of asthma progression (future severity depends on the realized past history of severity), thus enabling valid projections of asthma trajectories. The full history at year t can be represented by $\mathbf{H_{i,t}}$={$Y_{i,-2}$, $Y_{i,-1}$, $Y_{i,0}$, $Y_{i,1}$ … , $Y_{i,t}$}). Because the vector representing asthma history grows with each year of follow-up, a naïve incorporation of asthma history in the regression analysis of this approach requires different regression models for each year of follow-up, with potentially

different regression coefficients, thus making the interpretation of the effect of early risk factors on the course of the disease difficult.

Instead, our approach was to create a regression model with the Markov (memory-less) property, which replaced the variable of full asthma history with a reduced history variable, $\mathbf{H^c_{i,t}}=\{Y_{i,t-c}, \ldots, Y_{i,t}\}$. In this model, future severity is forecasted by current severity and severity in a fixed past c years ($c<t$), rather than severity in the entire past t years. In this case, because $\mathbf{H^c_{i,t}}$ has similar size and structure for all years, one regression model could be fitted to the whole data. A key assumption of this Markov model requires that conditional on this reduced history, the future trajectory is independent of the rest of the history, i.e., $P(Y_{i,t+1}| \mathbf{H^c_{i,t}}) \perp\!\!\!\perp \mathbf{H_{i,t-c-1}}$.

In order to choose the appropriate years of severity history that satisfy this Markov property, I started estimating severity in the future year ($Y_{i,t+1}$) based on severity in the current year, i.e., c=0, $\mathbf{H^c_{i,t}}=\{Y_{i,t}\}$, and checked whether regression residuals were still correlated with history in the year before the tested history , i.e., $Y_{i,t-1}$. Once conditional independence was achieved, the corresponding history vector $\mathbf{H^c_{i,t}}$ would be chosen for the model. My results showed that conditional on severity history in the past three years, i.e., $\mathbf{H^c_{i,t}} =\{Y_{i,t-2}, Y_{i,t-1}, Y_{i,t}\}$, a patient with either mild or moderate asthma in the year preceding the past three years, i.e., $Y_{i,t-3}$, had a similar likelihood of transition to severe asthma in the future year. Therefore, I considered conditional independence as achieved when I included severity history in the past three years, i.e., c=2, $\mathbf{H^c_{i,t}} =\{Y_{i,t-2}, Y_{i,t-1}, Y_{i,t}\}$. The history vector $\mathbf{H^c_{i,t}}$ entered the model as three dummy-coded variables; no interaction terms further improved the fit.

Overall, the vector of regression coefficients for the *i*th individual, $\mathbf{Y}_{i,t-c}$, consisted of three years of asthma history, and $\mathbf{X}_i$, covariates vector including covariates of interest and the index year; and with the first element being 1 to capture the intercept. This ordinal logistic regression model calculates three probabilities, $Pr\left(Y_{i,t+1} > k|\mathbf{X}_i, \boldsymbol{H}_{\boldsymbol{i,t}}^{\boldsymbol{c}}\right)$, for severity threshold k=0, 1, 2:

Eq.(2.1): $logit\left[Pr\left(Y_{i,t+1} > k|\mathbf{X}_i, \boldsymbol{H}_{\boldsymbol{i,t}}^{\boldsymbol{c}}\right)\right] = \boldsymbol{\beta_k}.\mathbf{X}_i + \boldsymbol{\alpha}_{\boldsymbol{k}}^{\mathbf{c}}.\mathbf{Y}_{i,t-c}$, where c=0, 1, 2.

In Eq.(2.1), exponents of the $\boldsymbol{\alpha}_0$, $\boldsymbol{\alpha}_1$, $\boldsymbol{\alpha}_2$ and $\boldsymbol{\beta}_0$, $\boldsymbol{\beta}_1$, $\boldsymbol{\beta}_2$ vectors correspond to, respectively, the effects of covariates (ORs) on the odds of entering into moderate/severe/death versus into mild, into severe/death versus into mild/moderate, and into death versus into mild/moderate/severe in the future year. By default, this ordered logistic regression model requires included variables to satisfy the proportional odds assumption, i.e., $\beta_0=\beta_1=\beta_2$ or $\alpha_0=\alpha_1=\alpha_2$. However, here I created a partial proportional odds model to allow regression intercepts to be different for each severity threshold k when a variable violates the proportional odds assumption.

2.2.5.3 Fitting the partial proportional odds regression

Using a GLM with GEE, I fitted such a model following the approach proposed by Stokes 2000.[109] First, the dataset was expanded both vertically and horizontally into three identical datasets, with the regression equation expressed in terms of a dummy variable $P_{i,t+1}$ which represented the three severity thresholds of outcome variable $Y_{i,t+1}$. The translation from $Y_{i,t+1}$ to $P_{i,t+1}$ is given in Table 2.1.

Table 2.1 Translation from original dataset to the 3 augmented datasets.

Dataset	Severity Variable	Severity State				Intercept (severity threshold)	Z (intercept indicator)	Pred
Original	$Y_{i,t}$	0 (mild)	1 (moderate)	2 (severe)	3 (death)			
New: #1	$P_{i,t}$	0	1	1	1	moderate/severe/death vs. mild	0	P_0
New: #2		0	0	1	1	severe/death vs. moderate/mild	1	P_1
New: #3		0	0	0	1	death vs. severe/moderate/mild	2	P_2

Obs, observations; Pred, predicted value

These three new datasets were combined to form one augmented dataset, which was then analyzed using the logistic model with the severity threshold indicator, $P_{i,t+1}$, as the dependent variable. The regression equation is given in Eq.(2.2) below. Given the large sample size and because I used a robust variance in the GEE model, it was reasonable to assume the independence working correlation structure for the serial dependence within the individual.[110]

Eq.(2.2): $$logit\left[Pr\left(P_{i,t+1}\right)\right] = \beta_1.\mathrm{Y}_t + \beta_2.Z + \beta_3.(\mathrm{Y}_t \times Z) + \beta_4.\mathrm{Y}_{t-1} + \beta_5.(\mathrm{Y}_{t-1} \times Z) + \beta_6.\mathrm{Y}_{t-2} + \beta_7.(\mathrm{Y}_{t-2} \times Z) + \beta_8.Age + \beta_9.(Age \times Z) + \beta_{10}.Sex + \beta_{11}.(Sex \times Z) + \beta_{12}.SES + \beta_{13}.(SES \times Z) + \beta_{14}.CCI + \beta_{15}.(CCI \times Z) + \beta_{16}.PDC + \beta_{17}.(PDC \times Z) + \beta_{18}.Index\ Year$$

where the interaction term between an independent variable and the intercept indicator, Z, captured the different regression intercepts for each severity threshold k, for variables which violated the proportional odds assumption (e.g., severity history in the past three years, baseline age, sex, SES and comorbidity) . The indicator of index year was the only variable which satisfied the proportional odds assumption.

Predicted values P_0, P_1 and P_2 from the abovementioned logistic model showed, respectively, the probability of being moderate/severe/death versus being mild, being severe/death versus being moderate/mild, and death versus being severe/moderate/mild, in the future year. Based on these predictions, I was able to calculate the transition probability of future severity, i.e., Q_i, using the transition probability function given in Table 2.2.

Table 2.2 Transition probability of future severity.

$Y_{i,t+1}$(future severity)	Q_i (transition probability)
0 (mild)	$1 - P_1$
1 (moderate)	$P_2 - P_1$
2 (severe)	$P_3 - P_2$
3 (death)	P_3

2.2.5.4 Quantifying of the 10-year disease trajectory

The final Markov model consists of 28 states (mild/moderate/severe asthma within the current and past 2 years=27 states, plus a state representing death) (Appendix B). Thus, our model quantifies the trajectory of asthma severity by calculating a 28-state transition probability matrix representing the likelihood of being in a given severity state in the next year for a patient with a given characteristics and severity history in the current year and past 2 years.

For each individual, the predicted probabilities of transitioning between particular severity states given a modified set of covariates $\mathbf{X'}_i$, representing possibly counterfactual scenarios (e.g., high SES versus low SES in the index year), were calculated for all potential asthma severity histories. Such probabilities were used to evolve the multi-state Markov model of asthma for 10 years, with initial state values being the observed asthma history in the index year and pre-index

2 years, i.e., $\mathbf{H}^{c}_{i,0}=\{Y_{i,-2}, Y_{i,-1}, Y_{i,0}\}$. To plot the population-averaged trajectories of asthma severity, marginal state probabilities associated with the (possibly counterfactual) scenarios were calculated by averaging state probabilities for each individual across the population within each year of follow-up, setting other covariates of each individual to the observed values.[111]

2.3 Results

With the initial case definition of asthma, I identified 285,287 patients with age between 14 to 55 years. Among them, 13,467 (5%) patients with a new onset of severe asthma were included in the final sample. The average follow-up was 5.5 years (Figure 2.1). Table 2.3 presents the characteristics of this sample in the index year. The mean age was 37 years, and 55% were female. Approximately, 47% of the sample was classified as having low SES and 85% had at least 1 comorbid condition. The majority (76%) experienced at least one moderate-to-severe exacerbation in their index year, only 10% had PDC of 80% and above.

Figure 2.1 Proportions of patients remaining in the cohort over the follow-up period.

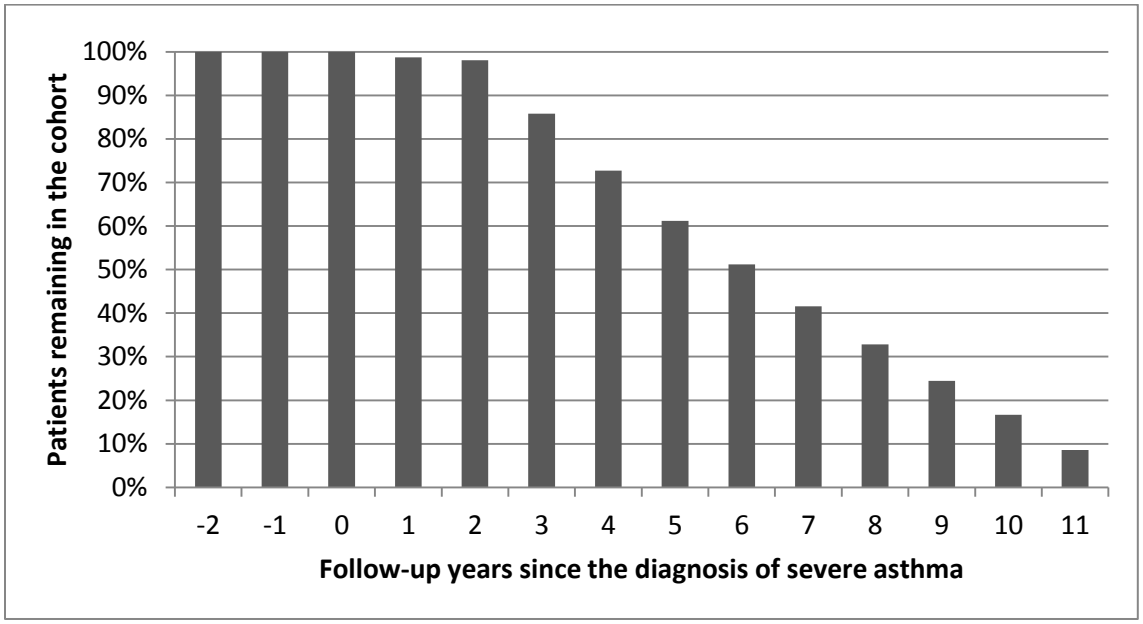


Table 2.3 Characteristics of study population in the index year.

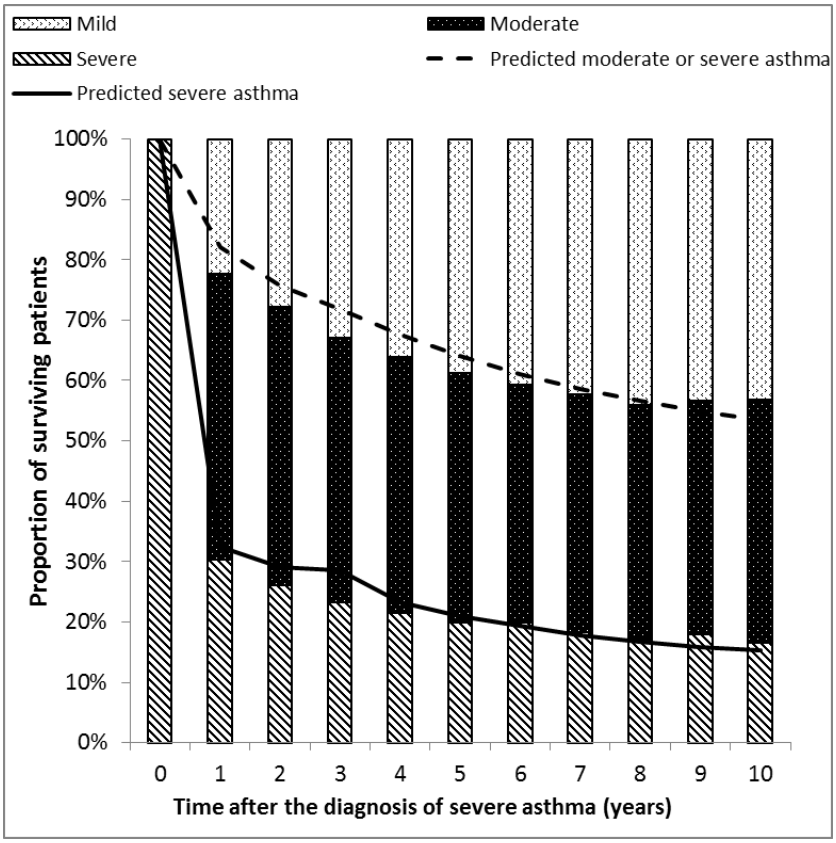
	Severe asthma patients (N=13,467)
Age, median (IQR)	36.8 (17.3)
Sex, N(%)	
Men	6,094 (45)
Women	7,373 (55)
SES, N(%)	
Low	6,326 (47)
Middle	2,649 (20)
High	4,492 (33)
Comorbidity, N(%)	
CCI=0	1,969 (15)
CCI=1	10,345 (77)
CCI=2	657 (5)
CCI≥3	496 (4)
Moderate-to-severe exacerbation, N(%)	
None	3,262 (24)
≥1 exacerbation	10,205 (76)
Proportion of days covered (PDC) by any asthma controller medications	
PDC < 50%	8,297 (62)
50% ≤PDC < 80%	3,777 (28)
PDC ≥ 80%	1,393 (10)
Severity in the past year, N (%)	
No asthma[a]	1,785 (13)
Mild	3,674 (27)
Moderate	8,008 (59)
Severity in the year before last year, N(%)	
No asthma[a]	3,262 (24)
Mild	4,192 (31)
Moderate	6,013 (45)

Abbreviations: N, number count; IQR, interquartile range.

[a] Prior to the index year, if a patient`s resource use records in a calendar year did not satisfy the case definition of asthma, this patient-year was defined as having no asthma. n the subsequent analysis, patient-years with no asthma prior to the index year were labelled as mild asthma.

While all patients were classified as having severe asthma in the index year, the proportions of patients remaining in the severe state consistently decreased rapidly over the first 4 years and almost plateaued afterwards (Figure 2.2). Ten years after the onset of severe asthma, 394 (3%) of individuals had died; of those remaining alive, 43%, 40% and 17% were categorised as having mild, moderate, and severe asthma, respectively (Figure 2.2). The predicted disease trajectory from the regression model aligned well with the observed trajectory of severe asthma (Figure 2.2).

Figure 2.2 Proportions of surviving patients with mild, moderate, and severe asthma over time.



Bars indicate observed frequencies in the study cohort; lines indicate predicted population-averaged distributions from the regression model.

Table 2.4 presents the full regression results in terms of associations between risk factors in the index year and severity history on the transitions between severity states in the future year. In general, greater severity in the preceding three years predicted greater severity in the future year. Severe asthma in the current year was also associated with a higher chance of death. Regarding risk factors at initial presentation of severe asthma, greater age was associated with a higher likelihood of being in more severe states in the future. Compared to women, men were less likely to transition to mild asthma, and were more likely to die; the chance of remaining in severe state was the same between women and men. Greater comorbidity in the index year was associated with higher likelihood of death or otherwise remaining in severe asthma; conversely, high SES was associated with lower likelihood of such transitions. Having greater PDC was positively associated with moderate and severe asthma in the future.

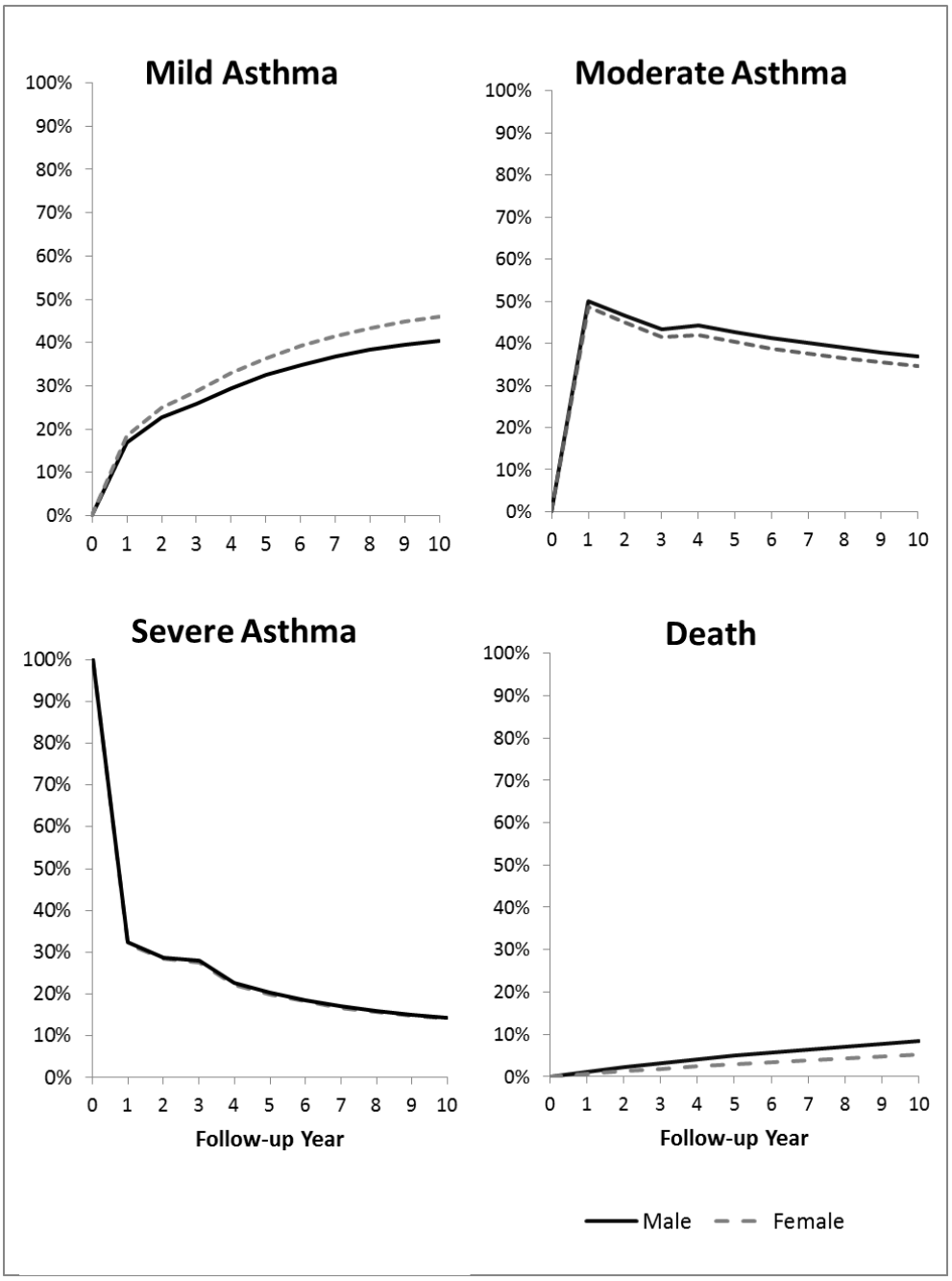
Figures 2.3-2.6 show how risk factors in the index year affected the ten-year trajectory of severe asthma. There were little sex-related differences in the long-term probability of leaving the severe state (Figure 2.3). Compared to high SES, low SES was associated with a 10% increase in patient-time with severe asthma over the next ten years (Figure 2.4). Higher comorbidity burden was associated with more patient-time in the severe state (CCI score =1 vs 0: 13%, CCI score $\geqslant$ 2 vs 0: 24% increase in person-time in severe asthma within ten years) (Figure 2.5). As compared with PDC of less than 50%, PDC between 50% and 80% and PDC of 80% or more were associated with 25% and 35% increases in person-time in severe asthma in the next 10 years, respectively (Figure 2.6). Being male, having low SES, and high comorbidity were associated with a higher ten-year risk of death, with the latter having the most prominent impact (Figure 2.3-2.6).

Table 2.4 Effects of independent variables on transitioning across severity states in the future year.

Independent variables	Severity state in any future year								
	Transition to moderate/severe/death vs. to mild			Transition to severe/death vs. to mild/moderate			Transition to death vs. to all other levels		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Severity in year T									
Mild	Reference			Reference			Reference		
Moderate	**6.86**	**(6.54–7.20)**	**<.0001**	**3.39**	**(3.12–3.68)**	**<.0001**	0.91	(0.67–1.23)	0.538
Severe	**14.95**	**(13.89–16.08)**	**<.0001**	**13.88**	**(12.74–15.12)**	**<.0001**	**1.78**	**(1.30–2.44)**	**0.000**
Severity in year T-1									
Mild	Reference			Reference			Reference		
Moderate	**2.55**	**(2.40–2.70)**	**<.0001**	**1.39**	**(1.27–1.51)**	**<.0001**	1.04	(0.73–1.50)	0.814
Severe	**2.79**	**(2.63–2.97)**	**<.0001**	**2.78**	**(2.55–3.02)**	**<.0001**	1.41	(1.00–1.98)	0.050
Severity in year T-2									
Mild	Reference			Reference			Reference		
Moderate	**1.81**	**(1.71–1.91)**	**<.0001**	**1.17**	**(1.09–1.25)**	**<.0001**	0.89	(0.66–1.20)	0.457
Severe	**1.75**	**(1.65–1.85)**	**<.0001**	**1.86**	**(1.73–2.00)**	**<.0001**	1.00	(0.74–1.35)	0.996
Age	**1.01**	**(1.01–1.01)**	**<.0001**	**1.01**	**(1.01–1.01)**	**<.0001**	**1.05**	**(1.04–1.06)**	**<.0001**
Sex									
Female	Reference			Reference			Reference		
Male	**1.12**	**(1.07–1.16)**	**<.0001**	1.01	(0.96–1.05)	0.812	**1.73**	**(1.41–2.12)**	**<.0001**
SES									
Low	Reference			Reference			Reference		
Middle	0.98	(0.93–1.04)	0.508	0.94	(0.89–1.00)	0.059	**0.59**	**(0.44–0.79)**	**0.000**
High	0.98	(0.94–1.03)	0.445	**0.88**	**(0.84–0.93)**	**<.0001**	**0.56**	**(0.44–0.72)**	**<.0001**
Comorbidity									
CCI score=0	Reference			Reference			Reference		
CCI score =1	1.05	(0.99–1.12)	0.101	**1.08**	**(1.01–1.16)**	**0.020**	**0.72**	**(0.54–0.96)**	**0.025**
CCI score =2	1.11	(0.99–1.24)	0.080	**1.32**	**(1.17–1.49)**	**<.0001**	**1.94**	**(1.32–2.87)**	**0.001**
CCI score ≥3	1.05	(0.92–1.19)	0.466	**1.48**	**(1.29–1.7)**	**<.0001**	**4.24**	**(2.96–6.09)**	**<.0001**
PDC of asthma controller medications									
PDC < 50%	Reference			Reference			Reference		
50% ≤PDC < 80%	**1.07**	**(1.02–1.12)**	**0.008**	**1.22**	**(1.16–1.29)**	**<.0001**	1.10	(0.88–1.39)	0.400
PDC ≥ 80%	**1.20**	**(1.11–1.3)**	**<.0001**	**1.26**	**(1.17–1.35)**	**<.0001**	0.87	(0.62–1.22)	0.414

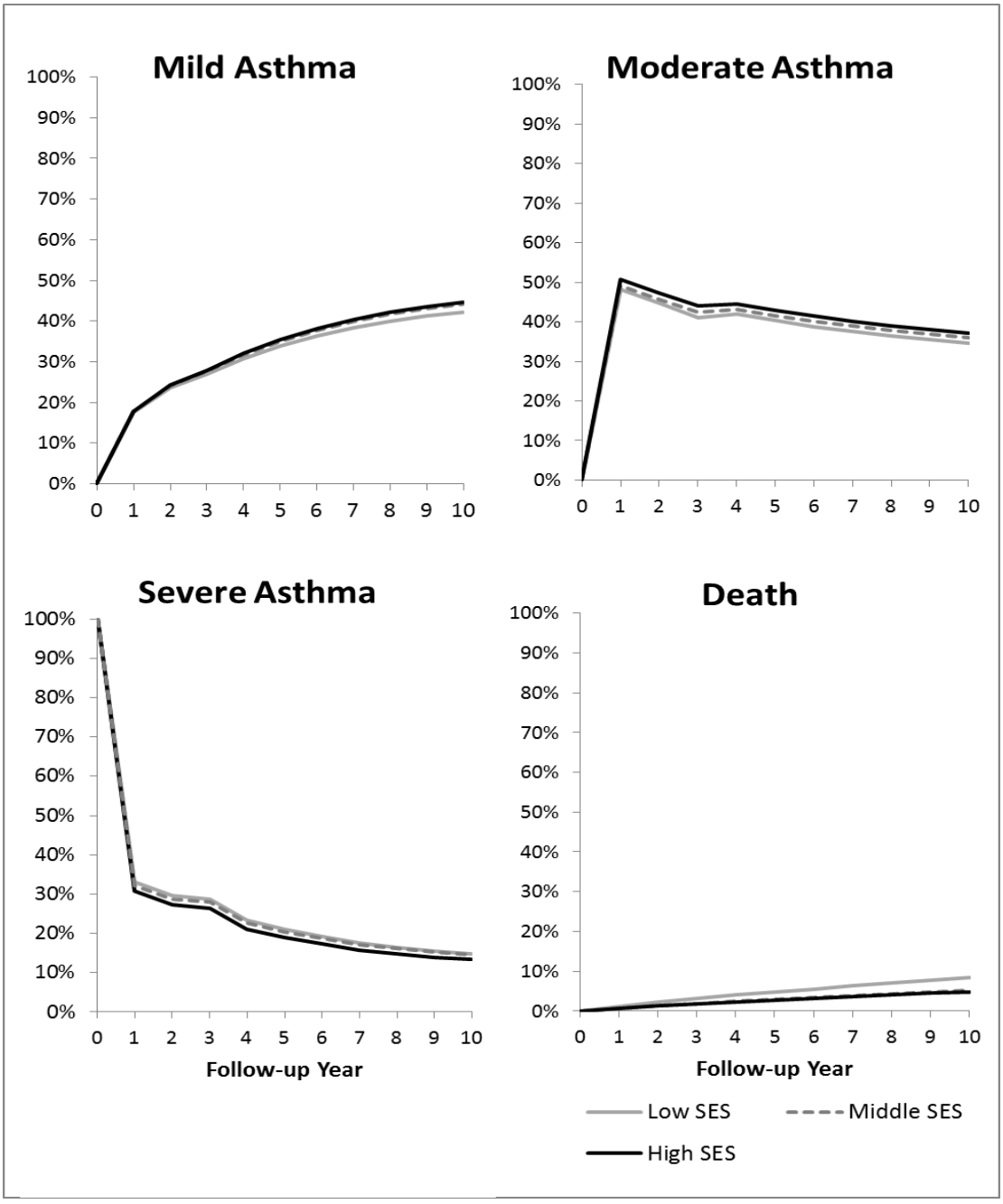
CI, confidence interval; OR, odds ratio; PDC, proportion of days covered with asthma controller medications. Bold text indicate statistical significance with a p-value of less than 0.05.

Figure 2.3The influence of sex on the long-term trajectory of severe asthma.



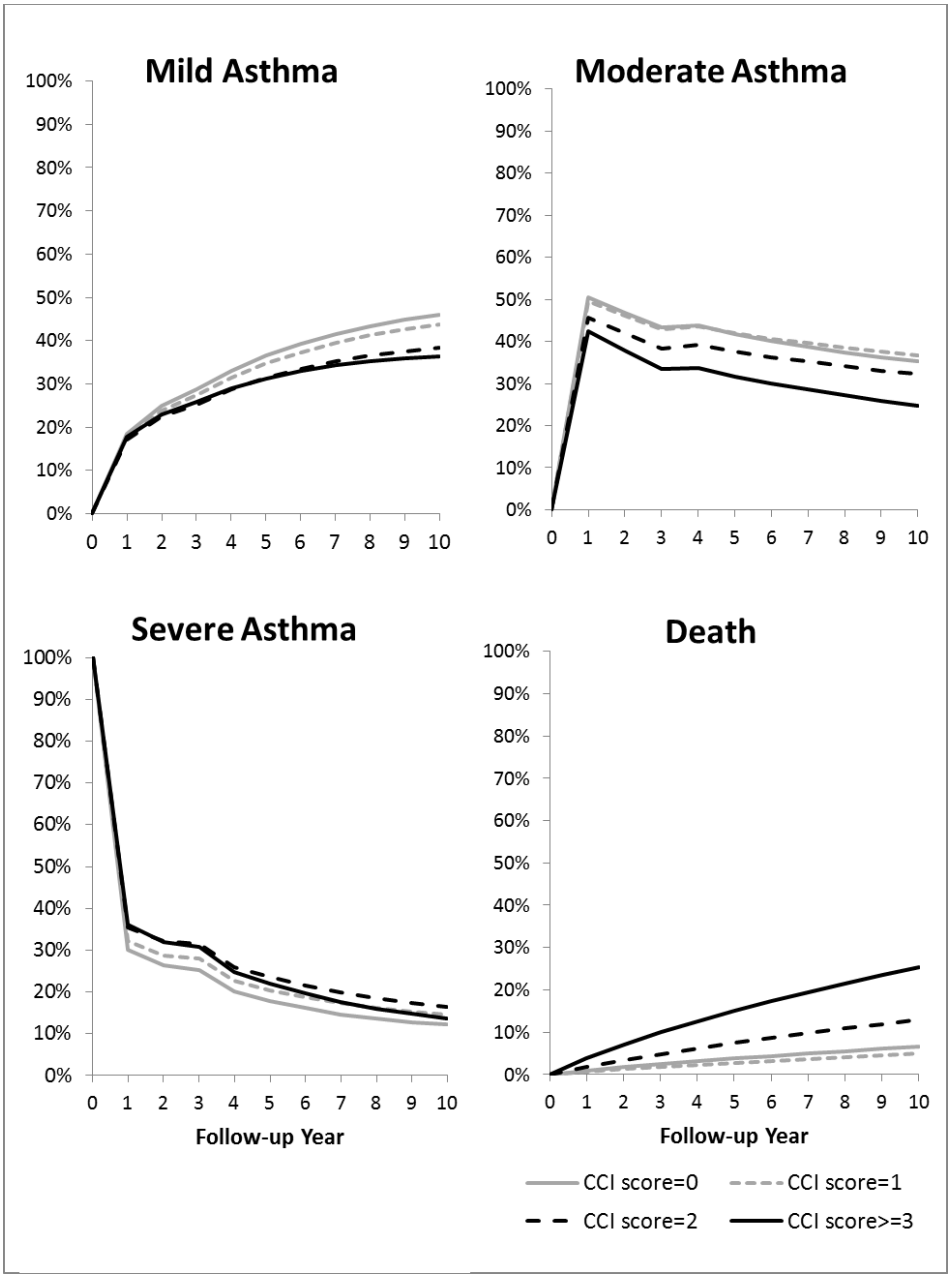
Plotted curves show adjusted probability of being in different severity states in the following ten years since following the index year, stratified by SES. Each graph corresponds to a different severity state: A) mild asthma, B) moderate asthma, C) severe asthma, D) death.

Figure 2.4 The influence of SES in the index year on the long-term trajectory of severe asthma.



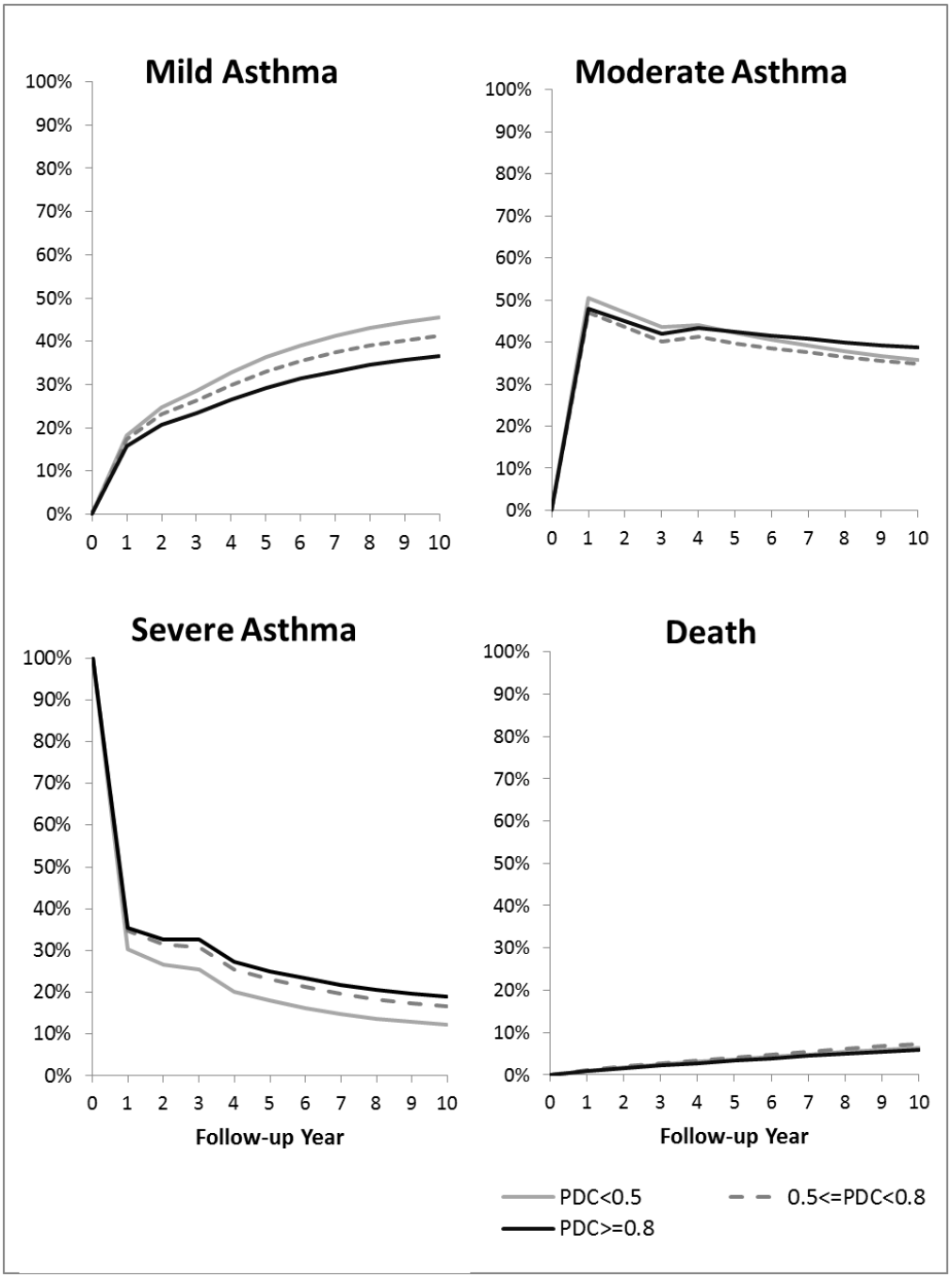
Plotted curves show adjusted probability of being in different severity states in the following ten years following since the index year, stratified by baseline SES. Each graph corresponds to a different severity state: A) mild asthma, B) moderate asthma, C) severe asthma, D) death.

Figure 2.5The influence of comorbidity in the index year on the long-term trajectory of severe asthma.



Plotted curves show adjusted probability of being in different severity states in the following ten years following since the index year, stratified by baseline SES. Each graph corresponds to a different severity state: A) mild asthma, B) moderate asthma, C) severe asthma, D) death.

Figure 2.6 The influence of PDC in the index year on the long-term trajectory of severe asthma.



Plotted curves show adjusted probability of being in different severity states in the following ten years since the index year, stratified by baseline SES. Each graph corresponds to a different severity state: A) mild asthma, B) moderate asthma, C) severe asthma, D) death.

2.4 Discussion

In this chapter I developed a multi-state Markov model to examine the natural history of severe asthma and to quantify the influences of risk factors at initial presentation of the disease on the subsequent course. The predicted and observed trajectories of severe asthma aligned well, suggesting that the model robustly fitted the data. It was found that the majority of patients who were categorised as severe in the first year, based on their asthma-related resource use patterns, changed to milder states in the subsequent years. High SES, less comorbidity burden, and PDC of less than 50% in the first year were independently associated with a better prognosis, whereas male and female patients appeared to have similar chances of remaining in the severe state over time.

In this cohort of patients with incident severe asthma, the probability of staying as severe considerably decreased in the first 4 years and then relatively stabilized. This is a typical manifestation of the 'regression to the mean' phenomenon, i.e., an inception cohort of severe asthma quickly transitioning to non-severe asthma after onset, indicates that incident new-onset of severe asthma may be a temporary state.[112] The extent of such phenomenon can be informative of the intrinsic variability of disease activity. My findings are consistent with the study by Ernst el. al. which showed a similar course for severe asthma, with 61% of the decrease in treatment intensity (interpreted as an indicator of non-severe asthma) occurring within the first five years.[28]

The long-term trajectory of severe asthma was subject to influences of risk factors that were known in the early course of the disease. This study found no significant sex-related difference in terms of 'outgrowing' severe asthma, which was consistent with prior studies.[28,35] On the other

hand, this is the first demonstration of the independent adverse impacts of low SES and high comorbidity on long-term course of severe asthma. The prognosis of severe asthma may be affected through multiple paths by SES. Although Canada provides universal health care and hence there are few SES-related barriers to access to and continuity of care,[113,114] low-SES is still associated with inappropriate medication management and poor asthma control.[115,116] Low SES is also associated with a combination of environmental and individual risk factors of asthma symptoms and exacerbations, including residential and occupational exposure to asthma triggers, tobacco smoke, and poor knowledge about asthma management.[47,53,54,117] Furthermore, both patients with low SES and high comorbidity have poorer overall health.[47,118] Meanwhile, many chronic conditions and their treatments affect the response to asthma treatments or increase difficulty in achieving asthma control.[38,119] All of these might adversely impact the remission of severe asthma.

On the other hand, the fact that patients with higher PDC of controller therapy in the first year may have been found to have a worse trajectory of severe asthma may be due to residual confounding by disease severity. This is because PDC is not only a measure of adherence but also an indicator of treatment intensity, whereas the latter plays a central role in the categorisation of asthma severity;[27] the residual variation in disease severity among individuals that are all categorised as having severe asthma might result in spurious correlation between treatment intensity and adverse future outcomes.

A major strength of this study is that it is based on a large population sample of patients in a well-defined geographic region, and thus, has a low risk of selection bias, leading to greater external validity and generalisability of our results. In addition, its robust and powerful statistical

approach, based on principles previously developed and validated in asthma,[111] enabled us to convert measures of relative effect such as odds ratio to more straightforward metrics representing the impact of early risk factors on disease trajectories. The methodology developed in this work can be used in many other contexts where long-term inference about the course of a chronic condition, and the influence of early risk factors, are of concern.

This study is also associated with some limitations. First, without access to objective measures such as lung function and patients' symptoms, the definition of severity from administrative data can only approximate clinically defined severe asthma, thus the findings of this study might not directly apply to the point of care. Second, as the algorithm I used to categorise levels of severity was partly based on the intensity of prescription drugs,[27] it is possible to misclassify patient-years into a milder state when patients were severe but less inclined to use asthma medications (or used alternative and complementary medicines), for instance, during pregnancy. On the other hand, it is also possible to misclassify milder patient-years into more severe states, because information regarding asthma medications in the administrative data represents the filled prescriptions but not necessarily the actual consumption of medications. However, the fact that severity classification was based not only on medication use but also on markers of exacerbations[27] reduced the chance that a severe patient-year was misclassified as a milder one. Thus, there was a greater likelihood of overestimating patient-years with severer than milder asthma. In this case, the misclassification bias in our study, if occurred, would probably lead to an underestimation of the proportion of patients who eventually transitioned to non-severe asthma. Finally, due to lack of access to external data, I could not externally validate the Markov transition cohort. Such external validation would add to the value of the presented framework

and enable prediction of future disease burden in other patient populations based on their risk factor profile.

2.5 Conclusions

A comprehensive statistical framework, based on a proposed Markov process of transitions between severity states, was developed and fitted using the data of the entire patient population of a well-defined geographic area, to understand the long-term trajectory of severe asthma. By correlating transitions between severity states with risk factors that were known at the initial presentation of the disease, the current model quantified the effects of early risk factors on the subsequent course of severe asthma. I found that incident severe asthma was generally benign because many patients transitioned to milder states over time. Predictors of poor long-term prognosis included low SES and high comorbidity, whereas there were little sex-related differences in the trajectory of being in the severe state. These results suggest that the long-term course of severe asthma can be potentially modified. Current asthma management guidelines set their primary emphasis on achieving and maintaining asthma control,[2] and the rationale behind such approach is the established relation between better asthma control and lower burden of asthma.[120] However, programs and interventions with the ability to modify the long-term trajectory of asthma would confer far-reaching benefits and affect the benefit-risk profile of asthma management guidelines.

The finding of the association between comorbidity and socioeconomic status and long-term asthma outcomes is novel and could have a major impact on both our understanding of the natural history of asthma and on the development of effective asthma management strategies.

The next two chapters examine the long-term direct medical costs of asthma and characterise the substantial influences of comorbidity and SES on the long-term burden of asthma.

Chapter 3: Socioeconomic status-related disparity in the economic burden of moderate-to-severe asthma under universal health care[1]

3.1 Synopsis

SES is an important determinant of health. The association between low SES and worse health has been observed in many settings.[121] Various causal theories have been proposed for the existence of such social gradient in health. For examples, low SES is associated with poor lifestyle habits (e.g., smoking, poor diet, physical inactivity), less routine medical check-ups or preventive screening, lack of proper access to health care due to unaffordability and non-financial reasons, and neighborhood disadvantages (e.g., deprived living environment, air pollution, lack of healthy food supply/recreational facilities, poor social capital, less health care services).[51–55] The poor health among the low SES population and their inadequate access to health care not only creates unnecessary economic burden but also poses ethical challenges to the society. Aiming at reducing socioeconomic inequities in health, several developed countries like Canada and France have established universal national health insurance to overcome economic barriers in access to health care.

In Canada, while universal health care tends to ameliorate the socioeconomic gap in mortality,[61] the corresponding gap in self-perceived health has widened over time,[62] probably related to long wait times and lack of universal coverage of medications. To date, it remains unclear whether and to what extent such universal health care systems have succeeded in reducing barriers to

[1] A version of this chapter has been published:
Chen W, Lynd LD, FitzGerald JM, Sadatsafavi M. Influences of Socioeconomic Status on Costs of Asthma Under Universal Health Coverage. Med Care. 2016 Aug;54(8):789-95.

good-quality health care. Asthma can be an appropriate case study for this purpose. Being a prevalent chronic disease that creates a tremendous economic burden,[9] asthma is seen as both a disease of affluence, as proposed by the hygiene hypothesis,[122] and a disease of poverty because of lack of proper access to care.[123,124] Although incurable, asthma can be effectively controlled with guideline-based treatments in most patients, i.e., optimization of ICSs and add-on controller medications. On the other hand, reliever medications like SABAs are to be used on an as-needed basis for symptomatic relief.[2]

Using the health administrative data of BC, in this chapter I examine the extent and trend of SES-related disparities in the excess costs of asthma over a sixteen-year period (1997 to 2012). As a secondary analysis, this chapter also explores the patterns of guideline-based asthma care, as indicated by the costs for asthma medications, as potential determinants of SES-related disparities in the excess costs of asthma.

3.2 Methods

3.2.1 Data source

Data were retrieved from the administrative health databases between January 1997 and March 2013 from of the BC Ministry of Health. These databases have been described in *Chapter 2, Section 2.2.1*. All inferences, opinions, and conclusions drawn in this study are those of the investigators, and do not reflect the opinions or policies of the Data Steward(s).

3.2.2 Study design and sample

This study used a retrospective matched cohort design, consisting of an asthma cohort and a non-asthma comparison cohort matched on age and sex.

Between January 1, 1997 and December 1, 2012, asthma patients who were registered in the BC health administrative data were initially identified using the same case definition that has been used in Chapter 3 and Chapter 4 (see Chapter 2 Methods for details).[45,101] To identify new patients with moderate-to-severe asthma, a validated severity algorithm,[27] developed specifically using Canadian administrative health data based on the Canadian Asthma Consensus Guidelines,[26] was applied to each complete twelve-month interval from the date the asthma case definition was satisfied. An *index date* was defined as the first day in the first twelve-month window in which the patient was identified as having moderate or severe asthma, after at least two years being registered in the BC health care plan. I restricted the sample to patients with moderate-to-severe asthma because the case definition for general asthma was based on asthma-related resource use in a restricted period of time (one year), which tended to overlook patients with mild asthma who consumed low amount of health care resources and might result in a 'dilution' bias (towards null).[125]

Each individual in this *asthma cohort* was matched to an individual from a general non-asthma population (those who did not satisfy the case definition of asthma) based on age (+/- 5 years) and sex to create a *comparison cohort*. Members of the comparison cohort were assigned the same index date as their matched asthma patients and should as well be registered in the administrative data for at least two years . In addition, the non-asthma cohort had to have at least

one physician visit, hospitalization or filled prescription within 12 months of the index date. This criterion was used to ensure both cohorts had at least one resource utilization record in this period given that for the asthma cohort, resource use is guaranteed due to the severity classification.

All participants were aged between 18 and 45 years on the index date, and had to have at least two years of data available before their index date to provide sufficient baseline data for confounder assessment. Follow-up time was from the index date to the earliest of death, termination of enrollment in the provincial health care services, or the end of study period.

3.2.3 Exposure variable

The main exposure variable, SES, was measured in the index year at both individual and neighborhood levels. Individual SES was determined by the receipt of social assistance in drug coverage records, which suggests personal financial hardship in basic needs.[60] Neighborhood SES was categorized into three levels (low, middle, high) based on the median neighborhood household income quintile in the index year, which was available in the administrative datasets. Low SES was defined as being in the lowest two quintiles, middle SES as the third quintile and high SES as the highest two quintiles. This variable correlates well with family household income and has been used in similar studies investigating SES-related disparities.[126–128] Given that individuals with missing SES values comprised less than 3% of the sample, I purposefully removed them from the regression analysis.

3.2.4 Cost variables

All-cause direct medical costs were reported in 2013 Canadian dollars ($) using the Consumer Price Index for inflation adjustment.[129] The overall costs were summed from three components, including the direct costs of inpatient visits, outpatient services and medication dispensations. All costs were estimated as total gross payments to a provider regardless of payer (health care system, third-party insurer, or out-of-pocket). Inpatient costs were calculated using the case mix methodology, which involves multiplying the record-level Resource Intensity Weight by the average costs of hospitalization in BC in the corresponding fiscal year to estimate the costs of each admission episode (Appendix C).[130] Outpatient costs and the costs of prescription medications were directly summed from the data. According to BC Ministry of Health, most ED services were paid as fee-for-services to physicians (thus being captured in the data), except for two tertiary care hospitals in Vancouver which pay salaries to physicians for ED coverage.[131] As for medication costs, in addition to the aggregate all-cause results, I also calculated the costs for a short, specific list of commonly dispensed asthma-related medications, divided into the two broad categories of controller and rescue medication. The former is used for long-term symptom control and reducing the risk of exacerbations, including ICS, long-acting beta agonists (LABA), combined ICS and LABA (ICS/LABA), leukotriene receptor antagonists (LTRA). The latter is used for immediate symptom relief and mainly included SABA (Appendix A).

3.2.5 Statistical analysis

All analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, NC, United States). A two-tailed p-value of less than 0.05 was used to determine statistical significance. Descriptive

statistics were compared using Chi-square tests for categorical variables and t-tests for continuous variables.

3.2.5.1 Overview of cost estimation

The primary outcome, excess direct medical costs of asthma ("excess costs"), was estimated as the adjusted difference in all-cause direct medical costs between an asthma patient and the matched individual. The main regression model was a survival-adjusted, multi-part GLM, which appropriately handles continuous death and censoring times, right-skewed, zero-inflated cost distributions and the accumulation of costs over time.[132] The coefficient for interaction between asthma status and SES indicators captured SES's effects on excess costs. The secular trend of SES-related disparities was estimated by including the calendar year of index date and its respective interactions with asthma status and SES in the regression model. We compared SES disparities in excess costs between two time periods: 1997 – 2004 and 2005 – 2012. The model was adjusted for age at the index date and baseline comorbidity status, including the number of hospitalizations and physician visits that were unrelated to asthma, and the CCI (excluding asthma from the score)[103] in the 12 months before the index date. The association between SES and cost of asthma-specific medications was examined using a separate two-part GLM model within the asthma cohort, with the same covariates as the main model.

3.2.5.2 Examining the effects of SES on excess costs of asthma

I used regression methods to assess the impact of SES, which was assessed in the index year, on excess costs over time. The primary outcome was the differences of excess costs across SES groups. The secondary outcome was the secular trend of such SES-related disparities. The unit of observation was accumulated direct medical costs over 4-month intervals within individuals, thus

an individual could contribute up to 45 observations (15 years). I used the survival-adjusted multi-part cost estimators proposed by Basu 2010.[132] Under the assumption of random censoring, the model comprised three parts as follows:

The first part was an accelerated failure time model with lognormal distribution, which estimated the probability of survival and hazard of death in any time interval.

The second part was a GEE model with normal distribution to estimate direct medical costs in time intervals where patients with death were observed.

The third part estimated direct medical costs in complete intervals where death was not observed, using a two-part GEE model with a logistic and an ordinary least square (OLS) component. The logistic component modeled the probability of zero costs during any interval as a function of covariates. Then, the OLS component modeled costs in the subset of individuals who incurred any costs during that interval.

For the primary outcome, covariates of interest included asthma status (asthma=1, no asthma=0), individual SES (iSES, as a dummy variable to indicate the receipt of social assistance), neighborhood SES (nSES, with reference being the low neighborhood SES group), and the first-order interactions between asthma status and each of the two SES measures, respectively. The effects of SES on excess costs of asthma were captured by the coefficients for the interaction terms between asthma status and SES measures. For the secondary outcome, I analyzed the first-order interactions between the index year with asthma status and the two SES measures, respectively. The three-way interaction terms were purposefully removed to improve the goodness-of-fit of the model. All three parts of the model was adjusted for age on the index date,

sex and aforementioned measures of comorbidity status. To capture changes in the accumulation of costs over time, I additionally included an indicator of numbers of time interval since the index date (k=1, 2,…,45) and its interactions with asthma status in the latter two parts of the model.

The regression functions of these three parts for the *k*th interval for an individual *i* are given as

Eq. 1: Survival in interval *k*

$$\log(t_k) = \beta_0 + \beta_1 Asthma_i + \beta_2 iSES_i + \beta_3 nSES_i + \beta_{12} iSES_i \times Asthma_i + \beta_{13} nSES_i \times Asthma_i + \beta_4 IndexYear_i + \beta_{14} Asthma_i \times IndexYear_i + \beta_5 Age_i + \beta_6 Gender_i + \beta_7 CCI_i + \beta_8 \# Hospitalizations_i + \beta_9 \# PhysicianVisits_i$$

Eq. 2: Costs in interval *k* when death occurred

$$Costs_{k,i} = \beta_0 + \beta_1 Asthma_i + \beta_2 iSES_i + \beta_3 nSES_i + \beta_{12} iSES_i \times Asthma_i + \beta_{13} nSES_i \times Asthma_i + \beta_4 IndexYear_i + \beta_{14} Asthma_i \times IndexYear_i + \beta_{24} iSES_i \times IndexYear_i + \beta_{24} nSES_i \times IndexYear_i + \beta_5 Interval_k + \beta_{15} Asthma_i \times Interval_k + \beta_6 Age_i + \beta_7 Gender_i + \beta_8 CCI_i + \beta_9 \# Hospitalizations_i + \beta_{10} \# PhysicianVisits_i$$

Eq. 3: Costs in interval *k* when death did not occur

Eq.*3.1: logistic component*

$$logit(\Pr[Costs_{k,i} = 0]) = Same\ as\ Eq.2.$$

Eq. *3.2: OLS component*

$$(Costs_{k,i} | Costs_{k,i} > 0) = Same\ as\ Eq.2.$$

where t_k is the survival time by the *k*th interval, $costs_{k,i}$ is the costs incurred at the *k*th interval for the *i*th subject, $interval_k$ is an indicator for the *k*th interval. The interaction terms between index year with asthma status and SES indicators were not included in Part 1 to avoid convergence problems.

As the final step, the estimated costs for the *k*th interval for subject *i* is a function of the three abovementioned estimators, given as

Eq. 4: Estimated overall costs for interval *k*

$$Estimated\ costs_{k,i} = \Pr\left(survival_{k\rightarrow k+1,i}\right) \times \{(1 - hazard[death]_{k,i}) \times Costs_{no\ death,k,i} + hazard[death]_{k,i} \times Costs_{death,k,i}\}$$

where $Pr(survival_{k->k+1,\,i})$ is the probability of survival through the *k*th interval for subject *i*, $hazard(death)_{k,i}$ is the hazard of death during the *k*th interval for subject *i*, $costs_{death,k,i}$ is the incurred costs for interval *k* for subject *i* if death is observed, whereas $costs_{no\ death,k,i}$ is the costs when death is not observed.

Of note, because the data only provided information on the year and month when death occurred, our cost estimator did not include a term that captures the duration between beginning of the interval and death, although this variable was included in the Basu 2010 model[132] to account for the stochastic nature of death (i.e., death occurs at different times in that interval). Because I used a GEE model in a population-based sample, cost estimates for intervals with death were derived by averaging the different time points that death occurred in that interval across the entire sample.

3.2.5.3 Examine the effects of SES on costs of asthma-related medications

Assuming the five common classes of asthma-related medications are rarely used in the comparison group, I estimated the direct costs of these medications within the asthma cohort only, with the impact of individual-level and neighborhood-level SES on costs assessed using a

two-part GEE model with a logistic and an ordinal least square (OLS) component. The regression function is given as below:

$$Costs\ of\ asthma\ drugs_{k,i} = \beta_0 + \beta_1 iSES_i + \beta_2 nSES_i + \beta_3 IndexYear_i + \beta_{13} iSES_i \times IndexYear_i + \beta_{23} nSES_i \times IndexYear_i + \beta_4 Interval_k + \beta_5 Age_i + \beta_6 Gender_i + \beta_7 CCI_i + \beta_8 \#\ Hospitalizations_i + \beta_9 \#\ PhysicianVisits_i$$

3.2.5.4 Quantifying adjusted excess costs across SES levels

Based on the regression results, I estimated the population-averaged, covariate-adjusted excess costs associated with low-, middle- and high-SES neighborhoods, as well as excess costs associated with receiving social assistance, respectively. The estimation was done in a counterfactual framework, in specific the G-formula calculations.[111]

I first estimated the 15-year direct costs for each participant under the two (potentially counterfactual) scenarios: whether the participant had asthma or not. Excess costs of asthma were calculated in accordance, being the difference of direct costs for each participant as if he/she had versus did not have asthma. Following it, I respectively calculated excess costs when each participant lived in low-, middle-, and high-SES neighborhoods (note that only one of these scenarios would be observed and the others would be counterfactual), or receive and did not receive social assistance (similarly, only one of these scenarios would be observed). Meanwhile, other covariates were set at their observed values. As the third step, at each level of neighborhood or individual SES, I respectively averaged the estimated excess costs across the entire sample. Finally, I divided the fifteen-year cumulative excess costs by 15 to derive the mean annual excess costs. Assuming all confounding covariates were controlled, such covariate-

adjusted differences can be interpreted as SES-attributed disparities.[111] Based on this framework, I further estimated the annual SES-related disparities in excess costs of asthma between the two periods of 1997-2004 and 2005-2012, as well as direct costs of the five above mentioned asthma-specific medications. Inference was obtained using parametric bootstrapping with 50 replications.

3.3 Results

The final matched sample included 29,283 asthma patients and an equal number of non-asthma individuals (both groups: mean age 34 years, 60% female). Table 3.1 describes the characteristics of the sample. At baseline, the asthma cohort had a lower proportion of subjects with high SES (35% vs. 41%, $p<0.001$) and more comorbidity burden (CCI: 0.24 vs. 0.07, $p<0.001$) as compared with the non-asthma cohort. On average, patients in the asthma and non-asthma cohorts incurred, respectively, $3,308 (95% CI: $3,277, $3,339) and $1,034 (95% CI: $1,022, $1,047), all-cause direct medical costs per year, with quantities remaining largely constant during the follow-up period. The adjusted excess costs of asthma were estimated at $1,211/person-year (PY) (95% CI, $645, $2192).). The regression-predicted cost trajectories aligned well with the observed cost trajectories (Figure 3.1).

Figure 3.1 Averaged cumulative all-cause direct medical costs, by asthma status.

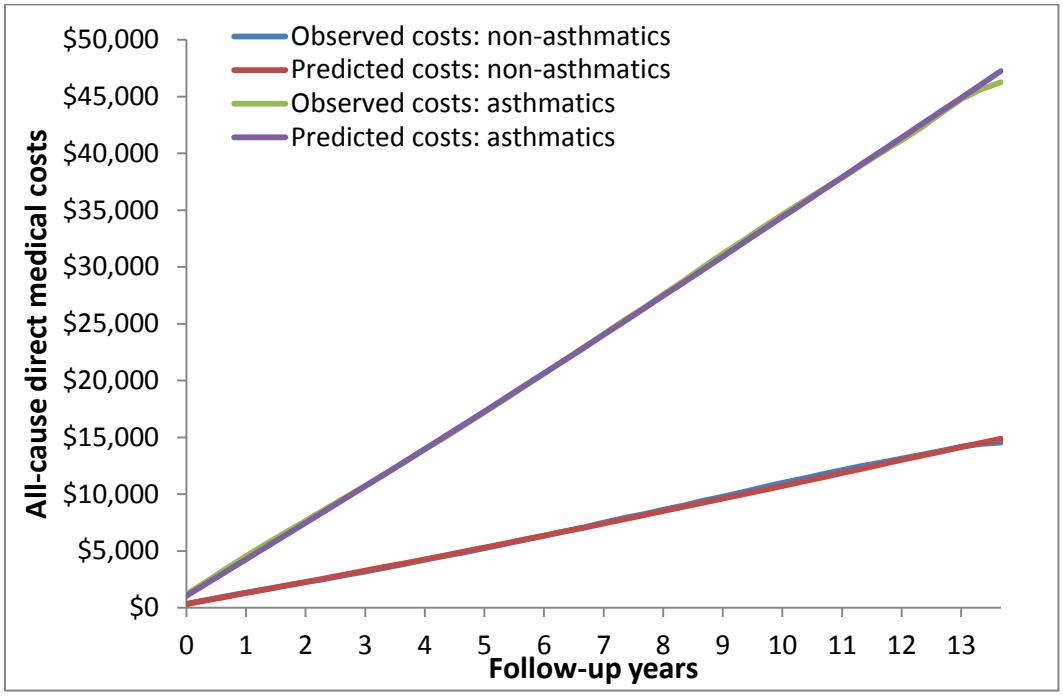


Table 3.1 Baseline characteristics of the study sample.

	Asthma Cohort (N=29,283)	Non-asthma Cohort (N=29,283)	P-value[a]
Age			
Mean (SD)	33.85 (8.06)	33.73 (7.83)	0.07
Male, n (%)	11,784 (40)	11,784 (40)	N/A (matching variable)
SES status, n (%)			
Low SES	13,396 (46)	11,444 (39)	<0.001
Middle SES	5,776 (20)	5,750 (20)	
High SES	10,111 (35)	12,089 (41)	
Variables measured in the 12 months prior to the index date			
Charlson Comorbidity Index[b]	0.24 (0.80)	0.07 (0.53)	<0.001
Number of non-asthma hospitalizations	0.24 (0.73)	0.11 (0.40)	<0.001
Number of non-asthma physician visits	14.96 (18.33)	7.35 (9.89)	<0.001
Number of non-asthma medications	23.72 (95.94)	5.76 (30.40)	<0.001
Number of asthma medications	2.05 (2.99)	0.03 (0.25)	<0.001

[a] P-values were obtained from Chi-square tests for categorical variables and t-tests for continuous variables.
[b] Charlson Comorbidity Index was modified to exclude asthma-related conditions.

Table 3.2 Annualized adjusted excess costs of moderate-to-severe asthma, by SES status.

	Excess Costs Per Patient-year ($) Adjusted difference between asthma and non-asthma individuals (95% Credible Interval)			
	Total	**Inpatient**	**Outpatient**	**Medications**
Individual-level SES				
Receiving social assistance	$1892.1 (1391.8─2831.7)	$543.1 (156.3─1286.2)	$333.8 (261.1─402.8)	$1015.2 (853.1─1188.3)
Other	$1186.4 (739.1─1962.7)	$303.3 (152.8─757.7)	$289.7 (208.3─370.6)	$593.4 (349.1─920.4)
Gap	**$705.7 (301.9─1013.7)**	$239.8 (-57.2─579.1)	**$44.1 (6.3─81.6)**	**$421.8 (243.3─554.6)**
Neighborhood-level SES				
Low	$1292.9 (887.1─2213.3)	$355.8 (163.4─1029.1)	$305.0 (222.0─393.9)	$649.3 (359.6─1172.8)
Middle	$1246.2 (798.4─2251.4)	$389.5 (148.2─1299.3)	$300.8 (215.6─389.8)	$656.3 (355.3─1157.8)
High	$1173.2 (761.7─2144.1)	$301.7 (148.6─910.5)	$282.8 (199.8─377.5)	$618.2 (339.2─1098.1)
Gap (low vs. high)	**$119.7 (18.2─168.1)**	$54.1 (-0.4─155)	**$22.2 (11.4─26.3)**	$31.1 (-44.8─110.8)

Bold characters indicate $p<0.05$.

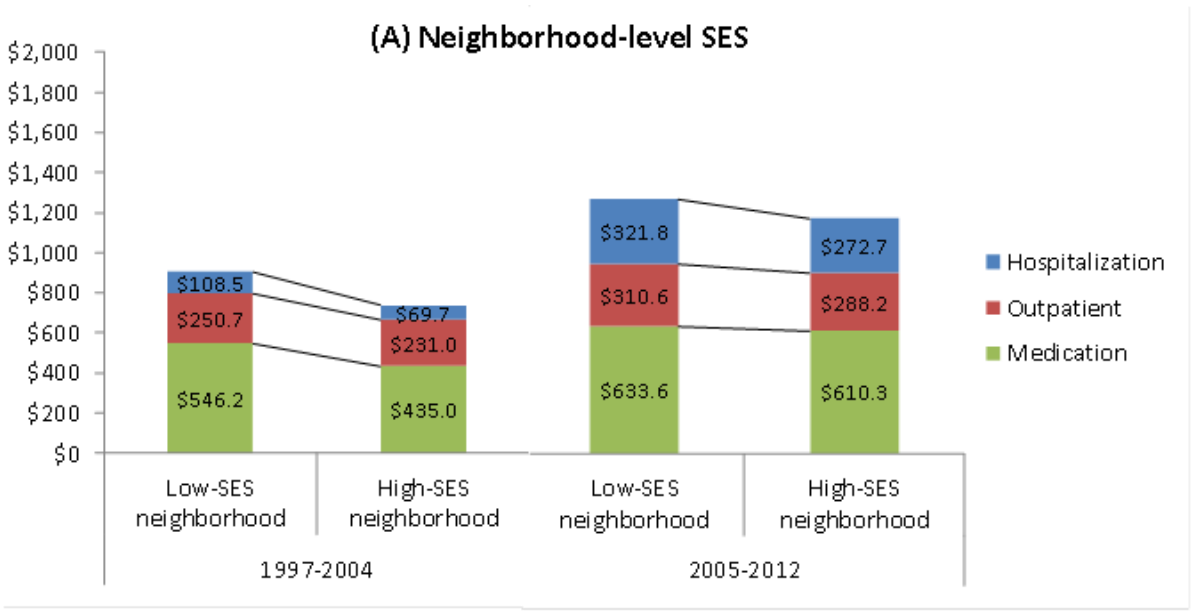
SES-related inequalities in the excess costs of asthma: Table 3.2 shows the effects of SES on excess costs. Compared to the rest of the sample, social assistance recipients incurred $705.7/PY(95% CI, $301.9–1013.7) higher expenses in total excess costs, $421.8/PY(95% CI, $243.3–554.6) and $44.1/PY(95% CI, $6.3–81.6) of which were excess medication and outpatient costs, respectively. The difference in excess inpatient costs was not statistically significant ($239/PY [95% CI, -$57.2–579.1]). Meanwhile, low neighborhood SES was also associated with higher excess costs compared to high neighborhood SES ($119.7/PY[95% CI, $18.2–168.1]). Within cost components, excess outpatient costs were higher in the low neighborhood SES ($22.2/PY[95% CI, $11.4–26.3]), there was also a tendency towards higher

excess hospitalization costs ($54.1/PY[95% CI, -$0.4–155.0]), but there were no differences in excess medication costs ($31.1/PY[95% CI, -$44.8–110.8]). Detailed results of regression analysis are provided in Appendix D.

Trend in SES-related inequalities: Figure 3.2 compares the trend of SES-gap between 1997-2004 and 2005-2012. The gap in excess costs in low versus high neighborhood SES was reduced by $30.2/PY (95% CI, -$60.7– -5.8) in the second period, with only medication costs showing a significantly reduced excess costs (reduction of $111.2[95% CI, $82.9–159.0]). On the other hand, disparities remained constant for the individual-level SES.

SES-related inequalities in the costs of asthma-specific medications: Social assistance recipients incurred lower costs of controller medications (-$45.3/PY[95% CI, -$84.0– -$9.7]) but higher costs of rescue medication ($16.5/PY[95% CI, $13.4–$19.9]) than those without social assistance. These disparities were consistent but smaller for neighborhood SES (low vs. high: -$15.0/PY[95% CI, -$35.2– -$0.6] for controller medications and $3.0/PY[95% CI, $1.7–$4.6] for rescue medications) (Figure 3.3). Across both individual and neighborhood measures, low-SES was consistently associated with higher costs of rescue medications in both 1997-2004 and 2005-2012, but with lower costs of controller medications only in 2005-2012 (Figure 3.4).

Figure 3.2 Annual mean excess costs of asthma in the periods of 1997-2004 and 2005-2012, by SES status.



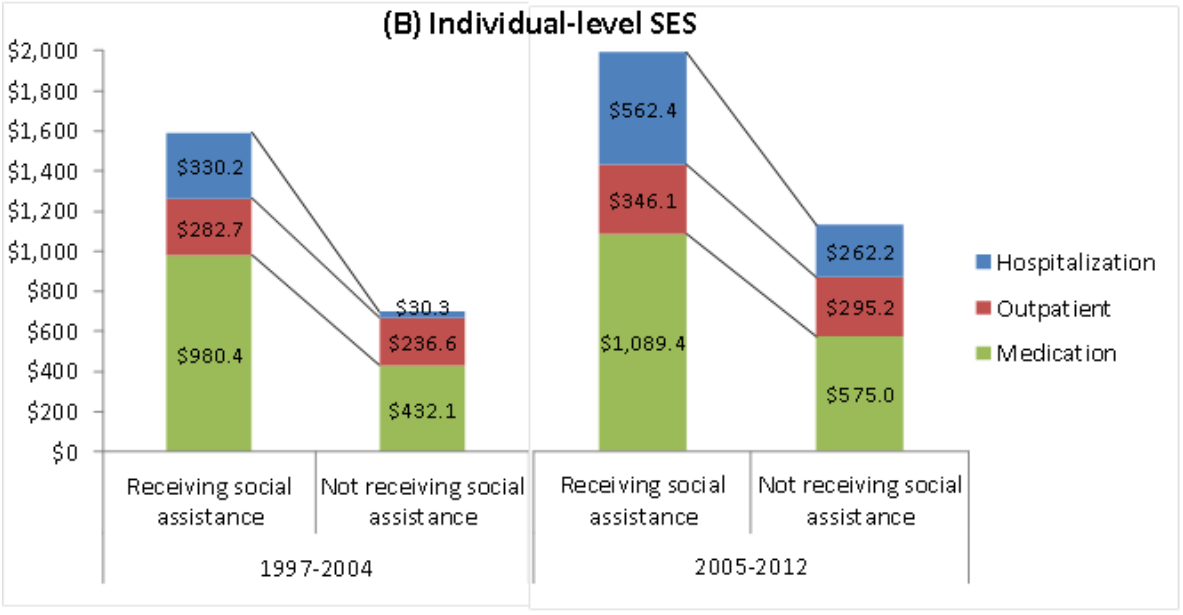


Figure 3.3 Annual mean costs of asthma-related medications, by SES status.

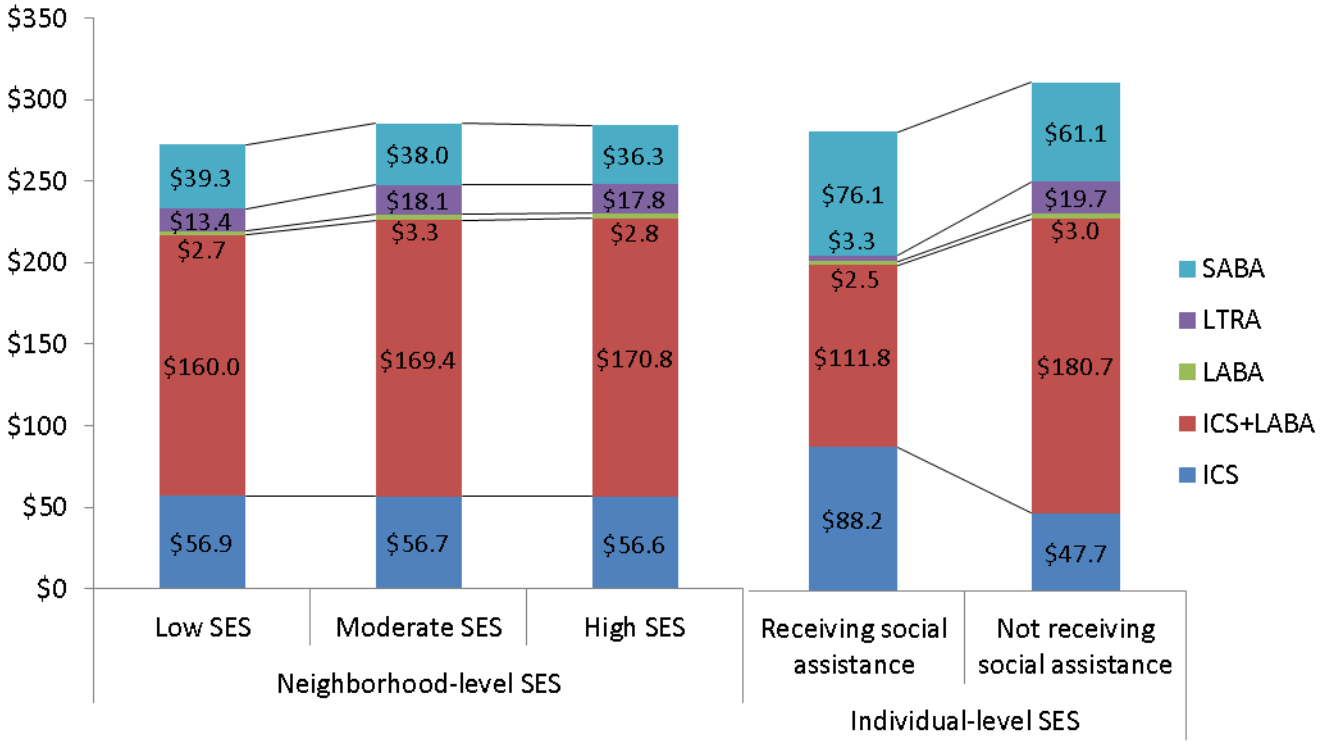
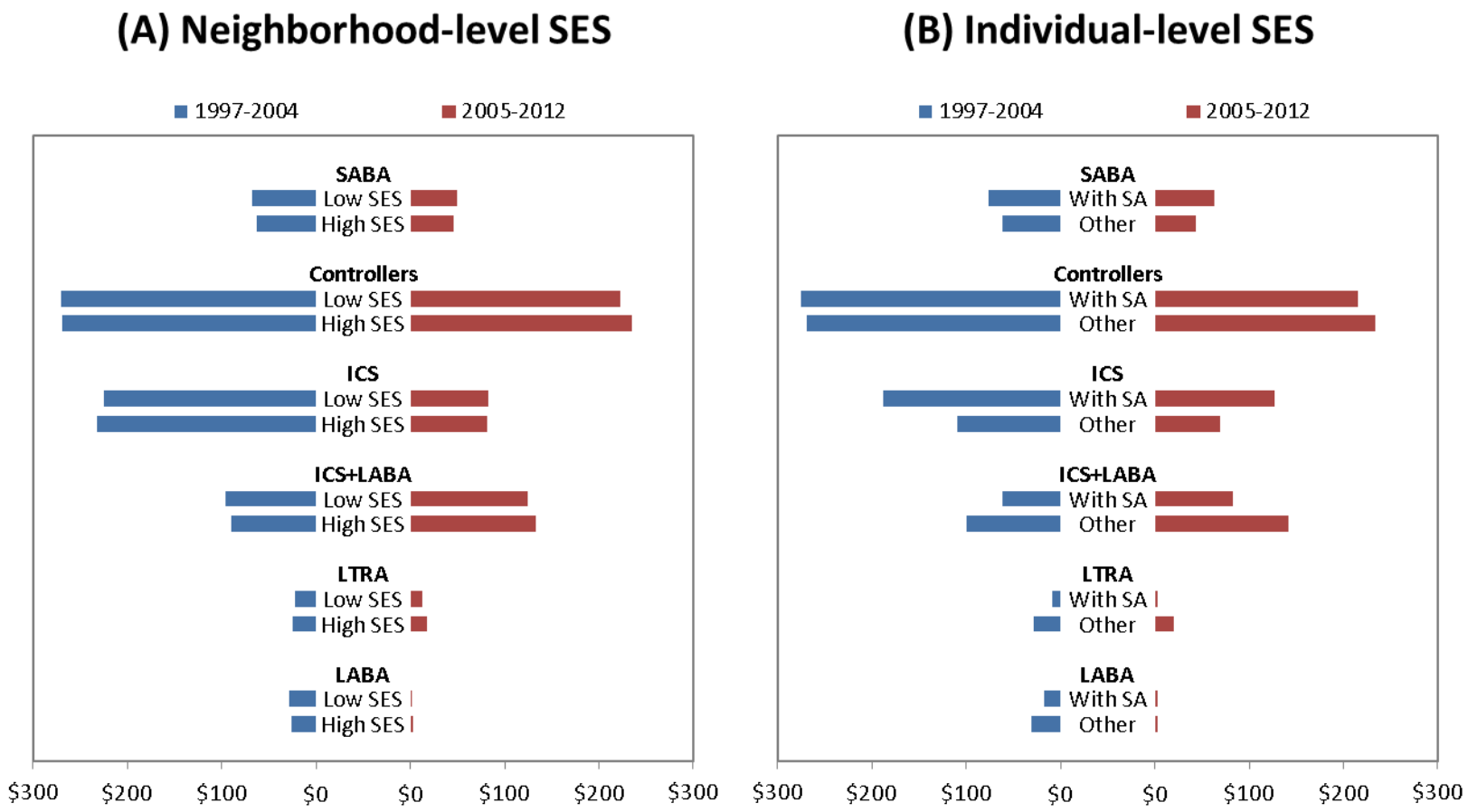


Figure 3.4 Annual mean costs of asthma-related medications in the periods of 1997-2004 and 2005-2012, by SES status.



3.4 Discussion

Canada has a single-payer, publicly administered health care system, with full coverage of inpatient and outpatient services for all legal residents, and drug coverage for individuals receiving social assistance; since 2003, income-based drug coverage has been implemented for non-recipients of social resistance.[60] Even with such a system, low SES was associated with substantially higher excess costs in patients with asthma. Compared to the rest of asthma patients, individuals who received social assistance incurred extra $706 per year, of which 60% was due to medications. Additionally, annual excess costs among people from low-SES neighborhoods were $120 higher than those from high-SES neighborhoods, mainly because of higher costs of outpatient visits. Over time, these SES-gaps remained constant at the individual level but narrowed at the neighborhood level, with the latter mainly driven by a vanishing SES gap in medication costs. At both levels, low SES was associated with lower dollars spent on controller medications of asthma and greater dollars spent on rescue medications.

Access to care is perceived as a major pathway for social gradients in health.[57] In private health care settings like US, the low-SES population can barely afford expensive health insurance and good-quality health care.[58] As a consequence, they end up using less ambulatory care[58] but incurring more expensive ED visits and hospitalizations.[59] Canada's universal health care setting should theoretically eliminate these inequalities, especially among patients with chronic diseases like asthma for which guideline-based effective medication treatment is widely available.[2] However, at both individual and neighborhood levels, I found the low-SES group showed indicators of sub-optimal care such as lower costs of controller medications and higher costs of rescue medications. Consistent with previous reports,[115,116] this pattern likely suggests poor

asthma control among the low-SES group, which would lead to more physician visits, prescriptions and subsequently higher asthma costs.[81,116]

This study is hypothesis generating with regard to the possible mechanisms mediating the effect of SES on access to care and outcomes. Sub-optimal care can be due to a lack of proper primary care, unaffordable medications, poor medication adherence among the poor,[133–136] or a shortage of family physician supply in the poor neighborhoods.[137] Asthma patients from low-SES neighborhoods tended to incur higher hospitalization costs than those from high-SES neighborhoods. This could be related to environmental factors beyond the reach of universal health care, including deprived living environment, air pollution, lack of a healthy food supply, recreational facilities, and low collective efficacy (i.e., low community engagement to gather health-related resources, eliminating environmental hazards, promote communication between neighbors, and so forth) in the poor neighborhoods.

Since Canada's universal health care system has minimized out-of-pocket expenses for the poor, the persistence of substantial asthma inequalities conveys important policy implication to other jurisdictions. Efforts should be made to improve guideline-based care among disadvantaged populations, such as ensuring good access to appropriate primary care in poor neighborhoods, expanding drug coverage and educating the importance of medication adherence. Also, health care programs should consider integrating neighborhood-level interventions into asthma management, such as reduction of environmental triggers, improving community health, raising asthma awareness and enhancing attachment to primary care.

This study has high external validity because I included all eligible residents from a well-defined and representable geographic region.[93] The robust statistical framework which appropriately adjusted for survival, handled zero-inflated and right-skewed medical cost data, and adopted the G-computation inference method further improved validity in quantifying life-time health care costs[132] and examining exposure-outcome associations.[111] This study also has several limitations. First, the algorithms used to identify asthma and calculate severity are based on records of resource use instead of a standardized approach for diagnosis.[27,45] Second, the individual-level measure of SES could only distinguish between the very poor who required assistance with basics needs versus the rest of the population. Furthermore, I did not adjust for potential confounders that were not recorded in the databases, such as smoking and education, which are worthy of further investigation. However, such factors can also be interpreted as being on the causal exposure-outcome association in this setting. Future research that can investigate the confounding or mediating role of such factors can generate important information.

3.5 Conclusions

In conclusion, this study found substantial socioeconomic inequalities in the direct costs in patients with asthma under a publicly funded health care system. Low SES, defined at both individual and neighborhood measures, was associated with greater excess costs of asthma. These disparities may be related to insufficient guideline-based care in the low-SES group, as low SES was consistently associated with indicators of inappropriate asthma management over time. Neighborhood characteristics may also contribute to these inequalities. The provision of universal health care alone does not guarantee equal access to good-quality health care. Continued efforts should be made to improve guideline based asthma management, reduce

exposure to asthma triggers, and ensure that primary care is provided to all patients. Future research should examine specific interventions aiming at facilitating access to high quality care for all individuals.

Chapter 4: Excess direct medical costs in patients with asthma and the role of asthma comorbidity*

4.1 Synopsis

Due to its high prevalence and the high burden of symptoms and risk of adverse outcomes such as exacerbations, asthma is associated with substantial economic burden on both society and individuals. The total direct costs of asthma in Canada in 1990 were estimated at $306 million (1990 Canadian dollars), including costs incurred by asthma-specific inpatient, emergency and outpatient services and medication use.[43] At the same time, patients with asthma are more likely to experience comorbid conditions than their counterparts in the general population without asthma.[63,138,139] This in turn results in a greater utilization of hospitalizations, emergency department visits and ambulatory care visits for their comorbidities.[65] The presence of comorbidities can complicate asthma management given its correlation with suboptimal asthma control,[38] lower quality of life,[65] and its negative impacts on the effect of asthma treatment.[38]

Thus, comorbidities may play an important role on the extra health care burden that asthma patients incur as compared with a non-asthma population. Fully informed, evidence-based policies and guidelines on the management of asthma should incorporate the burden of both asthma and comorbidities – and this requires valid and current evidence about the respective extent of their burden. However, most current asthma cost studies are focused on costs that are

* A version of this chapter has been accepted for publication:
Chen W, Lynd LD, FitzGerald JM, Marra CA, Balshaw R, To T, Sadatsafavi M. Excess medical costs in patients with asthma and the role of comorbidity. Eur Respir J. 2016. In press.

directly related to asthma[10] and do not include the costs attributable to the asthma-associated comorbidities.

This chapter uses fifteen years of health administrative data in BC, Canada, to estimate the contributions of asthma and comorbidities towards the economic burden of asthma from a health care payer's perspective. As a primary objective, this work estimated the excess direct medical costs (hereby referred to as "excess costs" for brevity), defined as the difference between all-cause direct medical costs in patients with incident asthma compared to those of a matched cohort of BC residents without asthma. As a secondary objective, this work further compared excess costs with the diagnosis code of either asthma or comorbidities, namely asthma-attributable and comorbidity-attributable excess costs, across age groups and over the clinical course of asthma. I hypothesized that comorbidity-attributable excess costs are substantial and that, under the joint influence of age and asthma, these costs will increase over time.

4.2 Methods

4.2.1 Data source

I retrieved data from the provincial health administrative databases for the period of January 1, 1997 to December 31, 2012 (16 years) from of the BC Ministry of Health. These databases have been described in *Chapter 2, Section 2.2.1*. All inferences, opinions, and conclusions drawn in this study are those of the authors, and do not reflect the opinions or policies of the Data Steward(s).

4.2.2 Asthma cohort

In order to create a cohort of patients with incident asthma, the first step was to identify all asthma patients who satisfied the validated case definition,[45,101] as described in *Chapter 2, Section 2.2.2*. Once identified, a look-back algorithm was applied to explore the patient's history to find the patient's first date of any inpatient or outpatient encounters with the primary diagnosis as asthma (ICD codes 493.x, J45.x, J46.x). This algorithm examined resource use records retrospectively in a 24-month rolling window, beginning from the day of satisfying the asthma case definition. For instance, if the algorithm identified any asthma-related medical care in a 24-month period, from the date of first asthma diagnosis in that period, it would jump back to a prior 24-month period to look for an earlier asthma diagnosis in patient`s resource use history, until there was no asthma diagnosis in an earlier 24-month interval. The first date of asthma-related resource use was defined as the index date, marking the start of follow-up. To include patients with incident rather than pre-existing/prevalent asthma, I restricted the sample to patients who were registered in the provincial health care system for at least 300 days per calendar year for at least 5 years prior to the index date. Given this five-year wash-out period, the period whose data were interrogated was between January 1, 2002 and December 31, 2012. In addition, in line with a prior study on the epidemiology of comorbidity in asthma,[139] the final asthma cohort included patients aged between 5 and 55 years at the index date.

4.2.3 Matched non-asthma cohort

As the basis of my comparator group, the ministry of health provided our lab with access to a random sample of 100,000 BC residents who had no asthma-specific health resource use records

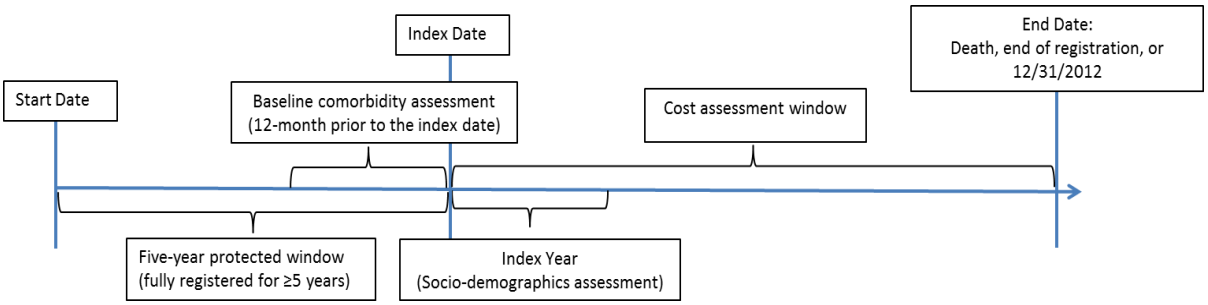
between January 1997 and December 2012. The ministry does not permit researchers to access the full provincial population due to privacy considerations.

To control for sample selection bias due to observable differences between the exposure (asthma) and comparison groups, the current work applied propensity score matching to select the comparison cohort. Relevant comparison subjects were matched with replacement using the nearest neighbor matching method, which was found to yield comparable results as the matching-without-replacement methods.[140] More specifically, a risk pool of comparison units was initially created by restricting the non-asthma population to those who were fully registered in the data for at least 5 years, with index date defined as the first day after 5 years in the databases, and between 5 and 55 years of age at index date. Then, a logistic regression was performed to estimate propensity scores for exposure (i.e., the probability of a subject being in the asthma cohort) for all individuals in the asthma cohort and the risk pool, with predictor variables: age groups (cut-offs of 18 and 45), neighborhood household income quintile, health services delivery area (all as observed in the index year), as well as comorbidity measures, all measured in the index year. Comorbidity measures included the number of non-asthma-related hospitalizations, physician visits, medication dispensations, and the CCI (excluding asthma from the score)[103] in the 12 months preceding the index date. Finally, this study performed a 1:1 nearest-neighbor matching to select for each exposed (asthma) individual one unexposed (non-asthma) individual, with relevant comparison subjects matched with replacement.

4.2.4 Study design

This is a retrospective longitudinal cohort study with matching on the exposure variable. Starting from the index date, all study subjects were followed to the earliest of death, loss-to-follow-up (i.e., the first date of the calendar year not registered in the Medical Services Plan), or December 31, 2012, whichever came first. Figure 4.1 provides the schematic presentation of the study design.

Figure 4.1 Schematic presentation of the study design.



4.2.5 Cost variables

The primary outcome was the all-cause excess direct medical costs (excess costs), defined as the difference in all-cause direct medical costs between the asthma and comparison group. The direct medical costs included three components: inpatient, outpatient, and costs of filled prescriptions. All costs were converted to 2013 Canadian dollars ($) using the Consumer Price Index.[129] Inpatient costs were calculated using the case mix methodology as described in Chapter 3.[130] Outpatient costs were directly obtained from the data. Costs for prescription drugs equal the actual reimbursement to the pharmacy (including out-of-pocket expenses) which was available in the data. Costs of emergency department services were mostly captured by fee-for-

service payments to physicians[131] and those that led to an inpatient episode were captured within the corresponding inpatient records.

Secondary outcomes were asthma-attributable and comorbidity-attributable excess costs. Asthma-related costs were calculated as the total direct costs of asthma-specific resource use, with a primary diagnosis code of asthma in the inpatient or outpatient claims (ICD-9: 493.x, ICD-10: J45, J46), or with asthma-specific medications (Appendix A). Comorbidity-related costs were stratified by the reference categorization of sixteen ICD-10 major disease categories, in accordance to the ICD codes recorded in the primary diagnosis field of the corresponding inpatient and outpatient claims.[141] Minor modifications had been made to these categories. First, diseases of the eye and adnexa (ICD-10: H00-H59) and diseases of the ear and mastoid process (ICD-10: H60-H95) were combined into one category: diseases of eye, ear and nose. For resource usage related to the presence of symptoms (ICD-10 code range R00-R69), we assigned them to related comorbid categories if the diagnosis code was grouped into that category in the diagnosis-related groups (DRG) based on General Equivalence Mappings.[142] ICD-9 codes, being used in the outpatient databases and up to 2002 in the inpatient databases, were converted to ICD-10 codes using validated cross-walk tables.[143] For medication records, I mapped the American Hospital Formulary Service (AHFS) major categories (available in the data) to ICD-10 major categories (Appendix E).[144] Some records of resource use and medication dispensations could not be assigned to any disease categories (e.g., codes for injury, poisoning, burns and other external causes, lab tests, miscellaneous drugs, or when there were no ICD or AHFS codes). We grouped costs associated with such records into an 'unattributable' category.

4.2.6 Statistical analysis

Descriptive analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, NC, United States). Regression analyses were performed using Stata/IC (V.12.1. College Station, Texas, USA). The standardized differences were calculated to compare differences in the distribution of matching variables between asthma cohort and the comparison group, with differences between categorical variables measured using the Mahalanobis distance method.[145] Effect size of the standardized difference below 0.20 was taken to indicate similarity in the distributions of the tested characteristic.[146] The crude prevalence of comorbid categories was reported as the occurrence of any resource use related to the comorbid condition during 2002 to 2012. A two-tailed p-value of less than 0.05 was used to determine statistical significance.

The unit of analysis was person-year. Follow-up time was divided into 12-month intervals starting from the index date (with last interval truncated if less than 300 days). To estimate excess costs and its trends, I used a multivariate regression model with interval-specific costs as the dependent variable. Separate models were conducted to estimate excess costs in total, excess costs attributable to asthma and to comorbid conditions. For all models, the independent variables of interest include the three-way interactions between exposure status (asthma=1, non-asthma=0), age group of the person-year, and the number of years since index date. I further adjusted for the calendar year at the beginning of each interval. Excess costs were estimated by contrasting the predicted overall costs or condition-attributable costs of being with versus without asthma. Hereby I respectively obtained estimates of overall excess costs, excess costs by age groups as well as excess costs in different years of asthma within each age group.

Similar to previous longitudinal studies on asthma costs,[45,46] I fitted the regressions using a GLM with a normal distribution and an identity link function. The use of normal distribution was in line with expert recommendation on the robustness of this assumption with large sample sizes.[147] Given the match-with-replacement strategy, I followed expert recommendation to fit a weighted regression, with comparison subjects weighted by the inverse of the frequency that they were matched to an asthma patient.[140] Of note, our data were clustered in multiple levels: observation units (person-years) within individuals, individuals within matched pairs, and matched pairs that shared the same comparison subject. However, since these multiple clusters were perfectly nested within the strata of comparison subjects, I used GEE clustering on the highest level (all matched pairs sharing the same unexposed member) to account for the multilevel correlation structure,[148,149] with the robust variance estimator to obtain valid inference on estimates.

Finally, a sensitivity analysis was performed in which individuals with short follow-up time (<12 months) were not excluded.

4.3 Results

A total of 145,742 asthma patients and an equal number of matched non-asthma subjects (from 31,998 unique non-asthma individuals) were included in the final sample (Figure 4.2). Table 4.1 summarizes the characteristics of the final matched sample at baseline. In the asthma and the comparison groups, the mean age at index date was 28.5 and 28.3 years, and there were 56% and 57% females, respectively. Baseline socio-demographic and clinical characteristics between asthma and comparison cohorts were considered balanced, as the standardized differences were far below 0.20.[146]

Figure 4.2 Flow chart of cohort selection.

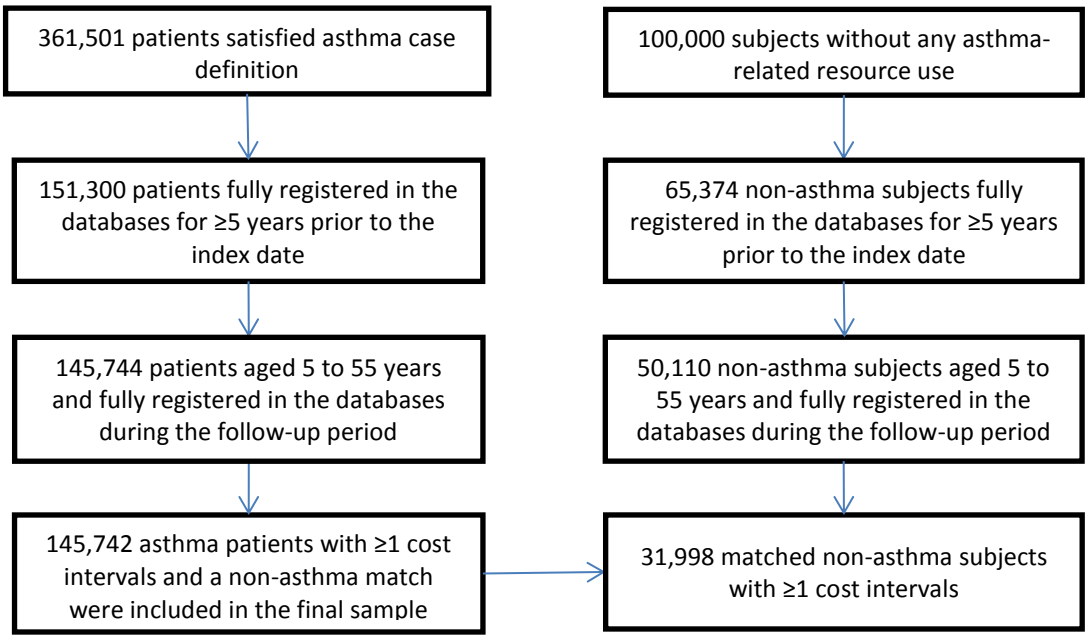


Table 4.1 Baseline characteristics of study participants aged 5 to 55 years in the asthma cohort and the non-asthma comparison group.

	Study Cohort		Standardized difference†
	Asthma (N=145,742)	Non-asthma (N=145,742)	
Age, years, mean (SD)	28.5(16)	28.3(15.6)	0.01
Age group (years)			0.09
≤18	35.4%	32.7%	
19-45	45.1%	49.7%	
>45	19.5%	17.6%	
Female	56.0%	56.9%	0.02
Comorbidity status: CCI*, mean (SD)	0.2(0.6)	0.2(0.9)	-0.01
# of non-asthma inpatient visits, mean (SD)	0.2(0.6)	0.2(0.5)	-0.01
# of non -asthma outpatient visits, mean (SD)	10.9(13.5)	11.4(14.9)	-0.03
# of non-asthma prescriptions, mean (SD)	10.8(49.8)	9(45.5)	0.04
Neighborhood household income quintiles			0.06
Q1	20.6%	18.6%	
Q2	20.6%	20.6%	
Q3	19.8%	20.3%	
Q4	19.2%	20.2%	
Q5	17.7%	18.4%	
Missing	2.1%	1.9%	
Health services delivery area			0.03
East Kootenay	1.4%	1.4%	
Kootenay-Boundary	1.5%	1.6%	
Okanagan	7.2%	7.4%	
Thompson/Cariboo	5.2%	5.2%	
Fraser East	7.4%	7.4%	
Fraser North	13.4%	13.0%	
Fraser South	18.6%	18.2%	
Richmond	3.7%	3.6%	
Vancouver	12.9%	12.7%	
North Shore/Coast Garibaldi	5.7%	6.1%	
South Vancouver Island	7.6%	7.9%	
Central Vancouver Island	5.5%	5.6%	
North Vancouver Island	2.7%	2.7%	
Northwest	1.9%	1.8%	
Northern Interior	3.6%	3.6%	
Northeast	1.5%	1.6%	
Unknown	0.2%	0.2%	

CCI, Charlson comorbidity index; SD, standard deviation

* CCI was modified to exclude asthma-related conditions.

†Difference in means or proportions divided by standard error. Imbalance was defined as absolute value of the standardized difference > 0.20.

Table 4.2 Prevalence of condition-related health care resource use during the follow-up period.

Comorbidity	Overall		Age 5 to 18 years		Age 19 to 45 years		Age over 45 years	
	Asthma	**Non-asthma**	**Asthma**	**Non-asthma**	**Asthma**	**Non-asthma**	**Asthma**	**Non-asthma**
Overall	99.0%	95.9%	98.9%	95.6%	98.9%	95.6%	99.3%	97.0%
Infectious and parasitic diseases	48.6%	43.0%	51.6%	47.5%	47.4%	41.6%	46.0%	38.9%
Neoplasms	23.4%	26.8%	11.7%	13.2%	26.4%	29.4%	37.3%	44.4%
Hematologic disorders	13.0%	12.5%	8.2%	6.4%	14.8%	14.8%	17.5%	17.5%
Endocrine, nutritional and metabolic diseases	68.1%	68.9%	54.4%	54.0%	73.3%	73.9%	80.9%	82.8%
Psychiatric disorders	47.8%	45.0%	33.5%	30.7%	55.6%	51.3%	55.8%	53.8%
Nervous diseases	48.0%	46.1%	40.5%	38.3%	50.9%	47.6%	55.1%	56.1%
Eye, ear, nose	66.5%	64.3%	81.6%	78.5%	55.9%	54.0%	63.6%	67.0%
Circulatory diseases	32.9%	32.0%	12.0%	10.4%	36.6%	35.3%	62.0%	62.9%
Respiratory disorders except asthma	85.8%	63.5%	86.8%	71.7%	85.1%	61.3%	85.5%	54.2%
Digestive disorders	44.2%	40.4%	32.3%	29.5%	48.2%	42.0%	56.4%	56.3%
Diseases of skin and subcutaneous tissue	69.2%	69.8%	69.3%	68.4%	69.7%	69.9%	67.8%	72.0%
Diseases of musculoskeletal and connective tissue	61.7%	59.6%	46.5%	42.3%	67.9%	65.5%	74.7%	74.7%
Genitourinary diseases	55.4%	58.1%	36.7%	39.8%	66.0%	66.6%	64.9%	67.8%
Pregnancy, childbirth and the puerperium	7.6%	10.8%	3.5%	4.5%	13.1%	17.9%	2.1%	2.4%
Perinatal-originated conditions	2.1%	2.0%	1.7%	1.2%	2.7%	2.9%	1.8%	1.0%
Complications from congenital abnormalities	4.2%	3.5%	6.3%	5.3%	2.9%	2.3%	3.3%	3.5%

Prevalence and Excess costs, Overall and by Conditions

Table 4.2 lists the prevalence of comorbidities in the sample. During the follow-up period, asthma individuals was more likely to use comorbidity-related health care resource compared to non-asthma cohort (99% vs. 96%), especially for other respiratory diseases and infectious and parasitic diseases (86% vs. 64%, 47% vs.43%, respectively). It was the opposite for pregnancy, childbirth and puerperium (8% vs. 11%).

Table 4.3 shows the adjusted excess costs across cost components and age. All-cause excess costs in patients with asthma were $1,186.5 per person-year (PY) (95% Confidence Interval [CI]: 1,130.4, 1,242.6). Among these, 12% were attributable to asthma ($145.2 [95% CI: 143.0, 147.4]), and 66% were attributable to the other major conditions ($787.7 [95% CI: 743.7, 831.7]). The remaining 22% were unattributable to any major disease category, which was mainly driven by outpatient encounters with diagnosis of general symptoms, lab tests, external causes, and outpatient encounters with no recorded diagnosis. This component was excluded from further investigation.

Figure 4.3 shows that significantly elevated costs were found for all included comorbidity categories in asthma patients. Excess costs were the highest for psychiatric disorders ($194.4/PY [95% CI: 176.0, 212.8]), followed by respiratory diseases other than asthma ($97.2/PY [95% CI: 90.0, 104.4]), digestive disorders ($86.7/PY [95% CI: 77.2, 96.2]), and diseases of nervous system ($81.1/PY [95% CI: 73.4, 88.9]) (Figure 1).

Hospitalizations accounted for 55% the excess costs attributable to other respiratory diseases, 33% to digestive disorders and 29% to psychiatric disorders, but only 5% to nervous diseases.

On the other hand, medication was responsible for 5% of the excess costs attributed to respiratory diseases (other than asthma), whereas 82% for nervous diseases, 52% for digestive disorders and 48% for psychiatric disorders (Figure 4.3).

Table 4.3 Adjusted excess costs of asthma per person-year, by age and cost components.

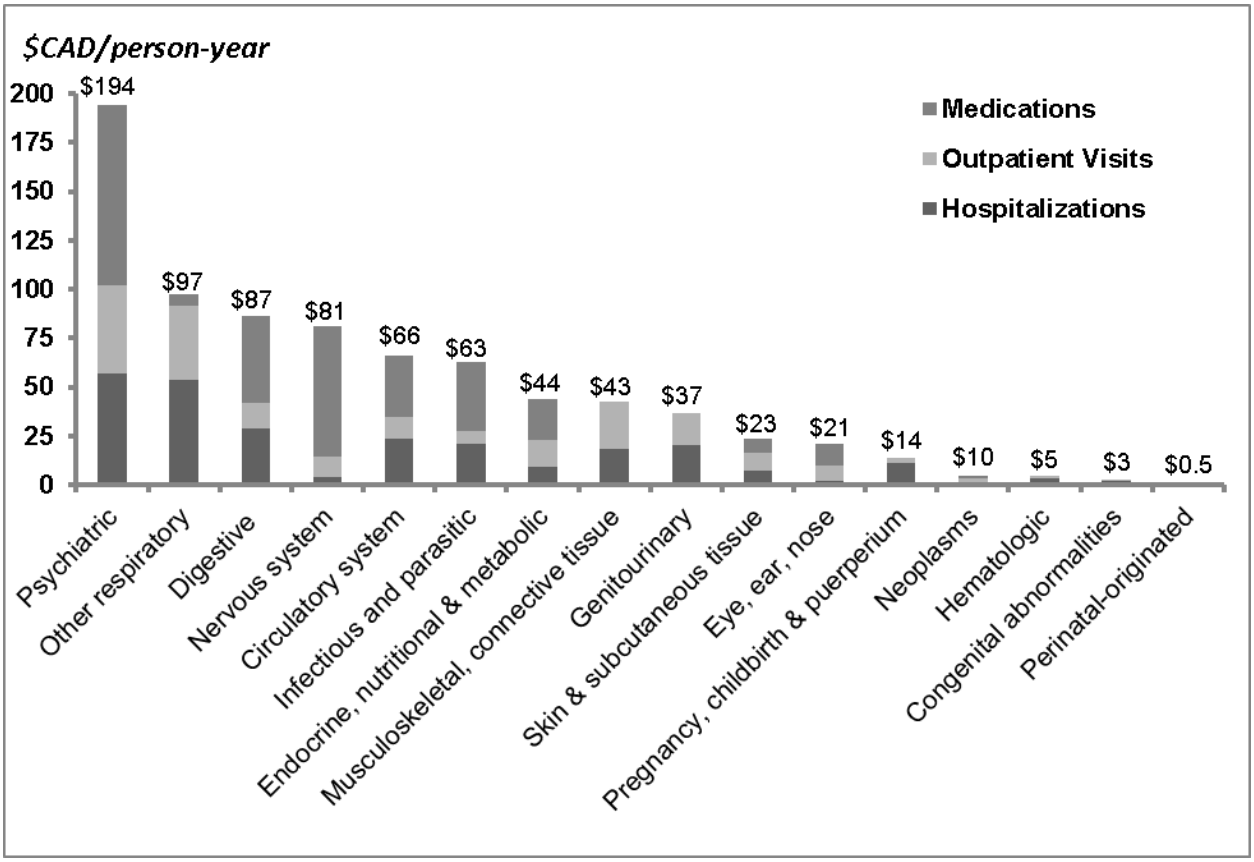
	Excess costs of asthma (vs. non-asthma) Mean (95% CI)			
	All-cause costs	Asthma-attributable costs	Costs attributable to major comorbidity categories*	Unattributable costs#
Overall	$1186.5 (1130.4,1242.6)	$145.2 (143, 147.4)	$787.7 (743.7, 831.7)	$253.6 (237.6, 269.6)
Cost components				
Hospitalizations	$316.6 (290.3, 343.0)	$6.3 (5.6, 7.0)	$267.3 (244.6, 289.9)	$43.1 (34.4, 51.7)
Outpatient visits	$377.5 (366.4, 388.6)	$30.4 (30.2, 30.7)	$203.6 (196.4, 210.8)	$143.4 (139.0, 147.9)
Medications	$492.3 (465.1, 519.6)	$108.4 (106.5, 110.4)	$316.8 (296.0, 337.6)	$67.1 (58.1, 76.1)
Age				
5-18 years	$395.8 (349.9, 441.6)	$108.6 (106.6, 110.6)	$211.5 (175.5, 247.4)	$75.7 (58.6, 92.7)
19-45 years	$1162.3 (1098.8,1225.8)	$126.4 (123.8, 129)	$778.0 (728.5, 827.5)	$257.9 (236.5, 279.3)
>45 years	$2025.9 (1909, 2142.7)	$213.5(208.3, 218.8)	$1386.0 (1292.9,1479.1)	$426.3 (394.2, 458.4)

CI, confidence interval

* The major comorbidity categories were defined by the ICD-10 major disease categories and related symptoms.

Include general symptoms, signs and findings, injury, poisoning, burning and external causes, factors influencing health status, other special purposes, the AHFS miscellaneous drug group, no ICD code, and no AHFS code.

Figure 4.3 Adjusted annual excess costs by attribution to asthma and comorbidities, by cost components.

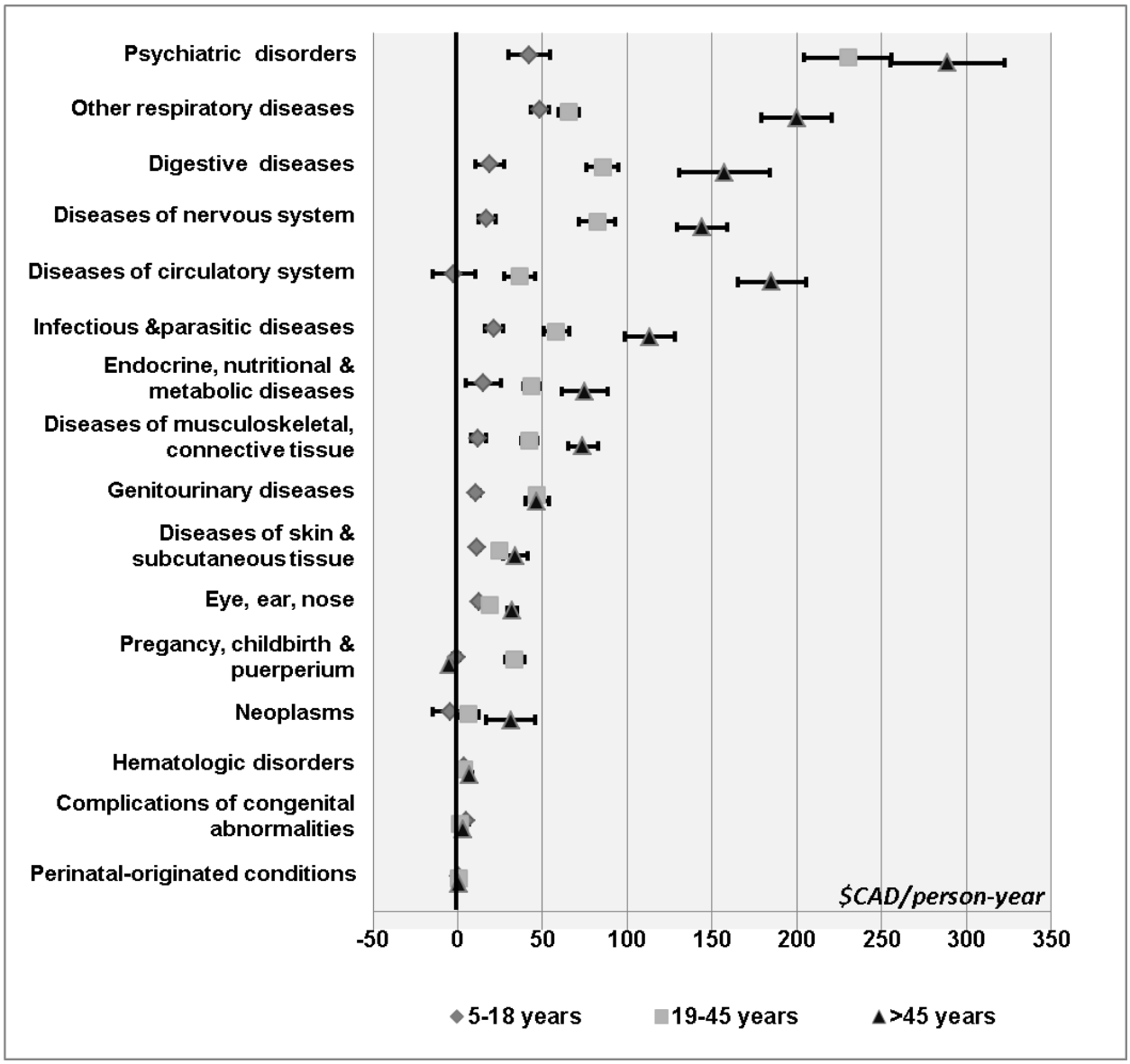


Excess costs across age groups

Figure 4.4 shows excess costs attributable to asthma and to comorbidities across age groups. Among individuals aged 5 to 18 years, annual all-cause excess costs were $395.8/PY (95% CI: 349.9, 441.6), with $108.6 (27%) attributable to asthma and $211.5 (53%) attributable to comorbidities (the rest falling under the 'unattributable' category). The corresponding estimates for individuals aged 19 to 45 years were $1162.3/PY (95% CI: 1,098.8, 1,225.8), $126.4 (11%), $778.0 (67%); and for individuals aged above 45 years were $2,025.9/PY (95% CI: 1,909.0, 2,142.7), $213.5 (11%), and $1,386.0 (68%).

The greatest increases of excess costs were found in psychiatric disorders (from $42.0/PY for 5-18 years of age to $288.8/PY for >45 years of age), diseases of circulatory system (from $0/PY to $185. 1/PY), and respiratory disorders other than asthma (from $48.3/PY to $199.7/PY).

Figure 4.4 Adjusted annual excess costs by attribution to asthma and comorbidities, by age groups.

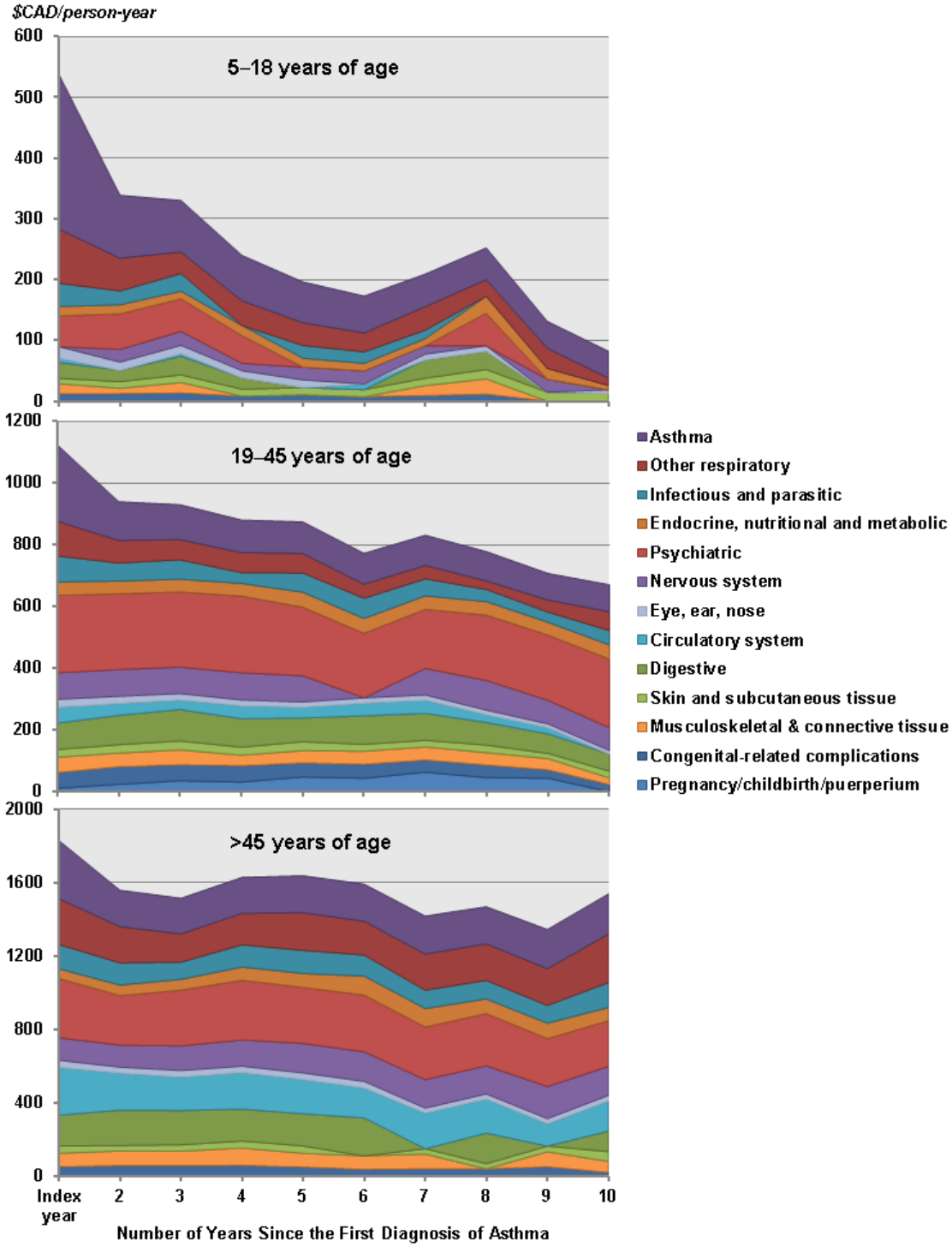


Trend of excess costs over the course of asthma

Figure 4.5 shows the trends of excess costs within each age group over a 10-year follow-up period. Asthma-attributable excess costs consistently decreased since the index date across all age groups, with greater decreases found in younger individuals. For age groups of 5-18 years and 19-45 years, comorbidity-attributable costs decreased over time (-$27.0/PY [95% CI: -40.1, -14.0], -$27.6/PY [95% CI: -36.9, -18.3]). For those aged over 45 years, comorbidity-attributable costs did not significantly change (-$15.2/PY [95% CI: -32.8, 2.4]).

In the sensitivity analysis, asthma patients with less than 12 months of follow up incurred $1591.3/PY [95% CI: 1280.4, 1902.2] excess costs, which only minimally changed compared to the first-year costs of those with at least 12 months of follow up.

Figure 4.5 Adjusted annual excess costs by attribution to asthma and comorbidities (which costed >$10/person-year), in the 10-year follow up period since asthma onset.



4.4 Discussion

This chapter provided key estimates on the excess direct medical costs in asthma patients, above and beyond the medical costs incurred by non-asthma individuals. Among the substantial total excess costs in asthma patients, only twelve percent were directly attributable to asthma-related resource use ($145/PY), whereas another sixty-six percent were attributable to the elevated costs of major comorbidity classes ($788/PY). The remaining twenty-two percent was unattributable to any specific conditions. Psychiatric disorders were the largest component of comorbidity costs, followed by respiratory disorders other than asthma, digestive diseases, and diseases of nervous system. Although comorbidity-attributable excess costs greatly increased with age, they tended to decrease over the course of asthma when up to 45 years of age but stay constant thereafter. These findings cast light on the true burden of asthma and its underlying constellation of comorbid conditions

Also based on health administrated data, Gershon and colleagues reported elevated rates of comorbidity-related outpatient, inpatient and emergency department claims in patients with asthma compared to a non-asthma population.[65,139] Our results largely agree with these findings, and extend to provide estimates of excess costs. Among the limited number of studies which reported excess costs in asthma patients, our estimated total excess costs in children were similar as that from a study performed in the United States.[70] As for asthma-attributable costs, our results aligned well with previous estimates from the same province.[45,46]

The observed excess costs and trends can be explained by several mechanisms. Firstly, consistent with previous studies,[63,138,139] this study found an elevated prevalence of most comorbidity classes in asthma patients, which could in turn lead to elevated attributable costs.

This is likely due to the inflammatory state underlying asthma or common risk factors related to environment and lifestyle that are not captured in administrative databases.[150] For instance, respiratory diseases other than asthma were much more prevalent in asthma which contributed to the second largest share of comorbidity-attributable excess costs. In particular, about one third of the substantial excess costs for individuals over 45 years of age came from asthma itself, other respiratory diseases and diseases of the circulatory system. This is consistent with the picture of COPD and its strong association with cardiovascular diseases, developing in a substantial fraction of individuals with asthma above 45 years of age.[151] Likewise, digestive disorders, the third largest component of comorbidity-attributable excess costs, were more prevalent in asthma which is likely due to allergic inflammatory changes occurring in the gastrointestinal mucosa.[152] However, the more costly comorbidities in asthma were not necessary the more prevalent ones, because excess costs are not only determined by increased incidence of a given condition but also by the difference in the severity (intensity) of the condition. For instance, psychological disorders were prevalent in roughly half of both asthma and comparison cohorts, but it generated much greater costs in asthma patients – even greater than that of asthma itself, with a third of costs induced by hospitalizations. Additionally, asthma or asthma-related intervention can also be on the causal pathway. For instance, activity limitation and sleep disturbance that associated with suboptimal asthma control can lead to or worsen psychiatric disorders,[153] while the latter was found to be the largest component of comorbidity-attributable excess costs. Evidence also suggests that corticosteroid use might increase the risk of depression.[154,155] Furthermore, comorbid conditions can complicate treatment strategies, increasing the need of medications and risk of adverse events, which eventually increase the overall excess costs. A good example was

the incremental costs attributable to pregnancy, childbirth and puerperium in asthma patients, although they experienced less of these conditions compared to non-asthma individuals.

It was not surprising that comorbidity-attributable excess costs increased with age. Apart from that, however, we found these costs decreased in younger adults and stayed constant in older adults over the course of asthma. This could be explained by the generally non-progressive course of asthma, as observed even in severe asthma.[28,156] It is also possible that acute onset of asthma boosted overall health care resource utilization, either due to the primary condition (asthma) itself or because the asthma-related encounter with the health care system in turn increased the chance of being diagnosed with comorbidities. But when asthma was better managed over time, it caused less life disruptions.

The fact that health care resource use records that were unattributable to any specific disease group were higher in the presence of asthma can be hypothesis generating and worth further investigation. It can be a further indication that aside from the primary condition, asthma patients are generally less healthy than the non-asthma population. It can also indicate a general tendency towards increased health care resource use in asthma patients.

A major strength of this study was the use of comprehensive records of all asthma patients from health administrative databases in BC, a well-defined geographical region with a single-payer system. Thus, this study was able to obtain precise estimates of costs that reflect real-world medical diagnoses, delivery, utilization and spending in BC. The population-based cohort also improves the external validity and generalizability of our estimates. The current work was further strengthened by the use of a propensity-score matched cohort design to rigorously adjust for

systematic differences between the asthma and comparison cohort prior to the follow-up period, which enabled us to derive more nearly unbiased estimates of all-cause costs and condition-specific costs that were incurred because of the presence of asthma. In addition, the follow up time of this study is sufficiently long to provide a comprehensive picture of dynamic fluctuation in the total and condition-specific excess costs over the long-term course of asthma.

This study had several limitations. Firstly, the estimation of condition-attributable excess costs might be associated with misclassification bias, as diagnostic codes can be assigned incorrectly and occasionally the diagnosis itself can be erroneous.[157] Mapping prescription drugs to disease categories is an inexact science as well.[157] Secondly, I used the first (most responsible) ICD codes for inpatient and outpatient records for attributing resource use to diseases, although comorbidities in other diagnosis fields and the omitted ones could have also contributed to the health care resource use. This limitation had a greater impact on the estimation of inpatient costs than outpatient costs, because each hospital visit typically recorded 4 to 5 diagnoses in the 25 diagnosis code fields whereas the majority of physician visits only documented the primary diagnosis. Third, asthma individuals were identified from the administrative data using a restrictive case definition that required intensive asthma treatment within a short period of time (12 months).[45,101] Inevitably, this algorithm might have excluded patients with mild asthma with intermittent resource uses. Finally, concordant reporting on the prevalence and economic burden of comorbid conditions would have provided insight about whether the higher burden of a given condition in asthma individuals is due to higher prevalence of the condition or higher severity of the disease (resulting in higher per-patient costs). Estimating accurate prevalence rates require application of validated case definitions for each comorbid condition. In addition to the

complexity of this process, the presence of asthma could have threatened the accuracy of case definition algorithms whose validity has typically been assessed in the general population. Future studies should apply validated case definitions for each comorbid condition.

Given the much higher share of comorbidity-attributable excess costs than those attributable to asthma itself, the current work highlights the importance of preventing, regular monitoring and managing of comorbidity in patients with asthma. While our findings seemingly support an emerging advanced view that human diseases should not be considered as invariably independent,[158] the underlying cause, effect and molecular pathways remain to be deciphered. Nonetheless, the economic effect of comorbidities should still be considered in the cost-effectiveness evaluation of asthma interventions. Current asthma management guidelines recommend achieving and maintaining asthma control which, compared to uncontrolled asthma, leads to decreased risk of adverse events and reduced asthma-related health care costs.[1,2,4] Since uncontrolled asthma contributes to certain comorbidities, especially psychiatric conditions,[153] simply ignoring the economic implications of comorbidities could lead to an underestimation of the effectiveness of targeted asthma interventions and miss the possible underlying disease network that interacts with asthma. Likewise, it will also fail to target the true effectiveness of broad-scope prevention and intervention methods which aim to improve overall health, including smoking cessation and physical activity programs. On the other hand, these findings also highlight the importance of investigating the potential role of asthma control in influencing the economic impact of comorbidities. In addition, given the profound economic implication of psychiatric disorders in asthma patients, future studies should compare excess costs attributable

to mood disorders versus to psychoses, providing more insight into in the underlying sources of psychological burden in these patients.

4.5 Conclusions

Using propensity score-matched population-based cohorts of asthma patients and comparison individuals with sixteen years of data in BC, Canada, in this chapter I estimated the excess direct medical costs in asthma patients, over and beyond the costs incurred by the comparison group. These findings suggest that subjects with asthma incur substantial costs, with costs attributable to major comorbidity classes five times higher than those attributable to asthma itself. The excess costs attributable to comorbidities greatly increased with age. The cost patterns over the course of asthma also varied by age, with comorbidity-attributable excess costs decreasing over time since the diagnosis of asthma in individuals up to 45 years of age and stayed constant thereafter. Psychiatric disorders, respiratory disorders other than asthma, digestive diseases and diseases of nervous system were responsible for the largest share of comorbidity-attributable excess costs. These findings can both inform policy and clinical practice and provide insight into the pathophysiology of asthma. For instance, the estimate of the economic and humanistic return on investment in asthma management strategies could be substantially different when both asthma and comorbidities are considered. Future studies should examine the role of risk factors and the long-term effects of asthma control and treatment adherence on the burden of comorbidity in asthma.

Chapter 5: The joint influence of comorbidity on health-related quality of life in patients with asthma*

5.1 Synopsis

Current evidence-based asthma management is primarily focused on achieving and maintaining asthma control which, compared to uncontrolled asthma, is associated with decreased risk of adverse events, fewer exacerbations, reduced health care costs, and improved quality of life.[1,2,4] When comparing asthma interventions, researchers often use asthma control as an intermediate outcome connecting the effect of interventions on policy-relevant outcomes such as HRQoL. As a societal preferences-based evaluation of HRQoL, health-state utility value (utility) allows quantification of the effects of interventions as quality-adjusted life years (QALYs), a key metric of cost-effectiveness analysis.[71] In particular, reliable estimates of the impact of asthma control on utility have attracted researchers' attention.[82,159] However, utility in patients with asthma is not solely determined by asthma itself. Several studies have shown negative effects of comorbid conditions on HRQoL in asthma patients, but such effect estimates may be biased because these studies failed to consider the concurrent impact of the primary disease (asthma control).[89,91,92]

Previous studies found that both generic (e.g., the EuroQol-5d [EQ5D][75]) and disease-specific instruments (e.g., the Asthma Quality of Life Questionnaire [AQLQ][160]) can be used to evaluate utilities in asthma.[82,159] However, current knowledge about the validity of utility instruments in asthma needs to be extended from an exclusive focus on asthma control or comorbidity in

* A version of this chapter has been published:
Chen W, Lynd LD, FitzGerald JM, Marra CA, Rousseau R, Sadatsafavi M. The added effect of comorbidity on health-related quality of life in patients with asthma. Qual Life Res. 2015 Oct;24(10):2507-17.

isolation to how these instruments are able to discriminate the effect of changes in asthma control and comorbidity at the same time. This is because interventions and strategies aimed at reducing the burden of asthma can vary in scope, ranging from active treatments targeted at reducing asthma symptoms (e.g., inhaled reliever or controller medications) to approaches that that are broader in scope affects both asthma and overall health, such as smoking cessation or weight reduction. Also, targeted asthma treatments can sometimes influence the risk of comorbidity, such as the demonstrated association between the use of inhaled corticosteroids and the risk of pneumonia[161] and diabetes.[162] Establishing cost-effectiveness profiles for these interventions requires a valid utility measure which can distinguish changes in both asthma control and comorbidities. Unfortunately, such evidence is currently lacking.

To bridge this knowledge gap, in this chapter I used a longitudinal cohort of adult asthma patients to examine the performance of generic and asthma-specific utility instruments in simultaneously distinguishing changes in asthma control and comorbidity. The primary objective was to evaluate changes in utility associated with different level of comorbidity burden and across different levels of asthma symptom control. The secondary objective was to explore the relative influence of asthma symptom control and comorbidities on utility obtained either from generic or disease-specific instruments.

5.2 Methods

5.2.1 Data source and sample

Data were collected from a sample of adult asthma patients enrolled in the Economic Burden of Asthma study in Canada (EBA), a prospective, one-year cohort study on the humanistic and

economic burden of asthma in Canada. Between December 2010 and August 2012, 618 subjects with a self-reported physician diagnosis of asthma were recruited via random digit dialing (both through landlines and cell phones) from Vancouver and Central Okanagan, two representative census subdivisions in British Columbia, Canada (2011 population of 603,502 and 179,839, respectively).[163] The sample size of the original cohort was designed to provide reliable estimate of the prevalence of asthma (with 95% confidence bound being within 10% of the point estimate). Subjects aged 1 to 85 years old with a parental or a self-reported physician diagnosis of asthma, plus a parental or a self-reported record of asthma-related health care resource usage in the past 5 years, were initially identified. Individuals were not eligible if they were unable to provide informed consent due to language difficulties or cognitive impairment, reported a ten-pack-year smoking history or greater, or had plans to leave the study area during the follow-up period. Pregnant women, those who planned to become pregnant in the next twelve months, and those in whom a methacholine challenge test was contraindicated (e.g., recent heart attack or stroke) were not eligible. Consenting individuals attended the study centers for the baseline visit, during which a comprehensive questionnaire was administered to collect information on the socio-demographic characteristics, asthma-related symptoms, use of medications, comorbid conditions and HRQoL.

Eligible subjects were followed for one year, with four follow-up visits at three–month intervals. Patients also underwent spirometry by a trained technician at the first and last visit. The present analysis was restricted to adults 19 years and older. Patients with enough information to assess asthma symptom control, comorbidity, and HRQoL for at least one visit were included in the final data set.

5.2.2 Outcome variables

At all five visits, HRQoL was measured using both a generic preference-based instrument (EQ5D, 3-level version[75]) and an asthma-specific instrument (AQLQ- short version [mini-AQLQ][164]).

The EQ5D is based on a validated self-administrated survey which consists of a descriptive health state classification system with 5 domains: mobility (i.e., the quality of being mobile), self-care, usual activity, pain/discomfort and anxiety/depression, as well as a "health thermometer" that represents subjective, global evaluation of the respondent's health status on a scale between 0 (worst imaginable health) and 100 (best imaginable health). This instrument generates a single utility value to describe an individual's health state on a scale anchored at 0 for death and 1 for perfect health, with a lower bound of -0.59 (for health states worth than death).[165]

The mini-AQLQ consists of 15 questions, each scored on a 7-point scale between 1 (worst symptoms/limitation) to 7 (least symptoms/limitation), in 4 domains of asthma-specific quality of life: symptoms, activity limitation, emotional function and environmental stimuli. Since Canadian valuation of utility is only available for EQ5D,[76] both EQ5D and AQLQ responses were converted into utility values using UK tariffs[80,165,166] to enable meaningful comparison between the two instruments. To calculate utility from AQLQ, AQLQ responses were first reduced from seven to five levels[167] which were then used to calculate AQ5D utilities, as described by Yang et al 2011.[80]

5.2.3 Exposure variables

Asthma symptom control: For each visit, patients were classified as having "controlled", "partially controlled", or "uncontrolled" asthma which was assessed using 2014 GINA criteria.[2] This classification is based on patients' self-report on four asthma symptom domains (daytime symptoms, limitation in activities, nocturnal symptoms and need for reliever/rescue treatment) with a recall period of three months.

Comorbidity: Comorbidity status was measured at the final visit via the Self-administered Comorbidity Questionnaire (SCQ) with a recall period of 12 months.[168] The SCQ is a validated instrument that has been shown to have a moderately strong correlation with the Charlson Index, a popular chart review-based comorbidity instrument[168] and to be equivalent to the Charlson index in terms of prediction power for physical functional capacity and HRQoL impairments.[169] The SGQ includes 13 common comorbid chronic conditions;[168] but this study purposefully excluded lung disorders from the assessment given that all individuals had asthma but no other respiratory diseases. Each reported condition can receive a maximum of 3 points (presence of disease, whether receiving treatments for the disease, and any functional limitation due to the disease). The maximum overall score was therefore 36, with higher scores indicating greater comorbidity.

Covariates: Additional socio-demographic information was collected at baseline, including age, sex, ethnicity, education (categorized as postsecondary education versus less than postsecondary education), annual household income (categorized as above versus below $60,000 Canadian

dollars), as well as baseline intensity of treatment as measured by PDC of asthma controller medication in the past 12 months (Appendix A).[170]

5.2.4 Statistical analysis

All analyses were performed using SAS Version 9.3 (SAS Institute Inc, Cary, NC, United States). The criterion for statistical significance was a two-tailed p-value (p) of less than 0.05. Descriptive statistics were calculated and comparisons were tested using Pearson chi-square tests for categorical variables and Kruskal-Wallis tests for utility scores. An unadjusted analysis assessed the bivariate association between utilities, HRQoL subdomains, symptom control, and comorbidity using Spearman's rho correlation.

The influence of symptom control and comorbidity burden on HRQoL was evaluated using regression methods, with utility scores as the dependent variable, asthma symptom control (controlled vs. partially controlled and controlled vs. uncontrolled asthma), comorbidity score, and potential confounding as independent variables. Since the distributions of both EQ5D and AQ5D utility scores were heavily skewed to the left as well as demonstrating a ceiling effect (a considerable proportion of individuals reporting a utility score of one [perfect utility]), inference based on OLS methods could be invalid. Thus, this study fitted a two-part regression model with both a logistic and an OLS component.[171] The logistic component modeled the probability of reporting a utility of less than one (imperfect utility) as a function of covariates. Then, the OLS component modeled the effects of covariates on utility in the subset of individuals who reported imperfect utility. To meet the assumptions of normal distribution and constant variance for regression residuals, utility scores were logit-transformed as the dependent variable for the OLS

component. For both components, the model adjusted for potential confounding variables, including age, sex, ethnicity, household income, education, intensity of asthma treatment at baseline, as well as an indicator for the study visit number. Both the logistic and logit-transformed OLS components were fitted using GLM with GEE to account for the clustering of observations within individuals.[172]

Primary objective: relationship between symptom control, comorbidity and quality of life.

Using the G-computation technique,[111] the regression coefficients from the logistic and logit-transformed OLS components were combined to estimate the marginal effect of variables of interest on utilities. In this context, the marginal effect of a variable is the change in the expected utility that occurs by changing the level of that variable, while keeping other variables constant. Since I have controlled for most covariates that could potentially confound the relationship between the variable of interest and utility scores (except for smoking which is more likely to act as a mediator rather than a confounder), such marginal effects can be interpreted causally.[111] The current work calculated the following marginal effects: 1) the change in expected utility scores across different levels of asthma symptom control; 2) the change in expected utility scores seen with an increase in the comorbidity score from zero to the sample mean, and from the sample mean to one standard deviation above the mean; 3) the expected utility score assessed at each point in the range of the comorbidity score (0-36), overall and within different levels of symptom control. Standard errors for marginal effects were based on parametric bootstrapping with 50 replications, i.e., random sampling with replacement of the entire sample for 50 times and estimating marginal effects based on these samples.

Secondary objective: strength of association of symptom control and comorbidity with quality of life.

The secondary objective was assessed using the coefficient of determination (R^2), i.e., the proportion of variation in utility explained by the model with particular predictors. First, this study built a reference two-part model with symptom control, comorbidity, and potential confounders, as described earlier. The first-order interaction between symptom control and comorbidity was tested (test stat value and p-value, please) but it did not further improve the fit and thus was not included in the reference model. Then, this study measured the change in R^2 to determine the influence of predictors when they were removed from the reference model (the more influential predictor results in the greater decrease in R^2). Using a similar framework, the impact of individual comorbid conditions on utilities were also measured. The model for this analysis included covariates, symptom control and all 12 comorbid conditions from the SCQ instrument as separate variables (each condition with values of 0 to 3). Again, the most influential comorbid condition was the one that resulted in the greatest decrease in R^2 when it was removed from the model.

5.3 Results

Sample characteristics

The final sample included 460 patients who met the inclusion and exclusion criteria. This sample contributed to 2,299 observations during the one-year follow up period. Three observations were removed because data on AQ5D scores were missing. Table 5.1 shows the baseline

characteristics of the final sample. The mean age at baseline was 52 years (SD=15), 67% were women and 83% were Caucasians. At baseline, 25%, 39%, and 36% of the patients had controlled, partially controlled, and uncontrolled asthma, respectively. The majority of patients (70%) reported having at least one chronic comorbid condition, with the average comorbidity score being 3.25 (SD=3.61). The most prevalent comorbid conditions were back pain (39%) and arthritis (28%) (Table 5.1).

The average baseline EQ5D and AQ5D utilities values were 0.91 (SD=0.12) and 0.88 (SD=0.12), respectively. During the follow up period, there were 1,283 (56%) and 250 (11%) observations with patients reporting perfect EQ5D and AQ5D utility scores, respectively, suggesting a ceiling effect especially with the EQ5D. The distribution of levels of symptom control and the mean utilities did not differ significantly across study visits (p-values: symptom control 0.22, EQ5D 0.06, AQ5D 0.92) (Table 5.2).

Bivariate association of symptom control and comorbidity with quality of life

Both asthma control (Spearman's rho correlation = -0.22 for EQ5D, $p<0.001$; -0.44 for AQ5D, $p<0.001$) and comorbidity (-0.40 for EQ5D, $p<0.001$; -0.13 for AQ5D, $p<0.001$) were inversely correlated with utilities. Distribution of utilities across levels of symptom control is summarized in Figure 5.1.

Table 5.1 Characteristics of the study sample.

	Study Population (N=460)
Baseline age, mean(SD)	52.01 (14.83)
Gender, %Female	67%
Ethnicity	
Caucasian	83%
Asian	13%
Other	4%
Annual household income >$60,000CAD	73%
Postsecondary education and above	76%
Baseline treatment Intensity	
PDC<50%	45%
50% ≤ PDC <80%	11%
PDC≥ 80%	44%
Baseline symptom control	
Controlled	25%
Partially controlled	39%
Uncontrolled	36%
Baseline EQ5D, mean(SD)	0.91 (0.12)
Baseline VAS, mean(SD)	0.74 (0.17)
Baseline AQ5D, mean(SD)	0.88 (0.12)
Overall SCQ comorbidity scores, mean(SD)	3.25 (3.61)
Reported ≥1 comorbidities in the past year	70%
Heart diseases	7%
Hypertension	18%
Diabetes	7%
Ulcer or stomach diseases	17%
Kidney disease	2%
Liver disease	1%
Anemia or other blood disease	10%
Cancer	2%
Depression	15%
Osteoarthritis, degenerative arthritis	28%
Back pain	39%
Rheumatoid arthritis	4%

%, percentage; CAD, Canadian dollars; PDC, proportions of days covered; SD, standard deviation.

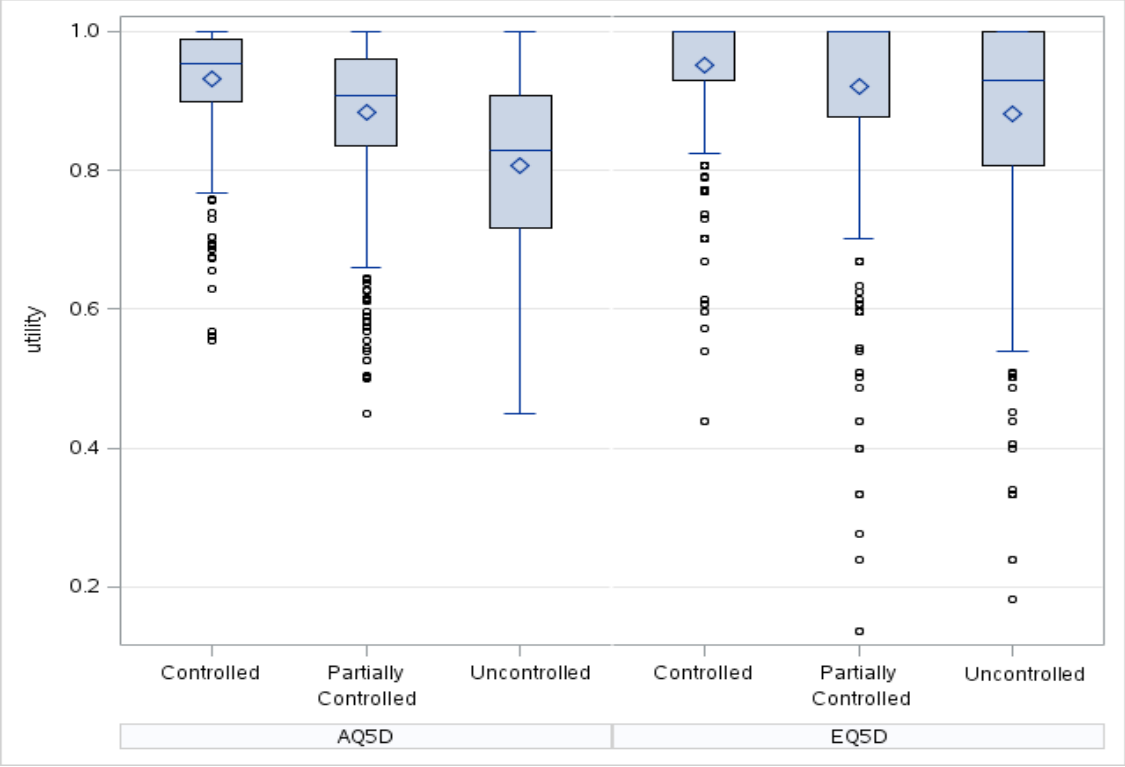
Table 5.2 Utility scores and asthma symptom control across visits.

			Visit					
		Overall	**1**	**2**	**3**	**4**	**5**	**p-value**
EQ5D (N=2299)	Mean	0.92	0.91	0.91	0.91	0.92	0.92	0.0571[a]
	SD	0.13	0.12	0.13	0.13	0.12	0.13	
AQ5D (N=2296)	Mean	0.87	0.88	0.87	0.87	0.87	0.87	0.917[a]
	SD	0.12	0.12	0.11	0.12	0.12	0.11	
Asthma control (N=2299)	Controlled	28.0%	25.2%	27.4%	29.4%	27.8%	30.3%	0.2243[b]
	Partially controlled	39.4%	39.1%	42.4%	41.1%	36.1%	38.1%	
	Uncontrolled	32.6%	35.7%	30.2%	29.6%	36.1%	31.6%	

[a] Kruskal-Wallis test for between-group vs within-group differences in the means.

[b] Pearson Chi-square for between-group vs within-group differences in the proportions.

Figure 5.1 Distributions of utility scores by asthma symptom control.



Lines: median values; hollow diamonds: means; hollow circles: outliers.

Primary outcome: marginal effects of symptom control and comorbidity on quality of life

Compared with controlled asthma, uncontrolled asthma was associated with statistically significantly lower EQ5D (difference -0.018 [95% CI, -0.028– -0.009]) and AQ5D (difference: -0.076 [95% CI, -0.115– -0.052]) utilities. Similarly, partially controlled asthma was associated with lower EQ5D (difference -0.012 [95% CI, -0.022– -0.005]) and AQ5D (difference -0.029 [95% CI, -0.044– -0.020]) utilities compared with controlled asthma (Table 5.3).

Table 5.3 Adjusted effects of symptom control on utility: results from the two-part regression.[a]

	Adjusted Change in Utility Scores					
	EQ5D			**AQ5D**		
Symptom Control	**Estimate**	**95% CI**	**p-value**	**Estimate**	**95% CI**	**p-value**
Partially controlled vs Controlled	-0.012	-0.022, -0.005	<.0001	-0.029	-0.044, -0.020	<.0001
Uncontrolled vs Controlled	-0.018	-0.028, -0.009	<.0001	-0.076	-0.115, -0.052	<.0001
Uncontrolled vs Partially controlled	-0.006	-0.009, -0.003	<.0001	-0.047	-0.071, -0.032	<.0001

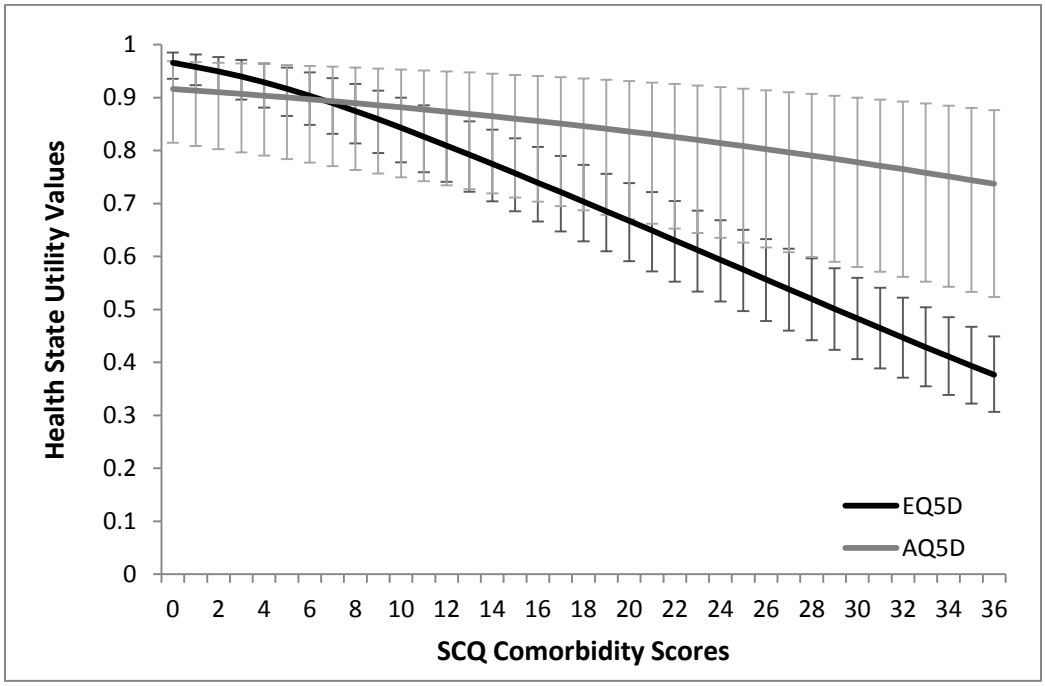
CI, confidence interval; p, p-values.

[a] The two-part model was adjusted for comorbidity, baseline age, sex, ethnicity, annual household income, baseline education level, baseline intensity of asthma controller therapies and the indicator for the corresponding study visit.

The marginal effects of comorbidity on utility are plotted in Figure 5.2, showing a monotonic inverse relationship across the entire range of comorbidity scores. Increasing comorbidity scores from zero to the sample mean (SCQ scores=3.25) was associated with both significantly lower EQ5D (difference -0.029 [95% CI, -0.043– -0.016]) and AQ5D (difference -0.010 [95% CI, -

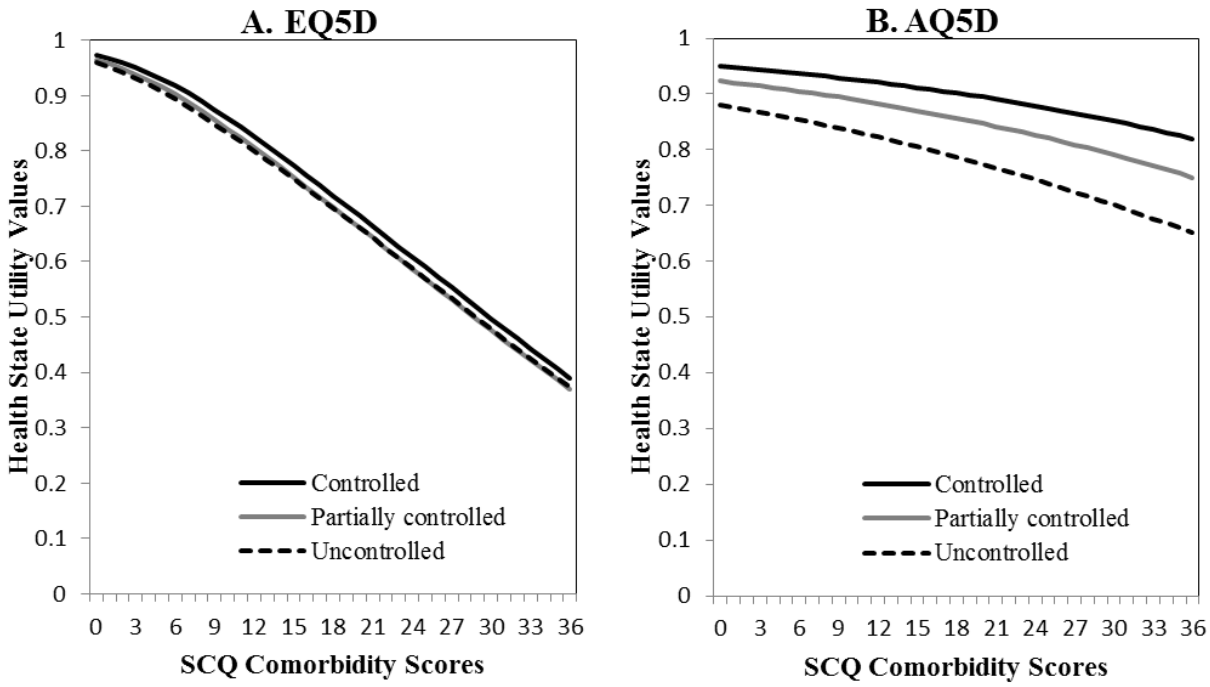
0.020– -0.004]) utilities. Further, an increase by one standard deviation (increase in SCQ scores of 3.61) above the mean was associated with significant reductions in EQ5D by -0.045 (95% CI, -0.031– -0.059), and in AQ5D by -0.012 (95% CI, -0.006– -0.024). The marginal effects of comorbidity stratified across levels of symptom control are displayed in Figure 5.3 (95% CIs were not provided for clarity of the figure). Across all levels of symptom control, an increase in comorbidity scores resulted in a continuous decrease in both EQ5D and AQ5D utilities. The magnitude of comorbidity-associated utility loss in EQ5D was very similar between different levels of symptom control whereas it varied considerably as when measured using the AQ5D.

Figure 5.2 Marginal estimates of utility values by comorbidity.



Adjusted means and 95% credible interval for two utility measures: EQ5D and AQ5D. The lines denote the predicted mean scores. The bars show 95% credible interval.

Figure 5.3 Marginal estimates of utility values by comorbidity and asthma symptom control.



The lines denote adjusted means for two utility measures, EQ5D and AQ5D, in symptomatically controlled, partially controlled, uncontrolled asthma.

Secondary outcomes: Strength of association between symptom control and comorbidity with quality of life

Table 5.4 illustrates the strength of the association between the independent variables and utilities. A model which only included covariates explained 11.0% and 10.2% of variation in EQ5D and AQ5D utilities, respectively. The full model (covariates + comorbidity + symptom control) explained 24.7% and 26.4% of the variation in EQ5D and AQ5D utilities, respectively. Removal of symptom control from the full model decreased the explained variation in utility scores by 0.7% for EQ5D but by 11.6% for AQ5D, indicating the much larger sensitivity of AQ5D than EQ5D to asthma symptom control. Removal of comorbidity from the full model

reduced the explained variation by 12.0% in EQ5D and 2.9% in AQ5D utilities, this time showing the higher sensitivity of EQ5D than AQ5D to the presence of comorbid conditions (i.e., the higher specificity of the AQ5D to asthma). The interaction of symptom control and comorbidity did not increase the explained variation in both utilities (EQ5D: 24.7% vs. 24.7%, AQ5D: 26.7% vs 26.4%). Among the twelve comorbid conditions included, depression was the most influential comorbidity on both EQ5D and AQ5D utilities; removal of depression reduced R^2 by 6.1% for EQ5D and by 1.7% for AQ5D.

Table 5.4 Proportions of variance explained by predictors (R^2).

Independent variables	EQ5D	AQ5D
Covariates+ Symptom Control + Comorbidity + Interaction[a]	24.7%	26.7%
Covariates+ Symptom Control + Comorbidity	24.7%	26.4%
Covariates+ Symptom Control	12.7%	23.5%
Covariates+ Comorbidity	24.0%	14.8%
Symptom Control Only	9.1%	17.1%
Comorbidity Only	22.3%	7.7%
Covariates Only	11.0%	10.2%
Covariates+ Asthma Control+ Comorbidity Components	30.0%	29.2%
EXCLUDING:		
Heart diseases	29.9%	29.2%
Hypertension	29.7%	29.1%
Diabetes	29.5%	28.9%
Ulcer or stomach diseases	30.1%	29.1%
Kidney disease	29.9%	29.0%
Liver disease	30.0%	29.2%
Anemia or other blood disease	30.1%	29.2%
Cancer	29.9%	29.2%
Depression	23.9%	27.5%
Osteoarthritis, degenerative arthritis	29.7%	29.1%
Back pain	28.4%	28.7%
Rheumatoid arthritis	28.8%	27.7%

[a] Interaction between levels of symptom control and comorbidity scores.

5.4 Discussion

In this chapter, I evaluated the validity of popular generic and disease-specific utility instruments in terms of their ability to simultaneously differentiate changes in asthma symptom control and comorbidity status. The full regression model explained a similar proportion of variability in utility estimated from both generic and asthma-specific instruments (24.7% of variation in EQ5D and 26.4% in AQ5D). Statistically, both EQ5D and AQ5D utilities discriminated changes in comorbidity and across all three levels of symptom control. However, EQ5D was much more sensitive to comorbidities than to asthma symptom control (12.0% vs. 0.7% of variation), whereas AQ5D was much more sensitive to asthma symptom control than to comorbidities (11.6% vs. 2.9%). Therefore, this current work estimated that changes in asthma symptom control had a much greater marginal impact on AQ5D than on EQ5D utilities. Conversely, increase in comorbidity burden leads to a much larger reduction in EQ5D than AQ5D utilities, both in general and across different levels of symptom control. Our findings are in line with the few studies which found that comorbidity greatly affects utilities measured by the generic instrument whereas the influences on disease-specific utilities are much smaller.[89,119]

This study can be viewed as an extension of previous studies on the validity of generic and disease-specific HRQoL measures in terms of distinguishing among levels of control in asthma.[82,84–86] Given the demonstrated significant impact of comorbidity on the utility values reported by asthma patients, ignoring comorbidity may lead to inaccurate estimation of the effectiveness of asthma treatments. For instance, when the treatment contributes to comorbidity or comorbidity negatively affects the treatment effects, the effectiveness of asthma treatments can be overestimated if the impact of comorbidity on utilities is not considered. On the other

hand, if the intervention improves not only asthma but also overall health, the effectiveness of the treatment will be underestimated without taking comorbidity into account.

The EQ5D has been considered valid and reliable for asthma studies,[87] although a recent study found EQ5D unable to discriminate between the moderate levels of control.[82] The current results showed that the marginal gain in EQ5D utility from symptomatically uncontrolled to controlled asthma was very subtle (0.018). Despite the statistical significance, such small incremental changes in utility can potentially result in huge incremental cost-effectiveness ratios (ICERs) for targeted asthma interventions, thus rarely showing such type of interventions cost-effective. These findings suggest that in the high-end of the utility scale (mild asthma patients) and in the presence of comorbidity, EQ5D is less capable of capturing asthma-associated changes in utility. This may be explained by the fact that the EQ5D was designed to measure health status irrespective of underlying diseases. Furthermore, compared to the overall comorbidity burden, patients may not continuously experience asthma manifestations and can better cope with and adapt to asthma over time.[173]

Compared to EQ5D, AQ5D was much better at differentiating among levels of asthma symptom control. Though to a lesser extent than with EQ5D, the presence of comorbidities also affected AQ5D utility measures. There may be a dose-response relation between overall disease burden and HRQoL, as indicated by previous studies in asthma and other diseases,[89,174,175] even in disease-specific HRQoL measures. It is also possible that the effect of comorbidity on utility is partly attributable to its potential associations with sub-optimal asthma control. However, our results do not support this hypothesis because the interaction between asthma control and comorbidity did not significantly affect utility. A prior study found that certain comorbidities

(e.g., hypertension, gastrointestinal conditions) acted as mediating factors in the effects of drug treatment on asthma-specific HRQoL measures.[38]

This study has several strengths. First, conclusions were drawn based on a relatively large longitudinal random sample and thus the results have a high level of external validity. Second, the use of validated and internationally accepted measures of HRQoL, asthma symptom control, and comorbidity further improved the validity and applicability of our findings. Third, associations were examined using an efficient and rigorous statistical framework that could properly handle the skewed nature of the outcome data and clustered observations.

On the other hand, the current study also has some limitations. First, this study sample was comprised of generally mild asthma patients, which may be attributable to the healthy volunteer bias as a result of the requirement for multiple visits to study sites. In this regard, I found the mean EQ5D utility values to be higher than those reported in the general adult population of the United Kingdom,[74] United States[74] and Canada.[76] The high EQ5D scores leaves less room for distinguishing small improvements in symptom control and comorbidity. Also, the generally healthy sample hampers our ability to extrapolate such associations to individuals with more severe asthma.[176] Second, there are potential biases associated with self-reported outcomes. For instance, study subjects were enrolled based on self-reported physician-diagnosis of asthma, which has the potential for diagnostic mislabelling. However, asthma management in the real world is inevitably affected by such mislabelling; thus the results can be more generalizable to clinical practice than those based on samples of diagnostically confirmed asthma patients. Additionally, individuals with self-reported comorbidities might also tend to report more asthma symptoms and a reduced HRQoL, causing reporting bias.

With these limitations in mind, this study has important implications for assessing outcomes and comparing treatment options in asthma. Firstly, by demonstrating high prevalence and significant impact of comorbidity on HRQoL, this study highlights the importance of considering comorbidity status in the estimation of asthma treatment effects. Secondly, it yields important information about the empirical measurement properties of generic and disease-specific instruments and their applicability to utility measurement to support cost-effectiveness analyses in asthma. Given symptom control as the cornerstone of contemporary evidence-based asthma management,[2] as well as the important role of comorbidity on utilities and its potential interaction with asthma treatments, researchers should carefully justify their choice of utility instruments in the design of studies on asthma interventions. For broad-scope interventions such as life style modification in asthma patients that lead to improvement in overall health, generic instruments like EQ5D tend to show a greater improvement in utility compared to asthma-specific instruments like AQ5D, and thus are more likely to show the intervention being cost-effective. Likewise, for interventions specifically targeted at improving asthma symptoms, AQ5D may be more prone to show them being cost-effective than EQ5D, particularly among patients with mild asthma and good overall health. However, for more aggressive interventions targeting severe asthma, it is recommended to compare utility outcomes measured by both generic and asthma-specific instruments to evaluate the influences of the intervention on both asthma and overall health. Future studies should investigate the interaction of asthma interventions with asthma control and comorbidity in determining HRQoL, and evaluate the within-individual changes in HRQoL as a function of changes in comorbidity over time.

5.5 Conclusion

Using a longitudinal random sample of patients with asthma in BC, Canada, in this Chapter I examined the validity of generic and disease-specific HRQoL instruments in terms of their ability to discriminate between changes in asthma control and comorbidity status at the same time. The association between both asthma symptom control, comorbidity status with utilities measured by a generic instrument (EQ5D) and an asthma-specific instrument (AQ5D) was estimated using a two-part GLM. I found that changes in comorbidity led to a much greater reduction and explained a much larger proportion of variability in EQ5D utilities compared to asthma symptom control, though it was the opposite in AQ5D utilities. These results indicate that EQ5D and AQ5D differentially capture the influences of asthma control and comorbidity in the utility of patients with asthma, with the former much more sensitive to comorbidity whereas the latter much more sensitive to asthma control. While both can be used in the economic evaluation of asthma interventions, researchers should select HRQoL instruments based on the specific purposes of the intervention and carefully compare the cost-effectiveness profiles measured from different HRQoL instruments before the decision-making recommendation.

Chapter 6: Interpretations and conclusion

This last chapter concludes my thesis work by summarizing the main study findings, reviewing the strengths and limitations and the implications of this area of research.

6.1 Summary of study findings

This thesis consisted of four separate studies: understanding the natural history of severe asthma, examining the socioeconomic gradient in health care costs of asthma, estimating the impact of comorbidity in health care costs of asthma, and assessing the joint influences of asthma control and comorbidity on health-related quality of life in asthma patients.

Current literature has mainly focused on biological indicators of asthma, namely lung function, to characterize the natural history of the disease. The conventional wisdom is that in severe asthma, lung function progressively declines over and beyond the age-related decline in the general population.[4] However, it is known that lung function poorly correlates with clinical and outcomes manifestations of asthma, which are the true determinants of its burden.[6] Using long-term 'real world' data of the entire asthma population of a well-defined geographic area, I showed that the clinical course of severe asthma was generally benign, as patients with incident severe asthma often transitioned to milder asthma in the long run. I estimated that 83% of patients with incident severe asthma, as suggested by the intensity of asthma-related health resource uses, would transition to mild/moderate asthma over the next ten years. Moreover, this study provides the first evidence that low socioeconomic status (SES) and comorbidity at onset of severe asthma were associated with poorer prognosis in terms of lower chance of transitioning to milder asthma. Such finding generated further questions as to what extent comorbidity and

socioeconomic status affect the economic and humanistic burden of asthma. Pursuing these questions motivated the design of the subsequent chapters in this thesis.

The results of the subsequent research in this thesis indicate that both low SES and comorbidity are associated with a greater economic burden due to asthma, and that comorbidity is an important determinant of quality of life in asthma patients. In this thesis, the economic burden of asthma was estimated as the excess direct medical costs ("excess costs" for brevity) in asthma patients, over and beyond the costs incurred by non-asthma individuals with similar characteristics. Excess costs capture the extra economic burden of asthma patients due to both their asthma and asthma-related comorbidities.

With my initial attention on the influence of SES on the economic burden of asthma, I hypothesized that the universal health care system in Canada should have largely reduced the potential socioeconomic disparities in asthma costs, as it should improve access to guideline-based health care in patients with asthma.[57] However, at both individual and neighborhood level, I documented substantial socioeconomic gradients in both the economic burden of asthma and indicators of guideline-based asthma care, where the low-SES group incurred much higher excess costs of asthma, together with higher expenses on rescue medications yet lower expenses on controller medications. Over time, the socioeconomic gaps in asthma costs remained constant at the individual level but slightly narrowed at the neighborhood level. Meanwhile, the socioeconomic gaps in costs of asthma medications persisted across both levels. These SES-related disparities in asthma costs and guideline-based asthma care may be correlated. In addition, the higher asthma costs in the low-SES group may be related to the worse population health of low-SES neighborhoods.

When estimating the economic burden of asthma from a health care payer's perspective, previous studies have predominantly focused on asthma-attributable health care resource utilization while largely ignoring the economic impact of asthma-related comorbidities.[10] By contrasting the overall direct costs in patients with asthma versus the non-asthma population, my estimated excess costs of asthma ($1,187/year) better reflects the true economic burden of asthma than asthma-attributable costs. Importantly, I showed that the contribution of comorbid conditions was five times higher than the contribution of asthma itself in determining the overall economic burden of asthma. Psychiatric diseases, respiratory diseases other than asthma, digestive disorders and diseases of nervous system had the greatest economic implications in asthma. Both all-cause and comorbidity-attributable excess costs greatly increased with age. However, within age groups, these costs did not increase over the course of asthma, which could be related to the non-progressive nature of asthma as reported in the second chapter.

Last, I further examined the role of comorbidity on health-related quality of life (HRQoL) in asthma. I realized that an important potential confounder/mediator of the impact of comorbidity on HRQoL is the status of asthma control. Current investigations on the humanistic burden of asthma are predominantly focused on the influence of asthma control on HRQoL,[82,84–86] while the few that have focused on comorbidities seldom considered the impact of asthma control.[89,91,92] In addition, HRQoL in asthma patients can be measured through either generic or disease-specific HRQoL measurement tools, and I realized that the choice of the instrument can have profound impact on the results of such a study. I showed that both asthma control and comorbidity had profound impact on asthma patients' HRQoL, and that asthma-specific HRQoL

was much more sensitive to changes in asthma control than to changes in comorbidity and vice versa for generic HRQoL.

6.2 Strength of the thesis research

A major strength of this thesis work is the focus on population-based study samples which improves the external validity and generalisability of its results. Three out of the four studies in this thesis were based on large real-world health-services use records (spanning over 16 years) of the entire asthma population of BC, one of the largest provinces of Canada[93]. As a result, the findings have a low risk of selection bias as the usual healthy volunteer bias. Likewise, the last study used a longitudinal population-based random sample of patients with asthma in two representative census subdivisions in BC.[163] In addition, the follow-up allowed this work to elucidate patterns and trends, and provide a relatively comprehensive picture of long-term changes in asthma outcomes. This work is further strengthened by the use of robust, modern analytical methods. In Chapter 2, the ten-year trajectory of severe asthma was estimated using a Generalized Linear Model (GLM) which estimated the transition probabilities of a four-state Markov process. Rather than ignoring possible relapse, as has been done in previous studies,[28] this framework captured the dynamic transitions between different states of asthma severity. In Chapter 3, I applied a survival-adjusted, multi-part GLM model[132] to address common problems in the estimation of longitudinal health care costs, such as incomplete data due to early withdrawal or death, zero-inflated and skewed cost data, and the high costs associated with death. In Chapter 4, the estimation of the economic burden of asthma was based on a propensity-score matched cohort, which improves the study validity by minimizing the disparity in the distribution of potential confounding factors between the asthma and non-asthma cohorts.

Because HRQoL data was also skewed, with the majority of patients reporting high to perfect quality of life, a two-part GEE model was specifically constructed in Chapter 5 to account for this feature of the data, as well as to properly handle the clustered nature of the data. Additionally, on several occasions, to enable causal interpretation on estimates of the independent effects of risk factors on outcomes, I have made extensive efforts to reduce confounding through 1) rigorous propensity score matching, 2) G-computation to decouple the estimation of the effect of interest from confounding effects,[111] 3) adjustments in multivariable analyses.

6.3 Limitations of the thesis research

However, this thesis work also has limitations. First, the data used to address research questions in this thesis are observational in nature. This means that my ability to remove the potential confounding effects were limited to the variables which were available in the datasets. Next, although this thesis is based on population-based samples of asthma patients to minimize selection bias, information bias such as misclassification is quite possible.[177] Misclassification can occur to administrative data when diagnostic codes were incorrectly assigned or the diagnosis itself was erroneous.[157] It is unclear whether the misclassification would be systematically different for asthma patients compared to the general population. Likewise, self-reported HRQoL outcomes, were analyzed in Chapter 5, could be associated with recall bias and reporting bias.[177] For instance, patients with self-reported comorbidities might tend to report more asthma symptoms and a reduced HRQoL. Third, the asthma samples used in this thesis are identified by extracting records using resource-use-based case definition algorithms or self-report of physician diagnosis rather than a standardized approach of clinical diagnosis. Asthma is

generally over-diagnosed in Canada[178] and this means a fraction of the self-reported asthma sample would not meet the clinical definition of asthma (e.g., a positive airway challenge test[179]). However, I consider this to be a positive aspect as individuals falsely diagnosed with asthma do contribute to societal burden of the disease. In fact, true asthma status was available in the data used for the analysis in Chapter 5 but was intentionally not used in the analysis due to its lack of relevance to the study objective. On the other hand, case definition algorithms for asthma based on resource use records, though validated,[101] are restrictive definitions that require relatively high-intensity asthma treatment. Thus, patients with mild asthma and less intensive resource uses might have been excluded from the study.

6.4 Contribution and implications of the research findings

My thesis presents a unique, coherent body of work on the complex longitudinal profiles of health outcomes in the general asthma population, including disease trajectory of asthma, health care costs and health-related quality of life in asthma patients. Given their relevance to asthma management and health care policy, the studies comprising this thesis contribute significantly to current literature. Modern asthma management guidelines consider asthma symptom control and future risk as the centerpiece of disease management and use it to guide treatment decisions.[2] Asthma can be effectively controlled with guideline-based care in most patients, which should, theoretically, lead to minimal life disruptions and eventually prevent unnecessary health care costs while keeping patients' quality of life at a high level.[2] However, rather than solely dependent on asthma control, the results of my thesis highlight the crucial need to consider asthma in a broader social and health context when disease management strategies are being planned.

In particular, my specific demonstrations of the substantial socioeconomic disparities in long-term asthma prognosis, costs and guideline-based asthma care in Canada convey significant policy implications for countries with universal health care and for those planning to expand coverage. These implications also extend beyond the boundaries of asthma into other chronic ambulatory diseases. Although Canada's universal health care system has minimized out-of-pocket expenses for the disadvantaged population, my study provides direct evidence that open access to health care is insufficient to guarantee guideline-based disease management in the low-SES population. This may help to explain the subsequent worse asthma outcomes associated with this group. The persistence of these inequalities across the individual and neighborhood levels might indicate a lack of adequate primary care or insufficient access to drug (e.g., inadequate drug coverage) among the low-SES group. Therefore, health care programs should strive to improve the supply and quality of primary care in low-SES neighborhoods, expanding drug coverage and encouraging guideline-based management and educating the importance of medication adherence among poor individuals. In addition, my findings about the worse population health in low-SES neighborhoods calls for immediate attention for health care programs to integrate neighborhood-level interventions into asthma management; e.g., programs to improve the living environment and healthy food supply in poor neighborhoods.

Furthermore, my thesis demonstrates that asthma control, the centerpiece of current guideline-based asthma care,[2] is not the only major determinant of health outcomes in asthma patients. Rather, patients' overall health, as indicated by comorbidity status, also plays a critical role in determining long-term asthma prognosis, health care costs and quality of life in the presence of primary disease (asthma). In fact, comorbidity's contribution to the overall economic burden of

asthma patients outweighs that of asthma itself, with the former also increasing with age at a much faster pace than the latter. This finding expands the current focus of asthma management guidelines from achieving optimal control to concurrently preventing and treating comorbidity in asthma patients; the benefits of this strategy will transcend beyond the period of intervention to improve long-term prognosis and reduce the long-term burden of asthma. This changes not only the scope of asthma management but also its intervention strategies, because it highlights the need to treat asthma as a part of the multi-morbidity rather than as an isolated identity. This will require more careful design of treatment plans to benefit both asthma and overall health and to avoid comorbidities and their complications. Consequently, the findings from my study have the potential to alter the cost-effectiveness profiles of both targeted asthma interventions through their possible interactions with comorbidity and broader-scale interventions intended to improve the overall health of asthma patients (e.g., smoking cessation programs and mental health support networks).

Despite the disproportionately high disease burden of severe asthma, the natural history of the long-term changes in underlying severity have not been intensively investigated. My demonstration of the failure of severe asthma to persist and progress for most individuals, as indicated by the waning in the intensity of asthma resource utilization over time, has direct relevance to the current management of severe asthma. Current management guidelines are paying increasingly more attention to formulate an optimal treatment strategy based on expensive, advanced medications such as omalizumab.[180] However, since my population-based study cohort seldom used such medications, my study shows that the majority of patients who start with suggesting severe asthma, as indicated by intensive conventional treatments in real-

world clinical practice, are able to outgrow it over time. This finding indicates that experiencing incident severe asthma in a particular year does not provide sufficient justification for the sustained use of advanced new asthma treatments. Additionally, in the economic analyses of treatments for severe asthma, researchers often focus on changes in asthma control by assuming constant asthma severity over time.[181–183] My study provides a better evidence base that should improve the real-world cost-effectiveness profiles of these treatment interventions, and this should greatly improve asthma management as well as the overall health care resources allocated for asthma.

In addition to the clinical and policy contribution, this thesis makes unique contributions to the methodology of longitudinal studies of asthma outcomes. The rigorous, innovative statistical framework of which this thesis developed to examine the natural history of severe asthma can be used in the disease trajectory studies of chronic diseases in general. Its ability to quantify the impact of rick factors on the future disease trajectory can be extended to studying a variety of different topics, such as the influences of early-life risk factors on life-time development of the disease, treatment effects on modifying future disease course, and so forth. Moreover, this thesis conveys important practical implications on the metric properties of generic and disease-specific HRQoL instruments regarding their ability to support the economic analysis of asthma interventions. According to the current findings, a generic instrument such as the EQ5D is more capable of detecting the effectiveness of broad-scope interventions that aims to improve overall health in asthma patients, while an asthma-specific instrument like AQ5D is more sensitive to the effectiveness of interventions that specifically aim to improve asthma symptoms. For aggressive intervention targeting more severe cases of asthma, researchers should carefully

compare the outcomes measured by generic and asthma-specific instruments because the relieving of severe asthma symptoms are also likely to simultaneously improve patients' overall health.

6.5 Future studies

Each component of this thesis, while addressing specific hypotheses and pursuing pre-defined research objectives, has resulted in the generation of further questions that need to be addressed by future research in these areas.

The clinical course of asthma can start from childhood and vary remarkably between young children, older children and adolescents, and adults.[4] Therefor, in search of the modifiable determinants of long-term course of asthma, future studies should identify early-life risk factors that influence the life time trajectory of asthma from childhood to adulthood. An important factor to study is the long-term effect of asthma treatments, as any long-term impact will convey important implications in clinical practice and asthma management guidelines.

Insufficient guideline-based care appears to be a major reason for the worse long-term asthma prognosis and substantially higher asthma costs in lower SES populations. Addressing the underlying reasons is paramount to designing appropriate intervention strategies to reduce these disparities. SES is likely to affect guideline-based care via multiple pathways, including non-adherence, lack of drug coverage, and non-preferential access to primary care,[133–136] as well as aggregate-level factors such as possibly insufficient supply of primary care in poor neighborhoods,[137] all of which are worthy of future investigation. In addition, to better inform health policy and management, the confounding impacts of education, ethnicity and the

mediating impacts from smoking and being attached to a primary physician should be further explored.

Another major finding of this thesis is the substantial influences of comorbidity on disease progression, health care costs, and HRQoL in asthma patients. The underlying mechanisms of such associations need to be elucidated. Although my current work does not find asthma control and comorbidity interact to a significant degree to determine asthma patients' quality of life, it is possible that these two factors still interact to affect other asthma outcomes such as health care costs, risk of severe exacerbations, or mortality, which should be further explored. In addition, the causal relationship between asthma control and comorbidity is an important area to be investigated. If the status of asthma control affects the long-term burden of comorbidity, then achieving and maintaining asthma control should convey an indirect benefit that has hitherto not been identified. This could have major implications in estimating the cost-benefit profile of asthma management strategies. Moreover, I found that psychiatric disorders were the largest component of excess medical costs in asthma patients, and that depression was the most influential comorbid factor in patients' HRQoL. As such, it is also worth to examine the separate the burden attributable to mood disorders versus psychoses. Such information will be directly relevant for designing targeted interventions for the prevention, diagnosis, and management of psychiatric disorders in asthma patients.

6.6 Conclusions

In this thesis, I have examined the natural history of severe asthma, long-term health care costs and health-related quality of life in asthma patients and their potential determinants.

Understanding the natural history of asthma and how costs and quality of life are affected in patients with asthma will improve our knowledge of asthma and asthma management. For the first time, I have shown that SES and comorbid conditions are both important determinants of the natural history of asthma. I have also provided first-hand evidence that there are substantial socioeconomic inequalities in both long-term health care costs and the management of asthma, with low SES population incurring higher costs and receiving inadequate guideline-based care. Moreover, in addition to asthma control, comorbid conditions also play a critical role in determining both health care costs and the quality of life of asthma patients. These findings convey important policy and clinical implications. With the knowledge that there are substantial socioeconomic disparities in asthma costs and that open access to health care does not ensure guideline-based care in poor individuals who have asthma, researchers and health care programs should investigate the underlying reasons for this disconnect and design targeted interventions to improve asthma management in these patients. This will greatly reduce the unnecessary economic burden of asthma. Further, my specific demonstration of the substantial role of comorbidity in long-term asthma prognosis and outcomes adds greatly to the asthma-control-centered management of current guidelines, highlighting the importance of taking comorbidity into account in disease management, cost-effectiveness analyses of asthma interventions, as well as the urgent need to investigate the underlying mechanism of comorbidity effects especially its interaction with asthma control in determining long-term outcomes.

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Appendices

Appendix A List of asthma-related medications.

Medication categories	Medication type	Active ingredient(s)	ATC	DIN	Used in case definition?
Inhaled corticosteroids (ICS)	Controller	Beclomethasone	R03BA01	2242030, 2242029, 374407, 828521, 828548, 872334, 893633, 897353, 1949993, 1950002, 2079976, 2213710, 2213729, 2215039, 2215047, 2215055, 2216531	Y
		Budesonide	R03BA02	2229099, 1978918, 1978926, 852074, 851752, 851760	Y
		Fluticasone	R03BA05	2237247, 2237246, 2237245, 2237244, 2244293, 2244292, 2244291, 2174731, 2174758, 2174766, 2174774, 2213583, 2213591, 2213605, 2213613	Y
		Ciclesonide	R03BA08	2285614, 2285606, 2303671	Y
Short-acting beta-agonists (SABA)	Reliever	Salbutamol	R03AC02	790419, 812463, 832758, 832766, 851841, 860808, 867179, 897345, 1926934, 1938851, 1938878, 1945203, 1947222, 1986864, 2022125, 2046741, 2048760, 2069571, 2084333, 2148617, 2154412, 2173360, 2208229, 2208237, 2208245 2212315, 2212323, 2213400, 2213419, 2213427, 2213478, 2213486, 2214997, 2215004, 2215616, 2215624, 2215632, 2216949, 2231430, 2231488, 2231678, 2231783, 2231784, 2232570, 2232987, 2236931, 2236932, 2236933, 2239365, 2239366, 2241497, 2243115, 2243828, 2244914, 2245669, 2259583, 2326450	Y
			R03CC02	620955, 620963, 874086, 894249, 894257, 1932691, 2035421, 2063689, 2091186, 2146843, 2146851, 2164434, 2164442, 2165368, 2165376, 2212390, 2213435, 2213443, 2213451, 2261324	Y
		Terbutaline	R03AC03	786616	Y
		Orciprenaline	R03CB03	249920, 3891, 2236783, 2229862, 2152568, 2192675	Y
Long-acting beta-agonists (LABA)	Controller	Salmeterol	R03AC12	2211742, 2214261, 2231129, 2136139, 2136147	Y
		Formoterol	R03AC13	2230898, 2237224, 2237225	Y
ICS and LABA in combination (ICS+LABA)	Controller	Budesonide, formoterol	R03AK07	2245385, 2245386	Y
		Fluticasone, salmeterol	R03AK06	2240835, 2245126, 2245127, 2240836, 2240837	Y

Medication categories	Medication type	Active ingredient(s)	ATC	DIN	Used in case definition?
Leukotriene receptor antagonists (LTRA)	Controller	Montelukast	R03DC03	2247997, 2238217, 2243602, 2238216	Y
		Zafirlukast	R03DC01	2236606	Y
Anti-immunoglobulin E monoclonal antibody	Controller	Omalizumab	R03DX05	2260565	Y
Inhaled mast cell stabilizers	Controller	Cromoglicic acid (cromolyn)	R03BC01	2231431, 2231671, 2046113, 534609, 555649, 261238, 638641, 2049082, 2219468	Y
Theophylline	Controller	Choline theophyllinate	R03DA02	346071, 405310, 441724, 441732, 451282, 458708, 458716, 476366, 476390, 476412, 503436, 511692, 536709, 565377, 589942, 589950, 792934	Y
		Theophylline	R03DA04	156701, 261203, 460982, 460990, 461008, 466409, 488070, 532223, 556742, 575151, 599905, 627410, 631698, 631701, 692689, 692697, 692700, 722065, 1926586, 1926594, 1926608, 1926616, 1926640, 1966219, 1966227, 1966235, 1966243, 1966251, 1966278, 1966286, 2014165, 2014181, 2230085, 2230086, 2230087	Y
		Aminophylline	R03DA05	14923, 178497, 497193, 497193, 497207, 582654, 582662, 868450, 2014270, 2014289	Y
Inhaled anticholinergics	Reliever	Ipratropium bromide	R01AX03	2246084, 2246083, 2163705, 2163713, 2240508, 2240072	N
			R03BB01	2126222, 2243827, 2231494, 731439, 576158, 2247686, 824216, 2026759, 1950681, 2239131, 2216221, 2210479, 2231785, 2236934, 2236935, 2237134, 2237135, 2239627, 2231135, 2231136, 2231245, 2231244, 2097141, 2097176, 2097168	N
		Ipratropium bromide, fenoterol	R03AK03	02148633	N
		Tiotropium bromide	R03BB04	02246793	N
Other beta-agonists	Reliever	Epinephrine	R03AA01	2017555, 466417, 525103, 1927582	N
		Ephedrine	R03CA02	2237085, 2229698, 2100231, 2100258, 2243148, 2236722, 2229678, 2219743, 2012111, 2229711, 38121, 2242961, 876534, 893323, 893331, 438847, 2242639, 2126419, 2126400	N
		Isoprenaline	R03AB02	2017652	N
		Orciprenaline	R03AB03	1923870, 1928449, 2017660, 254134, 3859	N

Medication categories	Medication type	Active ingredient(s)	ATC	DIN	Used in case definition?
Other corticosteroids	Controller	Cortisone	H02AB10	280437, 16241, 16446, 16438	N
		Triamcinolone	H02AB08	2194090, 15016, 15024, 2194082	N
		Prednisone	H02AB07	610623, 598194, 550957, 312770, 252417, 210188, 868426, 868434, 868442, 21695, 232378, 607517, 508586, 156876, 271373, 271381	N
		Prednisolone	H02AB06	21679, 2230619, 2152541, 2245532	N
		Methylprednisolone	H02AB04	1934325, 1934333, 1934341, 30759, 30767, 36129, 30988, 2245406, 2245400, 2245408, 2245407, 2241229, 2231893, 2231894, 2231895, 2232750, 2232748, 2063727, 2063697, 2063719, 2063700, 36137, 2230210, 2230211, 30678, 30651, 30643	N
		Betamethasone	H02AB01	2237835, 36366, 2063190, 176834, 28096, 28185	N
		Hydrocortisone	H02AB09	888222, 888230, 888206, 888214, 30910, 30929, 872520, 872539, 878618, 878626, 30635, 30600, 30619, 30627	N
		Dexamathasone	H02AB02	2261081, 2250055, 213624, 16462, 354309, 716715, 874582, 1977547, 664227, 2204274, 2204266, 295094, 285471, 489158, 2239534, 732893, 732885, 2260301, 2237044, 2260298, 2237046, 2237045, 1946897, 1964976, 1964968, 1964070, 2279363, 783900, 751863, 2311267, 2240687, 2240685, 2240684	N
Other xanthines	Controller	Theophylline, combination	R03DA54	545090, 476374, 334510, 356123, 792942, 721301, 317225, 828718, 640093, 828726, 828742, 307548	N
Other anti-allergic agents	Anti-allergic	Levocabastine	R01AC02	2020017	N
		Ketotifen	R06AX17	2221330, 2176084, 2230730, 2218305, 2231680, 2231679, 600784, 577308	N

Appendix B The 28-states transition probability matrix of Chapter 2's Markov model.

Asthma Severity in the Past 3 years			Probability of Severity Level in Year (T+1)			
Year (T-2)	**Year (T-1)**	**Year T**	**Mild**	**Moderate**	**Severe**	**Death**
Mild	Mild	Mild	Π_{0000}	Π_{0001}	Π_{0002}	Π_{0003}
Moderate	Mild	Mild	Π_{1000}	Π_{1001}	Π_{1002}	Π_{1003}
Severe	Mild	Mild	Π_{2000}	Π_{2001}	Π_{2002}	Π_{2003}
Mild	Moderate	Mild	Π_{0100}	Π_{0101}	Π_{0102}	Π_{0103}
Moderate	Moderate	Mild	Π_{1100}	Π_{1101}	Π_{1102}	Π_{1103}
Severe	Moderate	Mild	Π_{2100}	Π_{2101}	Π_{2102}	Π_{2103}
Mild	Severe	Mild	Π_{0200}	Π_{0201}	Π_{0202}	Π_{0203}
Moderate	Severe	Mild	Π_{1200}	Π_{1201}	Π_{1202}	Π_{1203}
Severe	Severe	Mild	Π_{2200}	Π_{2201}	Π_{2202}	Π_{2203}
Mild	Mild	Moderate	Π_{0010}	Π_{0011}	Π_{0012}	Π_{0013}
Moderate	Mild	Moderate	Π_{1010}	Π_{1011}	Π_{1012}	Π_{1013}
Severe	Mild	Moderate	Π_{2010}	Π_{2011}	Π_{2012}	Π_{2013}
Mild	Moderate	Moderate	Π_{0110}	Π_{0111}	Π_{0112}	Π_{0113}
Moderate	Moderate	Moderate	Π_{1110}	Π_{01111}	Π_{1112}	Π_{1113}
Severe	Moderate	Moderate	Π_{2110}	Π_{21111}	Π_{2112}	Π_{2113}
Mild	Severe	Moderate	Π_{0210}	Π_{0211}	Π_{0212}	Π_{0213}
Moderate	Severe	Moderate	Π_{1210}	Π_{1211}	Π_{1212}	Π_{1213}
Severe	Severe	Moderate	Π_{2210}	Π_{2211}	Π_{2212}	Π_{2213}
Mild	Mild	Severe	Π_{0020}	Π_{0021}	Π_{0022}	Π_{0023}
Moderate	Mild	Severe	Π_{1020}	Π_{1021}	Π_{1022}	Π_{1023}
Severe	Mild	Severe	Π_{2020}	Π_{2021}	Π_{2022}	Π_{2023}
Mild	Moderate	Severe	Π_{0120}	Π_{0121}	Π_{0122}	Π_{0123}
Moderate	Moderate	Severe	Π_{1120}	Π_{1121}	Π_{1122}	Π_{1123}
Severe	Moderate	Severe	Π_{2120}	Π_{2121}	Π_{2122}	Π_{2123}
Mild	Severe	Severe	Π_{0220}	Π_{0221}	Π_{0222}	Π_{0223}
Moderate	Severe	Severe	Π_{1220}	Π_{1221}	Π_{1222}	Π_{1223}
Severe	Severe	Severe	Π_{2220}	Π_{2221}	Π_{2222}	Π_{2223}
Any	Any	Death	0	0	0	1

Appendix C Costs per weighted case (CPWC) for the case mix methodology.

Calendar Year	CPWC
2012	$5,346
2011	$5,134
2010	$5,578
2009	$5,442
2008	$5,166
2007	$4,939
2006	$4,802
2005	$4,767
2004	$4,325
2003	$4,270
2002	$4,096
2001	$3,921
2000	$3,746
1999	$3,572
1998	$3,397
1997	$3,223

Appendix D Detailed regression results for excess direct medical costs of moderate-to-severe asthma in Chapter 3.

	Survival			Costs for non-death intervals						Costs for death intervals		
	Logged survival time			Pr(zero cost)			Cost if >$0			Cost		
	β	SE	p-value	β	SE	p-value	β	SE	p-value	β	SE	p-value
Intercept	227.751	14.661	<.0001	-67.547	34.815	0.052	-533853.0	166147.4	0.001	-5061495.0	2182312.0	0.020
Asthma												
No=0	Reference			Reference			Reference			Reference		
Yes=1	-0.575	0.093	<.0001	-9.944	32.241	0.758	-207504.0	189782.0	0.274	4435246.0	2130279.0	0.037
Neighborhood SES												
Low SES=1	Reference			Reference			Reference			Reference		
Middle SES=2	0.536	0.168	0.001	-25.635	23.056	0.266	-128719.0	163456.1	0.431	1369153.0	988779.9	0.166
High SES=3	0.033	0.104	0.750	-55.688	20.564	0.007	-34683.4	109374.3	0.751	1206634.0	1358898.0	0.375
nSES x Asthma												
1 0	-			-			-			-		
1 1	-			-			-			-		
2 0	Reference			Reference			Reference			Reference		
2 1	-0.537	0.182	0.003	-0.331	0.152	0.030	-635.3	551.1	0.249	22657.0	9006.5	0.012
3 0	Reference			Reference			Reference			Reference		
3 1	-0.006	0.121	0.959	-0.004	0.110	0.969	-133.2	484.6	0.784	24477.5	8921.1	0.006
Individual SES												
Others=0	Reference			Reference			Reference			Reference		
Social Assistance=1	-1.920	0.114	<.0001	67.620	17.789	0.000	-104126.0	140566.2	0.459	-297954.0	1006426.0	0.767
iSES x Asthma												
0 0	-			-			-			-		
0 1	-			-			-			-		

	Survival			Costs for non-death intervals						Costs for death intervals		
	Logged survival time			Pr(zero cost)			Cost if >$0			Cost		
	β	SE	p-value	β	SE	p-value	β	SE	p-value	β	SE	p-value
1 0	Reference			Reference			Reference			Reference		
1 1	1.119	0.120	<.0001	0.212	0.192	0.271	1170.0	1588.4	0.461	-35298.5	10637.0	0.001
Index Year	-0.108	0.007	<.0001	0.035	0.017	0.041	266.9	83.0	0.001	2532.3	1089.6	0.020
Index Year x Asthma												
Year x 0	-			-			-			-		
Year x 1	-			0.005	0.016	0.769	103.4	94.7	0.275	-2217.8	1063.5	0.037
Index Year x nSES												
Year x 1	-			-			-			-		
Year x 2	-			0.013	0.012	0.258	64.3	81.7	0.431	-694.4	494.6	0.160
Year x 3	-			0.028	0.010	0.007	17.2	54.6	0.752	-612.8	679.5	0.367
Index Year x iSES												
Year x 0	-			-			-			-		
Year x 1	-			-0.034	0.009	0.000	52.5	69.9	0.452	165.0	504.4	0.744
Cost Interval	-			0.018	0.006	0.001	94.2	23.5	<.0001	620.5	384.5	0.107
Interval x Asthma												
Int x 0	-			-			-			-		
Int x 1	-			0.001	0.006	0.843	65.4	25.8	0.011	-411.0	381.3	0.281
Age	-0.048	0.004	<.0001	-0.004	0.003	0.173	16.9	13.8	0.222	45.1	120.8	0.709
Sex												
Female	Reference			Reference			Reference			Reference		
Male	-0.335	0.046	<.0001	0.495	0.047	<.0001	979.7	256.5	0.000	-1495.3	2042.5	0.464
CCI	-0.245	0.014	<.0001	-0.081	0.018	<.0001	635.3	103.1	<.0001	325.8	275.4	0.237
# non-asthma hospitalization	-0.121	0.018	<.0001	-0.245	0.017	<.0001	344.2	78.7	<.0001	1000.7	594.8	0.093
# non-asthma physician visits	-0.006	0.001	<.0001	-0.011	0.001	<.0001	15.2	6.0	0.012	19.0	25.4	0.453
Scale	1.863	0.052	-	-			-			-		

Appendix E Mapping the American Hospital Formulary Service (AHFS) medication categories to ICD-10 disease categories.

Disease category	ICD 10 code	AHFS Category Level 1	AHFS level 1 code	AHFS Category Level 2	AHFS level 2 code
Certain infectious and parasitic diseases	A00-B99	ANTI-INFECTIVE AGENTS	8	ANTHELMINTICS	808
				ANTIBACTERIALS	812
				ANTIFUNGAL (SYSTEMIC)	814
				ANTIMYCOBACTERIALS	816
				ANTIPROTOZOALS	830
				ANTIVIRALS (SYSTEMIC)	818
				URINARY ANTI-INFECTIVES	836
Neoplasmse	C00-D48	ANTINEOPLASTIC AGENTS	10	ANTINEOPLASTIC AGENTS	1000
Diseases of the blood and blood-forming origin	D50-D89	NA	NA	NA	NA
Endocrine, nutritional and metabolic diseases	E00-E90	HORMONES AND SYNTHETIC SUBSTITUTES	68	ADRENALS	6804
				ANDROGENS	6808
				ANTIDIABETIC AGENTS	6820
				ANTIHYPOGLYCEMIC AGENTS	6822
				CONTRACEPTIVES	6812
				ESTROGENS AND ANTIESTROGENS	6816
				GONADOTROPINS	6818
				PARATHYROID	6824
				PITUITARY	6828
				PROGESTINS	6832
				SOMATOSTATIN AGONISTS AND ANTAGONISTS	6829
				SOMATOTROPIN AGONISTS AND ANTAGONISTS	6830
				THYROID AND ANTITHYROID AGENTS	6836

Disease category	ICD 10 code	AHFS Category Level 1	AHFS level 1 code	AHFS Category Level 2	AHFS level 2 code
Mental and behavioural disorders	F00-F99	CENTRAL NERVOUS SYSTEM AGENTS	28	ANTICONVULSANTS	2812
				PSYCHOTHERAPEUTIC AGENTS	2816
Diseases of the nervous system	G00-G99	CENTRAL NERVOUS SYSTEM AGENTS	28	ANALGESICS AND ANTIPYRETICS	2808
				ANOREXIGENICS;RESPIRATORY, CNS STIMULANTS	2820
				ANTIMANIC AGENTS	2828
				ANTIMIGRAINE AGENTS	2832
				ANTIPARKINSONIAN AGENTS (CNS)	2836
				ANXIOLYTICS, SEDATIVES AND HYPNOTICS	2824
				CENTRAL NERVOUS SYSTEM AGENTS, MISC.	2892
				GENERAL ANESTHETICS	2804
				OPIATE ANTAGONISTS	2810
Diseases of the eye and adnexa; Diseases of the ear and mastoid process (Combined into one category: diseases of the eye, ear and nose)	H00-H59 H60-H95	EYE, EAR, NOSE AND THROAT (EENT) PREPS.	52	ANTI-INFECTIVES (EENT)	5204
				ANTI-INFLAMMATORY AGENTS (EENT)	5208
				ANTIALLERGIC AGENTS	5202
				ANTIGLAUCOMA AGENTS	5240
				CONTACT LENS SOLUTIONS	5212
				EENT DRUGS, MISCELLANEOUS	5292
				LOCAL ANESTHETICS (EENT)	5216
				MOUTHWASHES AND GARGLES	5228
				MYDRIATICS	5224
				VASOCONSTRICTORS	5232

Disease category	ICD 10 code	AHFS Category Level 1	AHFS level 1 code	AHFS Category Level 2	AHFS level 2 code
Diseases of the circulatory system	I00-I99	BLOOD FORMATION,COAGULATION + THROMBOSIS	20	ANTIANEMIA DRUGS	2004
				ANTIHEMORRHAGIC AGENTS	2028
				ANTITHROMBOTIC AGENTS	2012
				HEMATOPOIETIC AGENTS	2016
				HEMORRHEOLOGIC AGENTS	2024
Diseases of the circulatory system	I00-I99	CARDIOVASCULAR DRUGS	24	ALPHA-ADRENERGIC BLOCKING AGENTS	2420
				ANTILIPEMIC AGENTS	2406
				BETA-ADRENERGIC BLOCKING AGENTS	2424
				CALCIUM-CHANNEL BLOCKING AGENTS	2428
				CARDIAC DRUGS	2404
				HYPOTENSIVE AGENTS	2408
				RENIN-ANGIOTENSIN-ALDOSTERONE SYS. INHIB	2432
				SCLEROSING AGENTS	2416
				VASODILATING AGENTS	2412
Diseases of the respiratory system	J00-J99	RESPIRATORY TRACT AGENTS	48	ANTI-INFLAMMATORY AGENTS (RESPIRATORY)	4810
				ANTITUSSIVES	4808
				CYSTIC FIBROSIS (CFTR) MODULATORS	4814
				EXPECTORANTS	4816
				MUCOLYTIC AGENTS	4824
				PHOSPHODIESTERASE TYPE 4 INHIBITORS	4832
				PULMONARY SURFACTANTS	4836
				RESPIRATORY TRACT AGENTS, MISCELLANEOUS	4892

Disease category	ICD 10 code	AHFS Category Level 1	AHFS level 1 code	AHFS Category Level 2	AHFS level 2 code
Diseases of the digestive system	K00-K93	GASTROINTESTINAL DRUGS	56	ANTACIDS AND ADSORBENTS	5604
				ANTI-INFLAMMATORY AGENTS (GI DRUGS)	5636
				ANTIDIARRHEA AGENTS	5608
				ANTIEMETICS	5622
				ANTIFLATULENTS	5610
				ANTIULCER AGENTS AND ACID SUPPRESSANTS	5628
				CATHARTICS AND LAXATIVES	5612
				CHOLELITHOLYTIC AGENTS	5614
				DIGESTANTS	5616
				EMETICS	5620
				GI DRUGS, MISCELLANEOUS	5692
				LIPOTROPIC AGENTS	5624
				PROKINETIC AGENTS	5632
Diseases of the skin and subcutaneous tis	L00-L99	SKIN AND MUCOUS MEMBRANE AGENTS	84	ANTI-INFECTIVES (SKIN + MUCOUS MEMBRANE)	8404
				ANTI-INFLAMMATORY AGENTS (SKIN + MUCOUS)	8406
				ANTIPRURITICS AND LOCAL ANESTHETICS	8408
				ASTRINGENTS	8412
				CELL STIMULANTS AND PROLIFERANTS	8416
				DEPIGMENTING AND PIGMENTING AGENTS	8450
				DETERGENTS	8420
				EMOLLIENTS, DEMULCENTS, AND PROTECTANTS	8424
				KERATOLYTIC AGENTS	8428
				KERATOPLASTIC AGENTS	8432

Disease category	ICD 10 code	AHFS Category Level 1	AHFS level 1 code	AHFS Category Level 2	AHFS level 2 code
Diseases of the skin and subcutaneous tis	L00-L99	SKIN AND MUCOUS MEMBRANE AGENTS	84	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	8492
				SUNSCREEN AGENTS	8480
Diseases of the musculoskeletal system an	M00-M99	NA	NA	NA	NA
Diseases of the genitourinary system	N00-N99	NA	NA	NA	NA
Pregnancy, childbirth and the puerperium	O00-O99	AUTONOMIC DRUGS	12	NA	NA
Certain conditions originating in the per	P00-P96	NA	NA	NA	NA
Congenital malformations, deformations, a	Q00-Q99	NA	NA	NA	NA
Symptoms, signs and abnormal clinical and	R00-R99	Not included	NA	NA	NA
Injury, poisoning and certain other conse	S00-T98	Not included	NA	NA	NA
Provisional codes for research and tempor	U00-U99	Not included	NA	NA	NA
External causes of morbidity and mortalit	V01-Y98	Not included	NA	NA	NA
Factors influencing health status and con	Z01-Z99	Not included	NA	NA	NA

Disease category	ICD 10 code	AHFS Category Level 1	AHFS level 1 code	AHFS Category Level 2	AHFS level 2 code
NA	MIS	ANTIHISTAMINE DRUGS	4	FIRST GENERATION ANTIHISTAMINES	404
				OTHER ANTIHISTAMINES	492
				SECOND GENERATION ANTIHISTAMINES	408
		AUTONOMIC DRUGS	12	ANTICHOLINERGIC AGENTS	1208
				AUTONOMIC DRUGS, MISCELLANEOUS	1292
				PARASYMPATHOMIMETIC (CHOLINERGIC AGENTS)	1204
				SKELETAL MUSCLE RELAXANTS	1220
				SYMPATHOLYTIC ADRENERGIC BLOCKING AGENTS	1216
				SYMPATHOMIMETIC (ADRENERGIC) AGENTS	1212
		BLOOD DERIVATIVES	16	BLOOD DERIVATIVES	1600
		DENTAL AGENTS	34	DENTAL AGENTS	3400
		DEVICES	94	DEVICES	9400
		DIAGNOSTIC AGENTS	36	ADRENOCORTICAL INSUFFICIENCY	3604
				DIAGNOSTIC AGENTS	3600
				DIPHTHERIA	3628
				DRUG HYPERSENSITIVITY	3630
				FUNGI	3632
				GALLBLADDER FUNCTION	3634
				GASTRIC FUNCTION	3636
				INTESTINAL ABSORPTION	3638
				KIDNEY FUNCTION	3640
				LIVER FUNCTION	3644
				MUMPS	3652

Disease category	ICD 10 code	AHFS Category Level 1	AHFS level 1 code	AHFS Category Level 2	AHFS level 2 code
NA	MIS	DIAGNOSTIC AGENTS	36	MYASTHENIA GRAVIS	3656
				OCULAR DISORDERS	3658
				PANCREATIC FUNCTION	3661
				PITUITARY FUNCTION	3666
				ROENTGENOGRAPHY	3668
				THYROID FUNCTION	3660
				TUBERCULOSIS	3684
				URINE AND FECES CONTENTS	3688
		DISINFECTANTS (FOR NON-DERMATOLOGIC USE)	38	DISINFECTANTS (FOR NON-DERMATOLOGIC USE)	3800
		ELECTROLYTIC, CALORIC, AND WATER BALANCE	40	ACIDIFYING AGENTS	4004
				ALKALINIZING AGENTS	4008
				AMMONIA DETOXICANTS	4010
				CALORIC AGENTS	4020
				DIURETICS	4028
				ION-REMOVING AGENTS	4018
				IRRIGATING SOLUTIONS	4036
				REPLACEMENT PREPARATIONS	4012
				SALT AND SUGAR SUBSTITUTES	4024
				URICOSURIC AGENTS	4040
		ENZYMES	44	ENZYMES	4400
		GOLD COMPOUNDS	60	GOLD COMPOUNDS	6000
		HEAVY METAL ANTAGONISTS	64	HEAVY METAL ANTAGONISTS	6400
		LOCAL ANESTHETICS (PARENTERAL)	72	LOCAL ANESTHETICS (PARENTERAL)	7200
		MISCELLANEOUS THERAPEUTIC AGENTS	92	5-ALPHA-REDUCTASE INHIBITORS	9208
				ALCOHOL DETERRENTS	9204

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NA	MIS	MISCELLANEOUS THERAPEUTIC AGENTS	92	ANTIDOTES	9212
				ANTIGOUT AGENTS	9216
				BONE RESORPTION INHIBITORS	9224
				CARIOSTATIC AGENTS	9228
				COMPLEMENT INHIBITORS	9232
				DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	9236
				GONADOTROPIN-RELEASING HORMONE ANTAGNTS	9240
				IMMUNOMODULATORY AGENTS	9220
				IMMUNOSUPPRESSIVE AGENTS	9244
				OTHER MISCELLANEOUS THERAPEUTIC AGENTS	9292
				PROTECTIVE AGENTS	9256
		OXYTOCICS	76	OXYTOCICS	7600
		PHARMACEUTICAL AIDS	96	PHARMACEUTICAL AIDS	9600
		SMOOTH MUSCLE RELAXANTS	86	GENITOURINARY SMOOTH MUSCLE RELAXANTS	8612
				RESPIRATORY SMOOTH MUSCLE RELAXANTS	8616
		VITAMINS	88	MULTIVITAMIN PREPARATIONS	8828
				VITAMIN A	8804
				VITAMIN B COMPLEX	8808
				VITAMIN C	8812
				VITAMIN D	8816
				VITAMIN E	8820
				VITAMIN K ACTIVITY	8824

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NA	MIS	CONTRACEPTIVES (E.G. FOAMS, DEVICES)	32	CONTRACEPTIVES (E.G. FOAMS, DEVICES)	3200
		SERUMS, TOXOIDS, AND VACCINES	80	SERUMS	8004
				TOXOIDS	8008
				VACCINES	8012