SOCIOECONOMIC STATUS AND INHALED CORTICOSTEROID USE IN CHILDHOOD ASTHMA: IMPACT ON HOSPITALIZATION

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A Thesis Submitted to the Faculty of Graduate Studies in
Partial Fulfillment of the Requirements for the Degree of

DOCTOR OF PHILOSOPHY

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THE UNIVERSITY OF MANITOBA

FACULTY OF GRADUATE STUDIES

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A Thesis/Practicum submitted to the Faculty of Graduate Studies of The University of Manitoba in partial fulfillment of the requirements of the degree of Doctor of Philosophy

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ABSTRACT

INTRODUCTION: Low income children are at greater risk for asthma hospitalization, which can be prevented with the utilization of inhaled corticosteroids drugs. Therefore, a population-based study of children was undertaken to determine: 1) the influence of socioeconomic status and pharmaceutical policy on inhaled corticosteroid utilization, and 2) the contribution of inhaled corticosteroid utilization to the association between socioeconomic status and asthma hospitalization.

METHODS: Using population-based health care administrative data, 16,862 children, aged 5-15 years, were selected by this case definition for asthma: 1) health care for asthma/bronchitis diagnoses, or 2) one+ prescriptions for prophylaxis drugs, or two+ prescriptions for bronchodilators during January 1, 1995- March 31, 1998, AND having one+ asthma drug prescriptions during January 1, 1995 - March 31, 1996. A drug treatment-based asthma severity measure was developed and applied to prescription data. Following validity assessments of the case definition and asthma severity measure, the proportionate use of inhaled corticosteroids was ascertained in relation to household income. Inhaled corticosteroid use was also assessed before and after a newly introduced, income-based drug reimbursement policy. The risk of asthma hospitalization by household income was determined, with adjustment for inhaled corticosteroid drug utilization.

RESULTS: Forty-five percent of children with asthma had at least one prescription for an inhaled corticosteroid over the time period January 1,1995 to March 31, 1996; inhaled corticosteroid utilization declined as neighbourhood income decreased. The adjusted relative risk for a new inhaled corticosteroid prescription was 0.9 among children living in low income or income assistance households, versus higher income children. Low income children with severe asthma received the fewest number of inhaled corticosteroid doses of all children, and this remained unchanged post income-based policy.

Continuous utilization of inhaled corticosteroids was associated with lower risk of asthma hospitalization (severity-adjusted RR=0.37, 95% CI:0.29-0.48). An increased risk of asthma hospitalization observed in income assistance and low income children, was eliminated following adjustment for continuity of inhaled corticosteroids and other factors.

CONCLUSION: Low income children with asthma were less likely to utilize inhaled corticosteroid drugs, which increases their risk of asthma hospitalization. An income-based pharmaceutical policy did not improve utilization of these drugs.

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LIST OF ABBREVIATIONS

1^{st}	first
2^{nd}	second
95% CI	95% Confidence Interval
AP	April
AU	August
B_2	beta2
DE	December
et al	and company
FE	February
$FEF_{25\%-75\%}$	forced expiratory flow between 25% and 75% of vital capacity
FEV_1	forced expiratory volume during 1 second of a forced vital capacity
HMO	health maintenance organization
ICD-9-CM	International Classification of Diseases
ICU	intensive care unit
IgE	immunoglobulin E
Inc	Incorporated
ICS	inhaled corticosteroid
JA	January
JL	July
JN	June
MA	May
MD	physician
MHSIP	Manitoba Health Services Insurance Plan
MR	March
n	number
NA	not available
NO	November
NS	not significant

NSAIDS	non-steroidal anti-inflammatory drugs
OC	October
OR	odds ratio
p	probability
PC_{20}	provocation concentration for 20% fall in FEV_1
PEFR	peak expiratory flow rate
PPV	positive predictive value
RCMP	Royal Canadian Mounted Police
RR	relative risk
RSV	respiratory syncytial virus
Rx	prescription
SD	standard deviation
SE	September
SP, ICA	single-parent, income assistance
UK	United Kingdom
URI	upper respiratory tract infection
US	United States
vs	versus
yo	years old

Chapter 1. Introduction

Asthma, a chronic condition which causes recurrent episodes of coughing, wheezing and breathlessness, affects one in every 10 children in Canada.[1] Although asthma has been known to humankind since antiquity,[2] only in recent times has its pathophysiology been clearly elucidated. Asthma is now viewed as an inflammatory disease which can be controlled by anti-inflammatory drugs, such as inhaled corticosteroids. [3;4] Research into asthma pathophysiology has been translated into present-day asthma treatment guidelines, which place emphasis on the use of inhaled corticosteroid drugs for the long-term management of airway inflammation.[5;6] Furthermore, epidemiologic research has linked the utilization of inhaled corticosteroid drugs and reduction of hospitalization for asthma. [7;8] Despite these advance in clinical knowledge, 20% of Canadian school-age children with asthma in 1995/96 had visited an emergency department, 4% had been hospitalized, and 16% had missed more than one week of school because of asthma in the previous year?[9]

Current research into asthma is directed at developing and improving drug therapies to control the inflammatory process of the disease. [10-12] This type of research addresses drug efficacy issues. Equally important are issues relating to the effectiveness of a drug following its introduction into a population, which is determined by factors such as patient access to the drug and adherence to therapy.[13] Population-based studies in the

1990's document that 50% of school-age children with asthma use inhaled corticosteroid drugs;[14] it is estimated that 50% of asthmatic children are non-adherent to drug therapy. [15] One outcome of non-use or discontinuous use of an anti-inflammatory therapy is increased risk of asthma exacerbation and hospitalization.[7;8;16] Asthma hospitalization reduces the quality of life of children with asthma and contributes to a significant proportion of health care costs. [17-19] Furthermore, it appears that lower income children are at higher risk for asthma hospitalization.[20;21]

The medical community recognizes the need for improved utilization of these agents; however, increased awareness of the household factors, as well as characteristics of the health care system, which determine utilization is required.[22] Lower income children are less likely to use inhaled corticosteroid drugs.[22;24] The literature suggests that lower income children are at higher risk of not receiving a prescription for an inhaled corticosteroid drug, [21;25] and of being non-adherent to the drug regimen, [26] but the empiric evidence is limited. The purpose of this dissertation research was to document the association between the social environment and utilization of inhaled corticosteroids in Canadian children, to determine what risk factors may explain this association, and whether the association has an impact on hospitalization for asthma.

To achieve this end, a population health framework was employed.[27] In this framework, health is affected by, amongst other factors, the health care system, individual response and the social environment. Relevant to asthma management is that the social environment impacts on disease, through the physical environment (eg. increasing

exposure to allergens) and the behaviour of individuals (eg. decreasing adherence to drug treatment). The health care environment also has a direct influence, in the form of policies which impose cost barriers to the acquisition of inhaled corticosteroid drugs. Population-based studies on pharmaceutical use are potentially useful to identify individual, social and health care system factors which are related to the utilization of pharmaceuticals. [28;29] For the dissertation research, population-based data sources on physician utilization, hospitalization and prescription drugs, maintained by the Manitoba Health Services Insurance Plan (MHSIP), were used. The MHSIP prescription database is one of the most comprehensive in Canada, and allows linkage of prescription data with other health care administrative data for the purposes of defining an asthma population and describing asthma treatment outcomes.[30]

This dissertation is presented as a series of five essays, which have been organized around five related research objectives. Each essay is composed of an introductory section which provides background information to the research objective, and a results section in which dissertation research findings are presented in the form of a publishable paper. The first two essays each describe the development of important measures used in the dissertation research, and the last three essays are anchored on the major research objectives.

The first essay describes the development of a case definition for childhood asthma. The strengths and weaknesses of four domains of a case definition for childhood asthma are described. Findings are presented for the dissertation research on the development and

validity assessment of a diagnosis and drug treatment-based case definition for childhood asthma, derived from health care administrative records.

The second essay describes four domains of asthma severity measures which can be incorporated into research. As with the case definition, the strengths and weakness of the four domains are described. For the dissertation research, a drug treatment-based asthma severity measure was developed for application to health care administrative records. The reliability and validity of the asthma severity measure were ascertained.

The third essay provides a review of the empiric evidence on socioeconomic status and the use of inhaled corticosteroids in children with asthma. Barriers to the optimal utilization of inhaled corticosteroids in lower income children are discussed. Results from the dissertation research are presented on the association between socioeconomic status and inhaled corticosteroid utilization in children with asthma, as determined from cross-sectional and longitudinal perspectives.

The fourth essay provides the reader with empiric evidence regarding the impact of pharmaceutical policy on drug utilization in a population. The research which follows is a longitudinal evaluation of inhaled corticosteroid utilization in Manitoban children before and after a change to an income-based pharmaceutical benefit policy.

The final essay summarizes the evidence regarding socioeconomic status and asthma hospitalization in children. Plausible explanations for increased asthma hospitalization in

lower income children are submitted. Dissertation research findings are presented on the association between socioeconomic status and hospitalization for asthma in children, and whether the association was explained by continuity of inhaled corticosteroid utilization or other risk factors for asthma hospitalization.

The dissertation is concluded with an overall discussion of research findings and their policy implications.

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Chapter 2. Case Definition for Childhood Asthma

The cornerstone of asthma epidemiologic research is being able to identify individuals with asthma. Although numerous definitions for asthma have been proposed, asthma defies a standard case definition.[1] The disease has been identified in children by the presence of wheezing, bronchial hyper-reactivity, treatment with asthma drugs or a physician-diagnosis of asthma. The success of these domains in defining asthma can be evaluated from theoretical and operational perspectives. The theoretical perspective assesses how well the domain is supported by the underlying concept of the disease and its management.[2] Crucial to evaluating the conceptual basis of the domain is whether it distinguishes asthma from other wheezing syndromes. The operationalization of the domain, known as the operational or case definition, specifies the activities necessary for the researcher to measure the concept.[3] The operational perspective encompasses validity and reliability assessments of the case definition, once it is applied to data sources.[2] The meaning of validity is the ability of the case definition to provide an unbiased representation of persons with asthma. [4] Reliability of the case definition refers to the extent to which it will identify the same children with asthma on repeated trials.

This chapter discusses conceptual and measurement issues relevant to defining asthma in children and is concluded with dissertation research findings on the development of a case definition for childhood asthma, which can be applied to health care administrative records.

2.1 Conceptual Basis of Definition

2.1.1 Physiologic measures

Physiologic measures of a disease describe the changes in body function due to the pathologic processes of the disease. Although asthma has been documented since the time of antiquity, our understanding of the underlying pathophysiologic processes has evolved slowly over the centuries.[5] Increasingly, asthma is being recognized as a "persistent" inflammatory disease.[6] Following exposure of the asthmatic airway to a variety of environmental stimuli including allergens, airway tissues are invaded with inflammatory cells such as mast cells, eosinophils and neutrophils, which release chemical mediators.[7-9] Chemical mediators such as the leukotrienes, cause bronchoconstriction, increased vascular permeability and edema, and increased mucous production; other mediators cause epithelial cell desquamation.[10;11] Loss of reparative mechanisms in asthma leads to prolonged inflammation and subsequent structural changes in the lung; the resultant damage leaves the airway sensitized or hyper-responsive.[7] This hyper-reactivity can be assessed through bronchial challenge tests, which measure the degree of bronchoconstriction to inhalation of irritants, such as methacholine or to airway stimulus arising from exercise.[12]

The outcome of airway inflammation and hyper-responsiveness is recurrent episodes of wheezing, dyspnea, chest tightness and cough, associated with the reversible airflow limitation.[7] Airflow limitation is assessed through pulmonary function tests, of which

the most common are: 1) forced expiratory volume during 1 second of a forced vital capacity maneuver (FEV_1), 2) forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25\%-75\%}$) and 3) peak expiratory flow (PEF), the greatest flow obtained on forced expiration after complete inspiration.[13] Vital capacity is the difference between the lung volume achieved during a maximum inhalation and the residual volume, which results from pushing out as much air as possible. Asthma is characterized by low flows (FEV_1, FEF_{25-75} ,PEF) with normal or low volumes. Lung function tests (FEV_1, FEF_{25-75}, PEF) are compared with predicted values for age, gender and height; normal values are usually greater than 80% of predicted values. A child's pulmonary function can also be followed longitudinally to assess changes in asthma control, in which tests are compared with a child's personal best value when the child is asymptomatic. Home PEF testing detects decreases in PEF or increases in circadian variation which indicate a deterioration of asthma control. Bronchial reactivity following challenge with methacholine, histamine or exercise is usually measured as the dose of the challenge agent (PC_{20}) which causes a 20% drop in FEV_1.[13] Pulmonary function tests can be performed reliably by many, but not all children by 5 to 6 years of age.[12]

The hallmark of asthma is airway obstruction which varies over time. Bronchial hyper-reactivity has been advocated as a good measure of asthma because it provides physiologic evidence of asthma when lung function tests are normal.[13] However, population-based studies of the prevalence of bronchial hyper-reactivity among schoolchildren show that bronchial reactivity is more prevalent than recent wheezing symptoms (Table 2.1). This is because not all children with hyper-responsive lungs will

Table 2.1. Prevalence of Childhood Asthma by Type of Case Definition

Study Population	Data Source	Case Definition	Prevalence (%)
Physiologic measures:			
2363 Australian children 8-11 years old (Salome 1987)	Study assessment records	Bronchial reactivity defined as a 20% decline in FEV_1 at an inhaled histamine dose of < 7.8 umol	17.9
1050 New Zealander children 8-9 years old (Mitchell 1989)	Study assessment records	Bronchial reactivity defined as a 20% decline in FEV_1 at an inhaled histamine dose of < 7.8 umol	20.4
2053 New Zealander children 7-10 years old (Pattemore, 1990)	Study assessment records	Bronchial reactivity defined as a 20% decline in FEV_1 at an inhaled histamine dose of < 7.8 umol	15.9
989 Canadian children 6-12 years old (Ernst,1995)	Study assessment records	Bronchial reactivity defined as a 10% decline in FEV_1 following 6 minutes of exercise	19.1
Functional measures:			
5472 British children 5-17 years old (Strachan 1994) All children	Parental reports	Ever wheezing	23.0
		Wheezing in the last 12 months	15.0
5-7 years old			16.7
8-10 years old			15.9
11-13 years old			14.2
14-17 years old			13.0
18737 Italian children 6-7 years old (SIDRIA 1997)	Parental reports	Ever wheezing	24.0
		Wheezing in the last 12 months	7.7
14,145 Canadian children 5-8 years old (Dales,1994)	Parental reports	Persistent wheezing defined as wheezing most days or nights, or wheezing apart from colds	13.0
989 Quebecois children 6-12 years old (Ernst,1995)	Parental reports	Ever wheezing	10.6
		Wheezing in the last 12 months (poor translation of term wheezing into French)	5.1
2053 New Zealander children 7-10 years old (Pattemore,1990)	Parental reports	Ever wheezing	26.3
		Wheezing in the last 12 months	14.4
2363 Australian children 8-11 years old (Salome,1987)	Parental reports	Ever wheezing	24.3
1050 New Zealander children 8-9 years old (Mitchell,1989)	Parental reports	Ever wheezing or exercise wheezing	27.2
		Wheezing or exercise wheezing in the last 12 months	16.2

Table 2.1. Prevalence of Childhood Asthma by Type of Case Definition (continued)

Study Population	Data Source	Case Definition	Prevalence (%)
Functional measures continued			
10,685 British children 1-15 years old (Neville 1992)	Physician records	One or more episodes of bronchospasm or wheeze	23.7
769 Irish children 2-5 years old (Steen 1992)	Physician records	One or more episodes of wheeze	34.5
Functional and physiologic measures:			
352 Australian children, 7-12 years old with asthma* (Toelle,1992)	Patient reports and study assessment	Bronchial reactivity defined as a 20% decline in FEV_1 after inhaled histamine, and wheezing in the last 12 months	30.1*
Health utilization measures:			
a) physician diagnosis			
5472 British children 5-17 years old (Strachan,1994)5-7 years old	Parental reports	Ever diagnosed by physician as having asthma	13.1
8-10 years old			12.8
11-13 years old			12.6
14-17 years old			13.6
			13.5
18737 Italian children 6-7 years old (SIDRIA,1997)	Parental reports	Ever diagnosed by physician as having asthma	8.7
2053 New Zealander children 7-10 years old (Pattemore,1990)	Parental reports	Ever diagnosed by physician as having asthma	14.3
989 Quebecois children 6-12 years old (Ernst,1995)	Parental reports	Ever diagnosed by physician as having asthma	12.1
2363 Australian children 8-11 years old (Salome,1987)	Parental reports	Ever diagnosed by physician or at a hospital as having asthma	12.8
1050 New Zealander children 8-9 years old (Mitchell,1989)	Parental reports	Ever diagnosed by physician as having asthma	14.3
10,685 British children 1-15 years old (Neville,1992)	Physician medical records	Asthma diagnosis	8.4
769 Irish children 2-5 years old (Steen,1992)	Physician medical records	Asthma diagnosis	7.9

Table 2.1. Prevalence of Childhood Asthma by Type of Case Definition (continued)

Study Population	Data Source	Case Definition	Prevalence (%)
Health care utilization measures continued:			
1990 population of Manitoban children (Manfreda, 1993)	Electronic physician claims records	Asthma diagnosis	
male, 5-9 years old			5.3
male, 10-14 years old			4.7
male, 15-19 years old			2.6
female, 5-9 years old			3.5
female, 10-14 years old			3.3
female, 15-19 years old			3.1
9027 Manitoban children, 0-14 years old (Erzen,1997)	Electronic physician claims or hospital administrative records	Asthma diagnosis	5.0
b) asthma medication use			
5472 British children 5-17 years old (Strachan,1994)	Parental reports	Any asthma drug prescribed in the last 12 months	9.7
989 Canadian children 6-12 years old (Ernst,1995)	Parental reports	Currently treated with asthma drugs	4.5
2363 Australian children 8-11 years old (Salome,1987)	Parental reports	Ever treated with asthma drugs	14.6
10,685 British children 1-15 years old Neville,1992)	Physician medical record	Use of asthma medication within last 3 months	5.4
17846 British children, 4-17 years old (Warner,1995)	Electronic prescription records	At least one prescription during a 12 month period	9.6
Health care utilization and functional measures:			
14,145 Canadian children 5-8 years old (Dales,1994)	Parental reports	Ever diagnosed with asthma and still has asthma	4.7
989 Quebecois children 6-12 years old (Ernst,1995)	Parental reports	Asthma attacks in the last 12 months	4.5
18737 Italian children 6-7 years old (SIDRIA,1997)	Parental reports	Child still has asthma or asthma attack in the last 12 months	4.1

have asthma symptoms subsequent to the ability of the bronchial challenge test to detect subclinical disease.[13;14] The prevalence of asthma symptoms among children with histamine-induced bronchial hyper-reactivity has ranged from 45% to 65 %.[15-17] The specificity of bronchial reactivity in defining children with wheezing has been reported to be 73%. [16;17] Moreover, lung hyper-reactivity is also present after respiratory viral illnesses.[18] Some have reported that only 23% to 47% of children with bronchospasm have had a prior diagnosis of asthma.[17;19] Although nearly all children with severe bronchial hyper-reactivity will have a diagnosis of asthma, [16;17] the lack of concordance between the presence of bronchial hyper-reactivity, wheezing symptoms and asthma diagnosis limits the usefulness of bronchial reactivity as a marker of "active" asthma in children.

In order to improve the specificity of bronchial reactivity in identifying asthma, some have proposed to define current asthma in children on the basis of both bronchial hyper-responsiveness and wheezing symptoms in the last 12 months.[20] Using this case definition, Toelle et al identified a group of children which differed from children with wheezing symptoms or bronchial hyper-responsiveness only, on the basis of a greater severity of bronchial hyper-responsiveness, and prevalence of asthma diagnosis, wheezing symptoms and use of asthma medications. Their current asthma definition also distinguished children with more severe asthma after 10 years of follow-up, than children with only wheezing or a physician diagnosis of asthma.[21] Thus, the concurrence of bronchial reactivity and wheezing may serve as a more appropriate marker of "current" asthma in children.

2.1.2 Functional status measures of asthma

Functional status measures describe the signs and symptoms of the disease and resulting impact on the daily activities of individuals;[2] the former are more relevant to the detection of asthma. Clinically, asthma manifests itself as recurrent episodes of wheezing, cough, dyspnea, chest retractions, tachypnea and pallor.[22]

a) Differentiating childhood asthma and transient wheezing syndromes

Wheezing in childhood is a heterogeneous condition, which presents as distinct phenotypes at different ages.[23-25] There exist infants and children who have acute and recurrent wheezing, but in whom these symptoms disappear with age. Strachan et al documented a decline in prevalence of recent wheezing from 17% in 5-7 year olds to 13% in 14-17 year olds, while the prevalence of ever wheezing remained constant at 23%. [26] Others have also documented a prevalence of ever wheezing which is higher than recent wheezing (Table 2.1). At least three phenotypes of wheezing in childhood have been described: 1) transient wheezing in infancy or early "wheezers", 2) transient wheezing in childhood or "late" wheezers and 3) persistent wheezing in childhood or "classic" asthma.[23;25] Fifty to sixty percent of children wheezing before the age of three years no longer experience wheezing at six years of age.[27;28] A similar proportion of children with wheezing at 7 years of age or less do not have wheezing once they reach the age of 11 years.[29] Eighty percent of children with wheezing before the ages of five to seven years are asymptomatic at 10-11 years of age. It has been hypothesized that the

peak prevalence for early transient wheezing, late transient wheezing and asthma occur between 6 months to three years, 3 to 6 years and 6-11 years, respectively. [30-32]

Eighty percent of children who develop asthma experience their first episode of wheeze before the age of 3 years.[25;33] How are these children distinguished from children with transient wheezing? In the Tuscon Children's Respiratory study, transient early wheezers were observed to have diminished airway function at one year of age, while persistent wheezers had normal lung function in comparison to non-wheezers.[27] Persistent wheezers were more likely than early transient wheezers to have markers of allergen sensitization (elevated immunoglobulin E [IgE] levels, positive skin tests). Other longitudinal studies have also documented an increased prevalence of atopy or allergic conditions such as allergic rhinitis and atopic dermatitis, among children with persistent wheezing.[28;29;34] In addition, bronchoalveolar lavage studies show that eosinophil and mast cell counts are significantly elevated in children who have atopic asthma, compared with those who have viral-associated wheezing.[35] Late transient wheezers have also been differentiated from persistent wheezers on the basis of their lack of response to bronchial hyper-responsiveness tests, which are indicative of IgE mediated airway inflammation.[30] Stein and collegues reported that non-atopic children who wheezed at 6 years, and not 11 years, exhibited abnormally high variability in lung function tests, but not increased bronchial hyper-responsiveness, as did persistent wheezers. Clinically, children with chronic cough and intermittent wheeze have been observed to be more likely than children with asthma to have earlier onset of symptoms, a

history of chronic otitis media, maternal smoking, lower socioeconomic status, and aboriginal lineage.[36]

The Tuscon study and others have documented that persistent wheezing is more common among children with a parental history of asthma.[27;34;37] An increased likelihood of parental asthma is not seen in children with early transient wheezing.[27] The familial aggregation in asthma is thought to be due to an interaction of genetic and environmental factors. [38] The onset of asthma has been linked to exposure to indoor allergens such as house dust mite (promoted by indoor humidity and wall-to-wall carpeting), cat dander, and cockroach debris, through: 1) evidence of allergen sensitization in asthmatic children from skin testing, measurement of serum IgE antibodies and bronchoprovocation challenge studies, [27;39-42] and 2) epidemiologic studies which show increased risk of asthma among children living in households with a higher load of dust mites, mold and cockroach allergen, [39;41;43-45] or in households with physical characteristics potentially contributing to higher allergen loads, such as high umidity and dampness.[44;46] Among children with a family history of allergy, the age of onset of wheezing has been reported to be inversely related to the level of dust mite exposure, especially among children who became sensitized.[45]

Additional risk factors have been identified, but it is unclear whether they are specific to asthma. Exposure to tobacco smoke early in life, either through maternal smoking during pregnancy or maternal/paternal smoking postnatally, increases the risk of developing both wheezing and asthma.[34;37;40;42;46;47] The Tuscon study reported that children with

early transient wheezing or persistent wheezing were significantly more likely than children without wheezing to have mothers who smoked around the time of their birth.[27] The effect of smoking is independent of a family history of asthma, [34;37] but appears to interact with socioeconomic status, such that an increased incidence of asthma is observed among children of low income, but not high income mothers who smoke.[48] Early exposure to viral infections such as respiratory syncytial virus (RSV), is associated with wheezing in younger children and may potentially contribute to the onset of asthma.[37;40;49] Sigurs et al's three-year cohort study of infants with and without RSV reported that children exposed to RSV were significantly more likely to experience recurrent wheezing at one and three years of age; the likelihood of wheezing at three years was substantially greater among children with a family history of asthma.[37] However, recently it has been posited that exposure to infection early in life protects against the development of asthma.[50-54] Other risk factors for asthma or wheezing, include male gender, young maternal age and no breast feeding.[29;37;46;48;55] Prematurity has been associated with an increased likelihood of asthma or wheezing, especially among children who developed bronchopulmonary dysplasia.[56-59] Croup and recurrent croup have been shown to be predictors of asthma or wheezing.[60]

In summary, children with asthma are more likely than children with transient wheezing, to have a family history of asthma and to have evidence of allergen sensitization. The clinical expression of transient wheezing and asthma is also different. The nature of transient wheezing is episodic and associated with viral infections or colds, which usually occur in the winter season. Children with asthma have interval symptoms, in addition to

viral-associated episodes.[27;31;61] Transient wheezing and asthma also differ in terms of their response to prophylactic treatment with inhaled corticosteroids. In contrast to the clear benefits shown in asthma, evaluations of inhaled corticosteroid use in children with episodic wheezing have been inconclusive, with some reporting reduced frequency of wheezing, while others have not.[62;63] Inhaled corticosteroids are not advocated for all infants who wheeze, but because of the uncertainty in diagnosis, therapeutic trials of corticosteroids are not discouraged.[64]

The problem of differentiating "early" transient wheezing and asthma in research trials can be overcome by excluding children less than 4-5 years of age, as has been the practice in many asthma epidemiologic studies.[65-67] However at this time, distinguishing asthma in 5-10 year old children from "late" transient wheezing is limited to identifying risk factors and clinical expression patterns. It is also conceivable that the two conditions are not entirely separate. Important to the research agenda is that transient wheezing and asthma are not easily distinguishable at the time of presentation to the physician.[23;64]

2.1.3 Health care utilization measures

a) Physician diagnosis of asthma

The theoretical basis for defining asthma by the presence of a physician diagnosis of asthma is that children with asthma will manifest symptoms and subsequently, be brought to a source of health care. The first caveat to this conceptual basis is that not all children with an illness are brought to a site of health care. In Kljakovc's medical record review,

31% of children with asthma symptoms, but no diagnosis of asthma, had not been seen by a physician.[68] Moreover, certain groups of children such as those living in low income households, are less likely to see a physician, potentially resulting in the systematic acquisition of a diagnosis of asthma.[69] Data from the US National Health Interview Survey reports that black and lower income children with parent-reported asthma have significantly fewer physician contacts than white and higher income children.[70;71] Although physician visits are increased in low income asthmatic children with activity limitations, their utilization remains significantly lower than that of higher income children with activity limitations.[70] In countries with universal health insurance, physician visitation rates are greater in lower income children with asthma, but they are less likely to be referred to specialists, the implications of which will be discussed later in this section.[72]

Physicians diagnose asthma following a clinical assessment of symptoms and physiologic measurements of lung function of children presenting for care.[1;73] Wheezing and cough are more common in children with a physician diagnosis of asthma, than those without.[68] Similarity in population-based studies of children between the prevalence of wheezing and the prevalence of a physician-diagnosis of asthma also suggests that a physician diagnosis is a valid measure of children with asthma symptoms. (Table 2.1) However, children experiencing wheezing are not necessarily the same children who have been diagnosed with asthma and vice versa. In Pattemore et al's evaluation of Australian children, 7-10 years old, 80% of children ever diagnosed with asthma had current symptoms of wheezing, breathless attacks or nocturnal cough, but only 40% of

symptomatic children had a physician diagnosis of asthma.[16] Similarly in Neville et al's medical record review of British children seeing a general practitioner, 85% of children with a diagnosis of asthma had experienced one or more episodes of wheezing.[74] Fifty-four percent of children with two or more episodes of wheezing, while only 30% of children with one or more episodes had received a definitive diagnosis of asthma.

As discussed in the previous section, not all wheezing in childhood represents asthma, and clinically, asthma is not easily distinguished from transient wheezing syndromes. Pattemore's and Neville's data which show that 20% of children with a previous diagnosis of asthma did not experience recent wheezing, gives us some indication of the extent to which a physician diagnosis of asthma may be assigned to a child with transient wheezing. Moreover, it has been posited that reports of the under-diagnosis of asthma in the 1980's have encouraged physicians to diagnose wheezing as asthma, instead of "wheezy bronchitis" in cases where it is uncertain whether the child had asthma.[61;75] Case definitions which are based on a physician diagnosis of asthma and current wheezing symptoms may be helpful in separating out children with transient wheezing. Utilizing this type of case definition lowers the prevalence of a physician-diagnosis of asthma by approximately one half (Table 2.1).

Conversely, some would argue that a lack of asthma diagnosis in 50% to 70% of wheezing children illustrates that asthma continues to be under-diagnosed, and that diagnosis-based definitions would exclude children with asthma.[16;74] The asthma

under-diagnosis hypothesis is also supported by empiric evidence of the differential distribution across sociodemographic groups of physician-diagnosis of asthma and wheezing symptoms in children. Wheezing or bronchospasm has been reported more often among low income children in Canada and the UK, but the diagnosis of asthma has not varied across income groups.[15;19;26] Other investigators have also reported a decrease in the frequency of asthma diagnoses among lower income children.[72;76] Conversely, a diagnosis of asthma, but not symptoms of wheezing has been observed more often in black children in the United States.[77] The latter findings have been explained as the outcome of black children utilizing emergency departments as their source of care and being diagnosed with asthma by physicians who are not familiar with their medical history. [78] Conversely, lack of a regular of medical care is also a plausible explanation for a decreased likelihood of asthma diagnosis among low income children who are less likely to see specialists.[72] However, it is difficult to conclude that differences in the income distribution of the prevalence of asthma and wheezing represent the systematic, under-diagnosis of asthma in low income children, rather than an increased prevalence of transient wheezing in these children. Low income infants are more likely to experience persistent respiratory symptoms and have low birth weight, which is associated with poorer lung function.[55;79]

b) Asthma drug utilization

Drug therapy is the cornerstone of asthma management; nonpharmacologic measures are adjunct measures.[80] Beta$_2$-adrenergic agonists, which stimulate B_2-receptors to relax airway smooth muscle, are administered for symptomatic relief of airway

obstruction.[81;82] Corticosteroids alter the underlying inflammatory processes by inhibiting the recruitment of inflammatory cells into the bronchioles, preventing or decreasing airway mucosal edema and mucous secretion. Other anti-inflammatory drugs such as cromolyn, inhibit the activation of inflammatory cells. Theoretically, one would expect that all children diagnosed with asthma would at some point be treated with an asthma drug. Neville at al's medical record review documented that almost all children in whom a diagnosis of asthma had been made, had received drug treatment for asthma in the past.[74] Over forty percent of children with a prior diagnosis of asthma or recent wheezing have been reported to be currently taking asthma drugs, and this proportion is increased to 86% of children with one or more episodes of wheezing.[26;74] These findings suggest that children who receive asthma drug treatment are those currently experiencing asthma symptoms. The estimated prevalence of children receiving asthma drug therapy falls between the prevalence of ever diagnosis of asthma, and of ever diagnosis of asthma plus current symptoms (Table 2.1). In addition, unlike symptom-based definitions, a drug-based case definition is independent of the degree of symptom control achieved with drug therapy; children on asthma drug therapy, but not experiencing symptoms can be identified.[83] Furthermore, classifying children according to asthma drug use can also be used to predict the prognosis of asthma in children as they age.[84]

Although commonly employed in asthma pharmacoepidemiologic research,[65;67;85;86] defining asthma on the basis of drug treatment lacks specificity because asthma drugs such as bronchodilators, are also used in the treatment of other respiratory disorders such

as chronic obstructive pulmonary diseases (adults only) and bronchitis.[87] Similarly, oral corticosteroids, which are used for the acute management of asthma, are utilized in a variety of endocrine, rheumatic, dermatologic and hematologic disorders. Methodologies employed to prevent the inadvertent inclusion of diseases other than asthma have included omitting: 1) prescriptions for bronchodilator mixtures primarily used to treat bronchitis and 2) oral corticosteroids not prescribed concurrently with other asthma drugs.[86;88] Bronchodilator use is much more prevalent in children with a diagnosis of asthma, but Kljakovic reported that 3% to 7% percent of children without a diagnosis of asthma had received bronchodilators for episodes of wheezing.[68;89] In Strachan et al's medical record review, almost 30% of children with a single episode of wheezing had received a bronchodilator;[90] however, the prevalence of bronchodilator use did increase substantially with the number of episodes of wheezing. On the other hand, treatment with inhaled corticosteroids decreases the frequency of bronchodilator use, [63] and infrequent prescriptions for bronchodilators may not be uncommon.

2.1.4 Summary of conceptual issues

From a theoretical perspective, the four approaches towards a case definition for asthma, outlined in this section, each have strengths and weaknesses. A case definition which is based on bronchial reactivity, although closely related to the underlying airway inflammation, may include children in whom asthma has not manifested. A case deifnition which is symptom or physician diagnosis-based may have less optimal specificity, as a result of including children with transient wheezing. Alternatively, a physician diagnosis-based definition may have lower positive predictive value arising

from the systematic exclusion of some groups of asthmatic children, such as those living in low income households, who have not used the health care system. Including the diagnosis of bronchitis in the case definition does not completely diminish this selection bias because children diagnosed with asthma are more likely to receive drug treatment.[76;91;92]

A medication-based cased definition has the benefit of not excluding children whose symptoms are well-controlled, and if carefully defined, excluding children with transient wheezing. However, as with the physician-diagnosis definition, this definition is dependent on utilization of the health care system. Therefore, it may be beneficial to combine several domains of the case definition, for example defining asthma on the basis of an asthma diagnosis or drug therapy. Early transient wheezing can be excluded by limiting the analysis to children 5 years and older.[65-67] Identifying risk factors such as history of allergy, or patterns of health care utilization for asthma during and outside of the winter season, may help delineate children with asthma from those with late transient wheezing.

2.2 Validity and reliability of the operationalized case definition

2.2.1 Functional and health care utilization measures from survey data

a) Parental report of wheezing symptoms

Symptom expression is the most commonly used measure in clinical and epidemiologic research on asthma, but little is known about their reliability and validity. Data on the

presence of asthma symptoms in children are often obtained from parental reports. The one-month repeatability of parental reports of wheezing and coughing in the past 12 months have shown to be high. [93] Higher reliability has been reported for parental reports of wheezing, than of cough in children.[17] Correlation of parental reports of asthma symptoms with lung function tests such as FEV_1 and bronchial hyper-reactivity, indicates that they are valid measures of asthma. Although population-based survey studies of randomly selected schoolchildren likely provide valid estimates of asthma, [16;26;94] different interpretations by parents of survey questions regarding the presence of "wheezing" may lead to the exclusion of certain groups of children.[19]

b) Parental report of an asthma diagnoses and asthma drug therapy

Survey data on the diagnosis of asthma and receipt of asthma drug therapy in children are primarily obtained from parental reports and depend on the ability of parents to recall and relate information about asthma in their children.[95] Some of parental knowledge about asthma is obtained during their interaction with physicians, which has been reported by some parents to be confusing.[73] Nevertheless, the validity of parental reports of a diagnosis of asthma is relatively high.[96] A comparison between parental reports of asthma symptoms and an asthma diagnosis recorded in a medical record documented that parents reported asthma in 84% of children with a physician diagnosis of asthma.[68] Thirty percent of children had parental reports of asthma symptoms but had never received a diagnosis of asthma; of these children, 30% had not seen a physician, 30% did not have asthma according to an external review of the medical record and 40% had been prescribed asthma drugs. The one month repeatability of parental reports of asthma being

diagnosed by a physician or in hospital has been reported to be high (kappa statistic=0.77).[17]

The reliability of parental reports of their child's utilization of asthma drugs, based on agreement between responses on two successive surveys, has also been high (kappa statistic=0.81).[17] The validity of parental reports of asthma drug therapy is lower than their reports of an asthma diagnosis. In the Kljakovic evaluation, parents reported asthma drug therapy in only 56% of children with a medical record for an asthma prescription drug.[68] On the other hand, drug therapy was reported by parents in 40% of children for whom there was no record for an asthma drug prescription during the study period (some prescription were written more than a year prior to study). Overall, parents identified drug therapy in 67% of children for whom a prescription for an asthma drug was ever written.[68] Parents were much more likely to report asthma drug use if their child had a physician diagnosis of asthma; thus, a systematic bias in the acquisition of an asthma diagnosis also affects the validity of a drug-based definition of asthma. Validity can also be compromised if certain groups of parents are less likely to recall asthma drug use, (known as recall bias) such as parents of low income children who have found to be less knowledgeable about asthma management.[97] Some studies have documented that antibiotics, antihistamines and decongestants have been identified by parents as drugs for the treatment of asthma.[98]

2.2.2 Physiologic, functional and health care utilization from medical records

a) Physician documentation of wheezing symptoms and bronchial reactivity

Physician medical records are potentially less reliable sources of asthma symptom information because they are dependent on the completeness of the record keeping. The reliability of clinical data abstracted from physician medical records of patients with asthma has been reported to be high, but not as high as that for sociodemographic data.[99] Kljakovic's record review documented that parents reported wheezing or coughing in 84% of children with an asthma diagnosis and in 31% of children without an asthma diagnosis; physicians recorded the same symptoms in the medical record for 54%-83% and 30%-35% of these children, respectively.[68] These findings suggest that the likelihood of recording asthma symptoms by physicians may be related to the time course of diagnosing asthma (for example, increased attention to wheezing symptoms prior to the diagnosis of asthma). In addition, the validity of medical record sources of wheezing in describing asthma in children is very much dependent on the sampling process for selecting physician practices, and the time frame for record review. Kljakovic's record review was conducted in a medical centre serving a European, middle class population.[68] In Donahue et al's medical record review, asthma symptoms were noted by physicians in 90% of encounters for asthma, but in only 9% of all encounters by asthmatics.[100]

The FEV_1, test has very good reproducibility and has been validated as a measure of airway obstruction by its close correlation with airway diameter.[13] The bronchial

methacholine challenge test is fairly reliable, and correlates well with cellular markers of airway inflammation and allergy skin tests. However, the reliability and potentially, validity of the bronchial reactivity measure is compromised by the fact that patient contact with a health care site is required to perform the test, that some children are unable to complete the test and that some parents may believe that the test is too invasive.[13] In Ernst et al's evaluation, 8% of parent declined participation in the bronchial challenge test and 3% of children did not complete the test successfully.[19] Peak flow meters can be used at home, but the PEF test has twice the measurement variability of FEV_1 and substantial non-compliance has been reported with peak flow meter use in low income families.[101] The physician record is also an unreliable data source for physiologic measures; Donahue et al reported that lung function tests such as peak flow measurements or spirometry (FEV_1), were recorded in 38% and 7% of encounters for asthma, respectively.[100]

b) Physician documentation of asthma diagnosis and asthma drug therapy

One would expect that the validity of a diagnosis of asthma recorded by a physician would be high. Validation of physician diagnoses recorded in medical record with expert reviews of the medical record have shown that an asthma morbidity score, based on an assessment of symptoms, drug use and hospitalization for asthma, was significantly higher in children with a diagnosis of asthma than those without.[68] However, validating a physician diagnosis of asthma requires review of physician records according to predetermined criteria, explicit or implicit, and involves judgment on the part of the reviewer or expert. Agreement between trained nurse abstractors on the likelihood of an

asthma diagnosis in a medical record, either documented by the physician, or determined from symptom and pulmonary function criteria, has been found to be only fair. [99] Viewing parent information as the gold standard in Kljakovic's evaluation, 60% of children with parental reports of asthma symptoms had a physician diagnosis in the physician record, while only 12% of children without symptoms had a physician diagnosis.[68] These findings suggest a low sensitivity for the physician record in identifying asthma, but some of the children with "asthma" symptoms may have transient wheezing, a condition which a physician would be much more familiar with than the parent.

The reliability of a physician diagnosis in a medical record also depends on the proportion of medical records sampled; in Donahue et al's medical record review, persons with asthma accounted for 95% of all patients, but only 10% of physician visits were identified as encounters for asthma.[100] The reliability of the medical record as a source of information for the prescription of asthma drugs also depends on the duration of the evaluation period. Kljakovic reported a decrease in the proportion of agreement between medical records of asthma prescriptions and parental reports of asthma drug use from 100% to 63%, when the evaluation period was reduced by one year.[68] Prescription records for asthma drugs were identified in the medical record in 50% of children whose parents did not recall asthma drug use. In some of these children asthma morbidity was high, suggesting that parental recall of asthma medication use may be more reflective of the actual drug use in the child.

2.2.3 Health care utilization from administrative data sources

a) Asthma diagnosis reported in computerized medical and hospital records

The advantage to using health administrative records, which are derived from information routinely collected for the purposes of managing a health care program, is the ability to obtain population estimates of disease.[102] Diagnoses associated with the receipt of services during a hospitalization, or a physician visits can be determined from health care administrative data. In Canada, up to 16 diagnoses can be listed in a hospitalization record; the first diagnosis is the diagnosis which is most responsible for the hospitalization. In Manitoba, only one diagnosis is listed on physician claims data. Generally speaking, physician claims and hospital abstract databases have been found to be valid and reliable in describing clinical diagnoses.[103;104] The reproducibility of asthma diagnosis coding in hospital abstract data of the UK National Health Service has been found to be high; 90% agreement on the first three digits of the primary diagnosis code was reported in a re-abstracting study.[105] Donahue et al's comparison of computerized records of an American health maintenance organization with their full-text physician record equivalents showed that an asthma diagnosis in the computerized record identified 90% of persons with asthma, either documented in the full-text record or assessed to be present by the reviewer.[100] A comparison of the re-abstracts of 1,279 hospital discharge records from 14 hospitals in Montreal with computerized information of the same records in the Quebec health insurance database, showed 95% agreement for asthma diagnoses.[106] There was lower agreement (76%) on respiratory diagnoses excluding asthma, such as bronchitis and influenza.

Validation studies of asthma diagnosis codes in health care administrative data encompass assessments of the original medical record by experts, as opposed to re-abstractions of the original record, or same-record comparisons among physician claims and hospital abstract data. [107] In a review of computerized inpatient and ambulatory medical records in a US health maintenance organization, which reported asthma diagnoses in any data field, 96% of the records exhibited a clinical picture in the original medical record which was consistent with asthma; however, a definite diagnosis of asthma was reported in only 66% of computerized records.[108] The latter finding was judged by the authors to be the outcome of insufficient documentation, prohibiting a full assessment of the chart for the presence of asthma. Their findings of an increased likelihood of a definitive asthma diagnosis for primary diagnoses of asthma recorded in hospital records, suggest that hospital records are more valid data sources for asthma diagnoses.

A complicating factor in using Canadian physician claims records is that diagnoses are censored because only one diagnosis is specified per physician visit, leading to under-coding of chronic conditions such as asthma, as acute conditions tend to be listed first.[107] We see some evidence of this in Saskatchewan's health insurance database records, for which concordance between physician claims and primary service, hospital discharge respiratory diagnosis codes for the same hospitalizations was as follows: 80% for asthma, 60% for non-specific bronchitis, and 19% for chronic bronchitis.[109] The majority of diagnoses on physician claim records which did not match hospital records of asthma were for acute conditions, such as pneumonia and non-specific bronchitis. A

substantial proportion of unmatched hospital diagnoses of chronic bronchitis were classified as asthma on the physician claim. Although not reported separately, asthma diagnoses for children are included in many of the validation studies. Other methods which exist for validating diagnoses data from administrative data include comparisons of disease prevalence based on administrative data with those derived from population-based questionnaires.[107] Using this methodology, we see that the point prevalence of asthma for children determined from health service contact records is similar to that for children diagnosed with asthma and current symptoms of asthma. (Table 2.1)

However, health care administrative data sources have the potential to introduce selection bias into asthma epidemiologic research because asthma is defined on the basis of contact with the health service system.(Table 2.2) Case ascertainment solely from diagnosis codes recorded in physician claims files omits asthmatic children who do not visit physicians, and ascertainment from hospital or physician specialist (allergists, respirologists) files omits children with mild asthma. [110] The marked variation in the frequency of physician consultations among children with asthma, ranging from 2.3 visits per year in children with infrequent asthma symptoms to 10.6 annual visits in children with major limitations in activity, [71] makes case ascertainment very time frame dependent.

Table 2.2. Case Ascertainment of Asthma in Pharmacoepidemiologic Studies

Citation	Data Source	Case Definition	Potential Selection Bias
Gerstman 1989	Michigan Medicaid (age 0-44 yr)	Two asthma diagnoses in physician/ hospital claims, and 2 anti-asthma prescription claims from 1980-1986	Include children with transient wheezing wheezing or respiratory infections (overestimate asthma)
Bosco 1993	Michigan Medicaid (age 5-14 yr)	One asthma diagnosis in physician/ hospital claims, and 1 anti-asthma prescription claim from 1980-1986	Include children with transient wheezing wheezing or respiratory infections (overestimate asthma)
Stempel 1996	4 HMO's (age $\geq$ 7 yrs)	One asthma diagnosis in physician claims or 2 anti-asthma prescriptions in 1993; excluded related diagnosis (bronchitis)	Omission of misdiagnosed asthma, likely low income individuals (underestimate asthma)
Vollmer 1997	Oregon HMO (age 15-55 yr)	Asthma hospitalization or 2 prescriptions for anti-asthmatic drugs in 1 year	Omission of persons seeing MD for asthma and receiving one Rx (underestimate mild asthma)
Erzen 1997	Manitoba health care insurance (all ages)	One asthma or related diagnosis in physician/hospital claims in 1 year	Omission of persons receiving asthma drugs, and not seeing physician (underestimate asthma)
Donahue 1997	New England HMO (all ages)	One asthma diagnosis in physician record, hospitalization or emergency visit in 1991-94; excluded 16% of persons with no prescription insurance	Omission of persons receiving asthma drugs, and not seeing physician, omit low income asthmatics (underestimate asthma)

HMO=health maintenance organization

Selection of children on the basis of a single physician diagnosis of asthma, especially if over a longer time period, has the potential to include children with transient wheezing, as discussed previously. However, restricting selection to more than one asthma diagnosis can exclude children with mild or well-controlled asthma, and has reported to decrease the prevalence of asthma by 60%.[111] Excluding related diagnoses such as bronchitis, may systematically exclude asthmatic children who are less likely to receive a diagnosis of asthma, such as children living in low income households. A diagnosis of bronchitis accounted for three-quarters of asthma and bronchitis diagnoses documented in Manitoba physician claims data; this proportion (80%) was much greater in lower, than higher income children (63%).[72;112] Similarly, selection bias with respect to socioeconomic status can also occur when the sampling frame is predominantly lower income children (ie. Medicaid database), or middle to higher income as in health maintenance organizations in the US.

b) Asthma drugs recorded in computerized prescription records

Electronic prescription databases have been utilized to determine the population prevalence of chronic diseases on the basis of drugs commonly used to treat chronic conditions.[113;114] The benefit to using prescriptions records over physician visit diagnoses as a measure for a disease, is that individuals with chronic diseases like asthma, are more likely to continuously receive prescriptions for drugs, which can be refilled without a physician visit, than to visit their physician regularly.[114] Moreover, a chronic disease index derived from prescription records has been reported to be a better indicator of outcomes such as mortality, than an index based on ambulatory care visits.[113]

Although not frequently evaluated, the validity and reliability of prescription databases has found to be high.[115] The Manitoba prescription database contains 90% of the prescriptions dispensed in the province, with slight under-representation of prescriptions for treaty status Indians.[116]

The major caveat to utilizing prescription drug data sources is that they do not provide information on how (or if) the drug was taken. Data obtained from home interviews has shown that 73% of drugs consumed by individuals matched pharmacy records of recently dispensed prescriptions with respect to the drug name, strength and directions for use.[117] In addition, identifying asthmatics on the basis of prescriptions for asthma drugs can introduce selection bias in an analysis. As discussed in the theoretical orientation section, inclusion of children on the basis of at least one asthma prescription can include children who have transient or episodic wheezing. Consequently, some researchers have defined persons with asthma on the basis of at least two prescriptions for an asthma drug over a 1 year period.[118;119] This methodology too, is problematic, with the potential of excluding children with mild asthma, or who are under-treated. In Donahue et al's review of computerized health records, one quarter of persons with a physician diagnosis of asthma had received only one prescription for an asthma drug during the year.[100] Children with mild asthma are less likely than children with more severe asthma to be treated with asthma drugs.[17;20;21] Moreover, there is a high non-compliance rate with asthma drug therapy, manifesting as irregular patterns of prescription refills in database records.[120]

2.2.4 Summary of validity and reliability issues

Questionnaire data sources on the occurrence of wheezing in children reported by parents are reliable and valid. Parental reports of the presence of an asthma diagnosis and use of asthma medications are also reliable, but because they are dependent on parental knowledge, have the potential to be biased. Physician medical records are valid, and also reliable data sources for these measures if the evaluation period and sampling frame is extensive. Medical records are poor sources of information on bronchial reactivity. Clinical study data are more reliable data sources for bronchial reactivity, but case ascertainment may be incomplete due to some of the difficulties in carrying out the test.

The major issues in employing health care administrative data to ascertain asthma revolve around the variability in health care utilization by children with asthma. Records for children with mild asthma will not be found as often, as those for children with more severe asthma. Combining data from physician claims, hospital and prescription databases can potentially diminish, but not eliminate some of the shortcomings in using single data sources of health administrative records In Donahue et al's comparison of computerized health records with physician records (defined as gold standard) showed that the presence of a physician diagnosis and at least one prescription for an anti-asthma drug identified 90% of persons with asthma, as recorded in the physician's record.[100] The specificity of the case definition was 80%. A summary of the limited evidence suggests that case ascertainment on the basis of at least one asthma diagnoses recorded in hospitalization and physician claims databases over a one year period, or two

prescriptions for a bronchodilator drug or one prescription for a prophylaxis drug, may enhance the detection of asthma in a population and decrease the risk of selection bias.

2.3 Summary of issues in developing a case definition of childhood asthma

All of the domains described have a good conceptual basis for defining asthma.(Table 2.3) The limitation of bronchial reactivity measures is that they are not widely used in the clinical diagnosis of asthma. Parental reports are good sources of wheezing symptoms and a physician diagnosis for asthma, and relatively good sources of drug therapy. Physician medical records are better sources of information on an asthma diagnosis and drug therapy, but they are quite dependent on the comprehensiveness of the record review. Health care administrative data do not provide data on wheezing symptoms, but the electronic form of these data allow for comprehensive searches for asthma diagnoses and prescription drugs.

The selection of a case definition is dependent on its functional use.[2] Very broad case definitions which select children on the basis of minimal criteria such as a single diagnosis of asthma or an asthma-like condition, are useful in descriptive studies of the diagnosis and treatment of asthma. For analytic studies where avoiding selection and misclassification bias is crucial, one may want to limit case definition to ensure that children who have "current" asthma are selected. Case ascertainment on the basis of asthma drug utilization would be an appropriate measure of current asthma. In these studies, it would be important to isolate children with transient wheezing, by limiting the

Table 2.3. Evaluation of Various Domains of a Case Definition for Childhood Asthma

Domain	Theoretical Adequacy	Operational Adequacy		
		Data Source	Reliability	Validity
1) Bronchial Reactivity	++, present in absence of symptoms, not reliable in children < 6 years old	study record	+++	++
		physician medical record	+	+
		health administrative record	NA	NA
2) Asthma Symptoms	++, difficult to distinguish asthma from transient wheezing syndrome	parental report	+++	+++
		physician medical record	++	++
		health administrative record	NA	NA
3) Physician diagnosis	++, difficult to distinguish asthma from transient wheezing syndrome, potential biased assignment of diagnosis	parental report	+++	++
		physician medical record	++	+++
		health administrative record	+++	++
4) Asthma drug therapy	++ (+++), need to distinguish from non-asthma uses of drugs	parental report	+++	++ (+++)*
		physician medical record	++	++ (+++)*
		health administrative record	+++	++ (+++)*

+=fair, ++=good, +++=very good, * reported use does not equivalent to actual use of drug, NA=not available

age group to children 5 years and older, and identifying children who have allergic diseases, and do not utilize the health care system for asthma solely in winter.

2.4 Proposed research and study hypotheses

Research was undertaken to develop a case definition for childhood asthma, which would identify children with persistent asthma and could be applied to health care administrative records. The performance of the case definition was tested by assessing the construct validity of its components.

Study Hypothesis I

The receipt of prescriptions for asthma drugs is associated with an increased likelihood of persistent asthma in children, defined as continued contact with the health care system for asthma.

Study Hypothesis II

The presence of health care contacts for allergic diagnoses is associated with an increased likelihood of persistent asthma in children, defined as continued contact with the health care system for asthma

Study Hypothesis III

In comparison to winter only health care utilization, year-round health care utilization is associated with an increased likelihood of persistent asthma in children, defined as continued contact with the health care system for asthma.

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A Case Definition of Childhood Asthma Derived From Health Care Administrative Records

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ABSTRACT

Background: The diagnosis of persistent asthma in childhood is complicated by the presence of other transient wheezing syndromes. This research was undertaken to develop a case definition for childhood asthma, which supplements a diagnosis-based definition and can be applied to health care administrative records.

Methods: Using population-based health care administrative data, a cohort of 48,146 children was assembled on the basis of the following case definition for asthma: 1) a physician contact or hospitalization for asthma or bronchitis diagnoses during the time period January 1, 1995- March 31, 1998, and 2) in the absence of a health care contact for an asthma-like diagnosis, at least one prescription for a prophylaxis drug, at least one prescription for ketotifen concomittant with a bronchodilator, or at least two prescriptions for bronchodilator drugs during the same time period. The validity of the case definition in identifying children with "persistent asthma," defined as continuous health care utilization for asthma over a 39-month period, was assessed.

Results: The asthma case definition identified 90% of children with a prescription for an asthma drug. Children selected on the basis of an asthma drug prescription were 3-6 times more likely than children without an asthma drug prescription to have "persistent asthma." To a lesser extent, "persistent asthma" was more likely among children with an asthma diagnosis, than in those without an asthma diagnosis. The presence of an asthma prescription drug and year-round asthma health care utilization patterns substantially increased the likelihood of "persistent asthma" in children with and without asthma

diagnoses. Children with bronchitis diagnoses who were subsequently diagnosed with asthma, were more likely than children with bronchitis-only diagnoses to have markers of "persistent asthma."

Conclusions: An asthma case definition which incorporates data on asthma drug prescriptions and health care utilization patterns, as well as diagnosis information, improves the likelihood of identifying children with persistent asthma.

INTRODUCTION

Our understanding of the natural history of asthma in childhood is contingent on the availability of case definitions which accurately identify children with asthma, and the availability of longitudinal data to observe the course of the disease.[1] Numerous case definitions for asthma have been employed, ranging from symptom or physiologic measures, to ones based on a physician-diagnosis or drug treatment. Each case definition must contend with validity and reliability issues–whether the case definition can distinguish asthma from other related respiratory diseases, and how consistently the definition can be reproduced for comparison purposes.[2] Symptom-based definitions derived from medical records or parental report are reproducible,[3-5] but cannot distinguish asthma from transient wheezing syndromes in children.[6-8] Physiologic measures of asthma, such as bronchial reactivity tests, are highly correlated with the underlying inflammatory process of asthma, but detect hyper-responsiveness in the absence of wheezing and are not commonly performed in non-research settings.[9-12] A physician-diagnosis of asthma is subject to the same limitations as symptom-based

definitions, and has the potential caveat of biased assignment of diagnosis.[13-15] Asthma drug therapy-based measures identify persons currently experiencing asthma symptoms, but because asthma drugs are also used in the treatment of other diseases, these measures may lack specificity.[16-18]

The increasing availability of longitudinal survey data on children facilitates the conduct of natural history studies of asthma in childhood, but population-based questionnaire studies are expensive to conduct and smaller scale studies can produce biased cohorts.[1] Health care administrative databases provide comprehensive records on whole populations which can be easily followed forward in time.[19] Combining various domains of case definitions may overcome the limitations of using health care utilization data, [20] and improves the validity of defining asthma. [21-23] In addition to traditional markers of asthma identified from administrative data such as asthma diagnosis and prescription drugs, measures which differentiate childhood asthma from transient wheezing syndromes such as the presence of allergic diagnoses, or of year-round versus winter-only health care utilization can further improve the validity of the case definition.[7;24-27] The objective of this research was to develop a case definition for childhood asthma, which supplements a diagnosis-based definition and can be applied to health care administrative records. The performance of the case definition was tested by assessing its face validity, criterion validity, and construct validity.

RESEARCH METHODS

Data sources:

Data for this study were obtained from four computerized databases maintained by the Manitoba Health Services Insurance Plan (MHSIP): 1) registration files, 2) records of physician reimbursement claims, 3) records of hospital separation abstracts, and 4) records of prescriptions dispensed in retail pharmacies. Data were also obtained from the registration files of Manitoba Family Services, a provincial income assistance agency. The MSHIP registration file contains a record for every individual registered to receive insured health services and records birthdate, sex and geographic location. Records of physician reimbursement for medical care provided are submitted under a fee-for-service arrangement, and contain information on patient diagnosis at the 3-digit level of the ICD-9-CM classification system and physician specialty. Separation abstracts for hospital services provided include information on 16 ICD-9-CM diagnostic codes, of which the first is the diagnosis that is most responsible for the hospital stay. Records of dispensed prescriptions, which are submitted by retail pharmacies for reimbursement by provincial drug insurance plans or for drug utilization review purposes, contain data on the date of prescription dispensing, drug name, strength, dosage form, and quantity, and a 9-digit drug identification number. Record linkages were achieved by the use of anonymous personal identifiers. Statistics Canada Census 1996 household income data, aggregated to the geographic unit of the enumeration area, were used to rank neighbourhood income quintiles from 20% of the population residing in the lowest income to 20% of the population residing in the highest income neighbourhoods.[28-30]

Study population:

A total of 174,208 children, aged 5-15 years as of January 1, 1995, and registered with the MSHIP registry until March 31, 1996 were identified. A cohort of 48,146 children was assembled on the basis of the following case definition for asthma: a) any health care contact (physician visit, hospitalization) for asthma or bronchitis (also included croup and bronchiolitis) diagnoses during the time period January 1, 1995 to March 31, 1998, OR b) in the absence of a health care contact for an asthma-like diagnosis, at least one prescription for a prophylaxis drug (inhaled corticosteroid, sodium cromoglycate), at least one prescription for ketotifen concomittant with a bronchodilator, or at least two prescriptions for bronchodilator drugs during the same time period.

Data analysis:

The case definition for childhood asthma was evaluated on the basis of face validity, criterion validity, discriminant construct validity and convergent construct validity. Face validity was assessed by comparing the prevalence of children meeting the case definition with literature values of asthma prevalence. Using a prescription for an asthma drug as the criterion (bronchodilator, inhaled corticosteroid, sodium cromoglycate, and ketotifen or oral steroid concomittant with bronchodilator), the criterion validity of the drug and diagnosis-based case definition for asthma, measured by sensitivity and specificity determinations, was compared to the criterion validity of a diagnosis-based (asthma or bronchitis) case definition. [31] Also for comparative purposes, the sensitivity and specificity of a prescription for an asthma drug was determined, using an asthma-like diagnosis as the criterion. Another domain of criterion validity, the positive predictive

value (PPV) of the case definition in predicting yearly health care utilization was determined and compared to the PPV of children with asthma-like diagnoses only or asthma drug prescriptions only.

Discriminant construct validity analysis was conducted to ascertain the ability of the drug and diagnosis domains of the case definition to distinguish between the constructs of "persistent asthma" and transient wheezing, and whether the addition of risk factors for asthma could improve upon their ability to do so.[32] To achieve this objective, a sub-cohort of children meeting the case definition and with health care contacts or prescriptions during January-December 1995 was assembled and followed forward in time to determine: 1) the proportion of children with continued health care contacts or prescriptions for asthma-like conditions during the time period January 1996-March 1998, and 2) the domains which were most likely to be associated with continued health care utilization, representing "persistent asthma." The diagnosis and drug domains of the case definition were initially evaluated. Children were categorized as having at least one contact for an asthma diagnosis or having contacts only for bronchitis diagnoses. Drug therapy measures classified children as follows: a) at least one prescription for a bronchodilator or not, b) at least one prescription for a prophylaxis drug (eg. inhaled corticoseroid, sodium cromoglycate) or not, and c) at least one prescription for an oral corticosteroid drug or not. In addition to diagnosis and drug measures, the following risk factors for the persistence of asthma were included: a) age, b) gender, c) prematurity status at birth, d) time since first contact with the health care system for bronchitis or asthma, e) number of hospitalizations for asthma or bronchitis from birth to start of study,

f) presence or absence of health care visits for hayfever, eczema or other allergic reactions, and g) pattern of health care utilization.[1;13;22;23;25;26;33-36] The latter was a dichotomous measure which categorized children with asthma health care contacts or prescriptions limited to the winter season (November-February) or with year-round asthma health care utilization.[24;27] The likelihood (odds ratio) of "persistent asthma" for individual domains was derived from multivariate logistic regression models as follows: 1) Model A contained diagnoses and drug therapy measures, 2) Model B contained Model A measures and risk factors for asthma. Multivariate logistic regression analysis yielded the most parsimonious model of factors associated with the persistence of "asthma." Both models included the socioeconomic variables of treaty Indian status, single-parented household, lowest income neighbourhood quintile household and single-parented, income assistance household, to adjust for differences in health care utilization.[37]

The convergent construct validity of the bronchitis diagnosis was assessed to determine the suitability of including a bronchitis diagnoses in a case definition of asthma.[32] This analysis assessed the convergence of three subcategories of bronchitis diagnoses on other constructs of asthma. The distribution of asthma drug treatment and risk factors was compared among three groups of children: 1) children with health care visits for bronchitis diagnoses during 1995 and continued health care utilization for asthma diagnosis during the time period, January 1, 1996-March 31, 1998, 2) children with bronchitis diagnoses during 1995 and continued utilization for bronchitis diagnoses, and 3) children with bronchitis diagnoses during 1995 and no further utilization. Using

children who subsequently acquired an asthma diagnosis as the reference group, the likelihood (odds ratio) of continued utilization for bronchitis or no further utilization was determined for individual asthma factors. A likelihood ratio greater or less than one indicated non-convergence with the reference group. Multivariate logistic regression analysis was conducted to determine the most parsimonious model of predictors for bronchitis outcomes. All analyses were conducted at the 95% level of confidence.

RESULTS

Of a total of 174,208 Manitoban children, aged 5-15 years as of January 1,1995, 45,704 (26.2%) had at least one physician visit or hospitalization attributed to asthma (primary or secondary diagnosis code), or to a diagnosis of bronchitis, bronchiolitis or croup, over the time period, January 1, 1995 – March 31, 1998. Similarly, 28,190 (16.2%) had received at least one prescription for an asthma drug during this time period. Fifty percent of children with an asthma-like diagnosis had a prescription for an asthma drug, and 82% of children with an asthma drug prescription had a health care visit for an asthma-like diagnosis. The specificity for an asthma drug prescription, using an asthma-like diagnosis as the criterion, was 96%. Conversely, the specificity for an asthma-like diagnosis, using an asthma drug prescription as the criterion was 85%. (Table 2.6.1)

A total of 48,146 children met the study case definition for asthma. In addition to children with asthma-like diagnoses, the case definition captured 2,442 children without asthma-like diagnoses who had at least one prescription for a prophylaxis drug, at least two

prescriptions for a bronchodilator drug, or one prescription for ketotifen concomittant with a bronchodilator drug. Excluded were children with no asthma-like diagnoses who had singular prescriptions for bronchodilators, alone or in combination with an oral corticosteroid, representing 11.1% of all children with bronchodilator prescriptions. In comparison to a diagnosis-based definition, the sensitivity of the case definition, using a asthma drug prescription as the criterion, was increased to 90%.

The health care utilization of three 1995 cohorts of children with "asthma," assembled on the basis of an asthma-like diagnosis, or a drug prescription, or the study case definition was followed over the next two-year time period to compare patterns of utilization (Table 2.6.2). The positive predictive value (PPV) of an asthma drug prescription in predicting yearly prescription use was 35%, while the PPV for an asthma-like diagnosis in predicting yearly health care utilization was 19%. The case definition had a PPV of 31.8% in predicting yearly prescription and/or health care use. Approximately 15% of children derived from either case definition "skipped" one year of prescription or health care utilization.

A cohort of 29,198 children who met the case definition and had health care contacts or prescriptions in 1995, was followed forward in time to determine "asthma persistence." Sixty percent of children had further health care utilization in 1996 and onwards, and were characterized as having "persistent asthma." Children with asthma diagnoses were almost twice as likely as children who had not been diagnosed with asthma, (bronchitis diagnoses only) to have "persistent asthma." (Table 2.6.3) The presence of an asthma

prescription drug was associated with "persistent asthma" to a greater extent than an asthma diagnosis. The presence of a prescription for an asthma drug, in combination with asthma or bronchitis diagnoses, further increased the likelihood of having "persistent asthma."(Table 2.6.4) Among children with asthma or bronchitis diagnoses, and no asthma drugs, a pattern of year-round health care utilization was associated with a greater than 5-fold likelihood of "persistent asthma," in comparison with winter-only utilization. Year-round utilization for asthma, concomittant with an asthma drug prescription, increased the likelihood of persistent asthma in children to a substantial degree. Other risk factors for "persistent asthma" such as history of allergy, increased duration since first physician contact for asthma and a greater number of previous hospitalizations for asthma, were independently associated with persistence of "asthma." Prematurity increased the likelihood of persistent asthma in univariate, but not multivariate analyses (data not shown). Sociodemographic measures such as treaty status Indian, low income area household and single-parent, income assistance households, which were included in models to adjust for variation in health care utilization, were also independently associated with an increased likelihood of "persistent asthma."

Fifteen thousand children had a health care contact for a bronchitis diagnoses during time period, January to December 1995. Excluding 3,951 children with a visit for an asthma diagnosis prior to the study period from time of birth, left a cohort of 11,043 children with an initial health care contact for bronchitis in 1995 or prior. Following these children forward in time until March 31, 1998, 13% had a subsequent health care visit for an asthma diagnosis, 23% continued to have health care visits for bronchitis diagnoses, and

64% had no further health care contacts for asthma or bronchitis diagnoses. Multivariate logistic regression models documented that in comparison to children with bronchitis and a subsequent diagnosis of asthma, the likelihood of no further health care contacts for bronchitis was substantially increased in the presence of winter-only health care utilization, and significantly decreased in the presence of allergic diagnoses and asthma drug therapy.(Table 2.6.5) Similarly, the likelihood of continued bronchitis diagnoses, in comparison to the acquisition of an asthma diagnosis, was increased in the presence of winter-only utilization and significantly decreased in the presence of asthma drug therapy.(Table 2.6.6) In addition. the likelihood of continued bronchitis diagnoses was significantly increased among children born prematurely and among children with a longer duration of time since first physician contact for bronchitis diagnoses. The likelihood of continued bronchitis diagnoses was significantly increased in children with a greater number of previous hospitalizations for bronchitis in univariate, but not multivariate analyses. Independent of disease and treatment factors, this likelihood was significantly greater among lower income or single-parented children.

DISCUSSION

Over a three-year time period, 27.6% of Manitoban children, aged 5-15 years, were identified as having asthma on the basis of asthma drug prescriptions and health care contacts for asthma-like diagnoses. This treatment prevalence appears much higher than the 11% prevalence of "current" asthma in Winnipeg children, aged 5-19 years, defined on the basis of an asthma diagnosis, and recent asthma symptoms or receipt of asthma

drugs in the 1995/96 Student Lung Health Survey. [38] However, this survey also reported that an additional 20% of Canadian students had asthma symptoms or received asthma drugs, but had not been given a diagnosis of asthma. Selecting children on the basis of an asthma-like diagnosis, identified 82% of children with an asthma drug, as reported by others. [4;18] The drug and diagnosis-based case definition identified 90% of children with an asthma drug. Osborne at al reported that among individuals receiving asthma drug prescriptions over a 3-year period, 80% had a diagnosis of asthma and 100% had an asthma-like condition recorded in the medical record.[39] Using an asthma-like diagnosis as the gold standard, 50% of children had prescriptions for asthma drugs, also similar to literature reports.[4;18] While 98% of children with asthma have been observed to receive an asthma drug in the past, this proportion decreases to 46% in children with current asthma drug therapy. [18] The criterion of two or more bronchodilators in the absence of a diagnosis improved the specificity of drug component of definition, and excluded 11% of children using bronchodilators, which is compatible with reports that 10% of children use bronchodilators for non-asthma indications.[16] Furthermore, the value of combining asthma drug prescriptions with asthma-like diagnoses in a case definition was enhanced detection of children with asthma during a one-year period. Surveys tell us that children with asthma are more likely to receive a prescription for an asthma drug in the past year, than to see a physician. [38;40]

Discriminant validity analysis helped us compile a list of domains which would be most useful in identifying children with "persistent asthma," a construct which has been utilized to distinguish asthma from transient wheezing syndromes.[25] The domains were

measured concurrently with the outcome of "asthma persistence," necessitating the reporting of measures of association and not risk. The asthma drug therapy domain of the case definition was more closely associated with "persistent asthma" than a physician diagnosis of asthma. Children with prescriptions for bronchodilator drugs were six times more likely, and children with inhaled corticosteroid drug prescriptions were 3 times more likely to have "persistent asthma" than children with no asthma drug prescriptions. Asthma drug therapy has been reported to be a predictor of persistence of asthma symptoms at 10 years of age.[33] Independent of drug therapy, the likelihood of "persistent asthma" was 1.7 times greater in the presence of an asthma diagnosis, than a bronchitis diagnosis. In Toelle et al's evaluation of three case definitions of asthma in children, children diagnosed with asthma had an increased prevalence of more severe asthma 10 years later, than children with wheezing symptoms, who had not been diagnosed with asthma.[22] In our study, the association between "persistent asthma," and asthma or bronchitis diagnoses was substantially improved if there also existed prescription records for asthma drugs. However, the presence of inhaled corticosteroids prescriptions increased the likelihood of asthma persistence to a lesser extent than did prescriptions for other asthma drugs, especially in children with bronchitis diagnoses. Inhaled corticosteroids are very effective in preventing asthma exacerbations and their use indicates more severe asthma. [41] Their use in children with bronchitis diagnoses suggests short-term treatment of viral-induced bronchitis. [42;43]

Children who met the case definition and had other risk factors for asthma were more likely to have "persistent asthma," than those without these risk factors. A history of

allergic conditions is a well-known risk factor for the development of asthma, and distinguishes children with transient wheezing from those with asthma.[25;33] Other risk factors for "persistent asthma," such as longer duration since first health care contact for asthma/bronchitis and increased hospitalization at an earlier age have also been documented.[22;27;45] Prematurity at birth was not a significant predictor in the multivariate model, but potentially was correlated with other risk factors.[35] Year-round health care utilization for asthma-like diagnoses or asthma drug prescriptions was associated with "persistent asthma" to a substantial degree. This finding is compatible with clinical observations of wheezing in children; children with asthma have year-round symptoms, whereas those with transient wheezing have winter-only symptoms.[27] Moreover, it has been recently documented that children with viral-associated wheeze in the winter season are differentiated from children with continuous symptoms by the presence of bronchial inflammatory cells, indicative of asthma.[24] We translated the concept of year-round asthma symptom occurrence into the measure of year-round asthma health care utilization patterns, with the anticipation that it would predict asthma persistence. Due to the strength of the association between year-round health care utilization patterns and persistent of asthma, we believe that this measure is a valuable addition to the case definition of asthma in childhood.

We conducted a convergent validity analysis of bronchitis diagnoses to determine whether they represented mis-diagnosed asthma. Bronchitis is a lower respiratory tract infection which causes reversible bronchial inflammation. Although bronchitis is more likely than asthma to be associated with sputum production,[46] symptoms and

pulmonary function abnormalities are similar in these two conditions, and respiratory infection-induced exacerbations of asthma resemble bronchitis.[47] Patients with acute bronchitis or croup are significantly more likely to be diagnosed with asthma in the future.[48] In our cohort, 13% of children with an initial bronchitis diagnosis subsequently acquired a diagnosis of asthma. These children were more likely than children with no further or continued bronchitis diagnoses to have year-round than winter-only health care utilization for asthma, and to be treated with asthma drugs.[7;24;33] Furthermore, two potentially distinct entities of bronchitis emerged from our data: 1) bronchitis which goes away, similar to transient wheezing of childhood, and is predicted by winter only utilization and absence of allergy, [6;27] and 2) continued bronchitis which differs from asthma on the basis of prematurity at birth, earlier presentation of symptoms, and socioeconomic status measures, such as low income or single-parent household status. The latter findings mirror a recent comparison of bronchitis and asthma in a group of children in British Columbia, in which children with chronic bronchitis were also more likely than children with asthma to have a history of chronic otitis media, of maternal smoking and aboriginal status.[49] However, our findings may also be interpreted as evidence for the mis-diagnosis of asthma in lower income children.

The caveat to using case definition of asthma based on health care utilization data is the omission of children with asthma who do not utilize the health care system. The literature reports that as many as 30% of children with asthma symptoms have not seen a physician in the past year.[4,38] However, almost all children with a diagnosis of asthma will

receive drug therapy at some point, and a high proportion of children experiencing current asthma symptoms are treated with drug therapy. [17,18] By applying the case definition over a 3-year time period, and including children with asthma drug therapy, but no asthma diagnoses, we enhanced the detection of children with asthma. Low income children have lower rates of asthma drug utilization and physician visitation for asthma, [17,37] which would impact on our measure of asthma persistence. Sociodemographic factors were included in multivariate models to adjust for variation in health care utilization. We found that lower income, single-parented or treaty status Indian children were significantly more likely to have persistent asthma. Asthma of greater severity has been reported among lower income children.[44]

The identification of asthma in childhood is complicated by the presence of other transient wheezing syndromes, which are indistinguishable clinically from asthma and compromise the validity of asthma diagnosis information contained in health care administrative databases.[6] A case definition which incorporates data on asthma drug prescriptions and health care utilization patterns, as well as diagnosis information, improves the likelihood of identifying children with persistent asthma. Traditionally, bronchitis diagnoses have been included in case definitions for "total respiratory morbidity," but excluded from definitions for asthma.[13] Our findings suggest that children with bronchitis diagnoses, and concomittant asthma drug therapy, health care visits for allergic disorders or year-round health care utilization for bronchitis are more likely to have asthma than children without these characteristics. In summary, we have identified predictors of childhood asthma which can be created from health care

administrative databases and utilized in longitudinal studies of the natural history of asthma. Our case definition was found to have face, criterion and construct validity. Further study is required to assess its reproducibility.

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Table 2.6.1. Sensitivity and Specificity of Asthma Case Definition

Diagnosis-based case definition

	Asthma drug Prescription	No asthma drug prescription	Total
Asthma-like diagnosis	23033 (81.7%)	22671	45704
No asthma-like diagnosis	5157	123347 (84.5%)	128504
Total	28190	146018	174208

Study case definition (diagnosis and asthma drug prescription)

	Asthma drug Prescription	No asthma drug prescription	Total
Asthma-like diagnosis or asthma drug prescription	25475 (90.4%)	22671	48146
No diagnosis or asthma drug prescription	2715	123347 (84.5%)	126062
Total	28190	146018	174208

Table 2.6.2. Positive Predicted Value (PPV) for Annual Asthma Health Care Contacts or Prescriptions

	Number with record in 1996, 1997 and 1998	Total	PPV
Asthma-like diagnosis in 1995	4858 had health care visit for asthma-like diagnosis	25141	19.3%
Asthma drug prescription in 1995	6390 had asthma drug prescription	18159	35.2%
Asthma-like diagnosis or asthma drug prescription in 1995 (case definition)	9272 had asthma-like diagnosis or asthma drug prescription	29198	31.8%

Table 2.6.3. Likelihood of Persistent Asthma*in Children with Asthma Diagnoses and Asthma Drug Prescriptions

Factor		% children with Persistent asthma	Adjusted** Odds Ratio (95% CI) for Asthma diagnosis or drug vs. none
Asthma diagnosis	(n=18,955)	75.5%	1.72 (1.61-1.84)
Bronchitis diagnosis	(n=10,243)	33.3%	1.00 reference
Bronchodilator drug	(n=15,669)	84.3%	5.51 (5.16-5.88)
No bronchodilator	(n=13,529)	33.2%	1.00 reference
Maintenance drugs***	(n=10,690)	86.6%	2.71 (2.51-2.92)
No maintenance drugs	(n=18,508)	45.7%	1.00 reference
Oral corticosteroids	(n = 4,796)	93.0%	6.59 (5.83-7.46)
No oral corticosteroids	(n=24,402)	54.3%	1.00 reference

*continued health care utilization for asthma-like diagnoses and prescriptions for asthma drugs,
adjusted for factors in table, and treaty status Indian, single-parent income assistance household and neighbourhood income, * inhaled corticosteroid, sodium cromoglycate, ketotifen and salmeterol

Table 2.6.4. Likelihood of Persistent Asthma* in Children with Asthma Diagnoses, Asthma Drug Prescriptions and other Asthma Risk Factors

Factor	Adjusted** Odds Ratio (95% CI)	
	Model A	Model B
	Asthma drug versus no drug	Year-round utilization +factor vs. winter-only utilization+no drug
Asthma diagnosis and		
No asthma drugs	1.00 reference	5.66 (4.90-6.53)
Bronchodilator	6.22 (5.75-6.73)	31.12 (26.38-36.74)
Maintenance drug***	2.88 (2.65-3.12)	11.42 (7.90-16.51)
Oral corticosteroid drug	4.28 (3.72-4.92)	19.25 (14.92-24.84)
Bronchitis diagnosis and		
No asthma drugs	1.00 reference	3.91 (3.48-4.40)
Bronchodilator	4.37 (3.89-4.91)	14.88 (12.61-17.56)
Maintenance drug***	1.84 (1.49-2.26)	5.24 (3.79-7.26)
Oral corticosteroid drug	16.31 (12.71-20.94)	45.37 (34.42-59.79)
	Risk factor versus none	Risk factor versus none
Male gender		0.93 (0.87-0.99)
Presence of allergic diagnoses		1.29 (1.21-1.37)
Yearly asthma/bronchitis hospitalizations from birth (increase in number)		2.26 (1.72-2.98)
Time since first contact for asthma or bronchitis (one year increase)		1.05 (1.03-1.06)
Age (one year increase)		NS
Treaty status Indian	1.30 (1.16-1.46)	1.17 (1.04-1.32)
Lowest income neighbourhood	1.27 (1.17-1.38)	1.22 (1.13-1.33)
Single-parent, income assistance household	1.21 (1.10-1.34)	1.19 (1.07-1.31)

*continued health care utilization for asthma-like diagnoses and prescriptions for asthma drugs
adjusted for factors in table, * inhaled corticosteroid, sodium cromoglycate, ketotifen and salmeterol

Table 2.6.5. Likelihood of No Further Bronchitis Diagnoses versus Acquisition of Asthma Diagnoses

Risk Factor	Bronchitis (n=7101)	Asthma (n=1447)	Unadjusted Odds Ratio (95% CI)	Adjusted* Odds Ratio (95% CI)
Sociodemographic				
Age (mean,SD)	9.30, 3.20	8.85, 3.2	1.05 (1.03-1.06)	1.04 (1.01-1.07)
Male gender (%) (vs female)	50.2	46.7	1.15 (1.03-1.29)	1.24 (1.06-1.45)
Treaty status Indian (%) (vs non-Treaty)	9.5	9.7	1.02 (0.84-1.24)	NS
Single-parent household (%) (vs two-parent)	27.4	29.3	0.91 (0.80-1.03)	NS
Low income area** (%) (vs higher income)	20.9	18.9	1.13 (0.98-1.31)	NS
SP, ICA*** household (%) (vs non SP, ICA)	11.2	13.1	0.84 (0.71-1.00)	NS
Disease-related				
Premature birth (%) (vs not premature)	5.4	5.6	0.97 (0.76-1.24)	NS
Allergic diagnoses (%) (vs no allergy)	30.7	42.2	0.61 (0.54-0.68)	0.73 (0.62-0.85)
Winter-only utilization (%) (vs year-round)	40.9	5.3	12.48 (9.86-15.80)	5.99 (4.60-7.81)
Prior annual bronchitis hospitalizations (mean, SD)	0.014, 0.075	0.016, 0.076	0.71 (0.36-1.40)	NS
Years since first contact For bronchitis (mean, SD)	4.92, 4.44	5.21, 4.18	0.98 (0.97-1.00)	0.97 (0.95-0.99)
Treatment-related				
Bronchodilator drug (%) (vs no bronchodilator)	10.7	74.6	0.04 (0.04-0.05)	0.08 (0.07-0.09)
Maintenance drugs**** (%) (vs no prophylaxis drugs)	2.3	45.2	0.03 (0.02-0.03)	0.08 (0.06-0.10)
Oral corticosteroids (%) (vs no oral corticosteroids)	3.7	17.1	0.18 (0.15-0.22)	0.48 (0.37-0.64)

*adjusted for other factors in table, **lowest income quintile, ***single-parent, income assistance household
**** inhaled corticosteroid, sodium cromoglycate, ketotifen and salmeterol

Table 2.6.6. Likelihood of Continued Bronchitis Diagnoses versus Acquisition of Asthma Diagnoses

Risk Factor	Bronchitis (n=2495)	Asthma (n=1447)	Unadjusted Odds Ratio (95% CI)	Adjusted* Odds Ratio (95% CI)
Sociodemographic				
Age (mean,SD)	9.11, 3.35	8.85, 3.19	1.02 (1.00-1.04)	NS
Male gender (%) (vs female)	46.6	46.7	1.00 (0.88-1.14)	NS
Treaty status Indian (%) (vs non-Treaty)	16.1	9.5	1.83 (1.49-2.25)	NS
Single-parent household (%) (vs two-parent)	36.8	29.3	1.41 (1.22-1.62)	1.37 (1.13-1.66)
Low income area** (%) (vs higher income)	30.7	18.8	1.90 (1.63-2.22)	1.54 (1.24-1.90)
SP, ICA*** household (%) (vs non SP, ICA)	17.8	13.1	1.45 (1.20-1.74)	NS
Disease-related				
Premature birth (%) (vs not premature)	6.7	5.6	1.21 (0.92-1.59)	1.48 (1.03-2.14)
Allergic diagnoses (%) (vs no allergy)	36.3	42.2	0.78 (0.68-0.89)	0.86 (0.72-1.02)
Winter-only utilization (%) (vs year-round)	14.2	5.3	3.00 (2.30-3.84)	1.83 (1.34-2.49)
Prior annual bronchitis hospitalization (mean, SD)	0.032, 0.122	0.016, 0.076	6.46 (2.77-15.1)	NS
Years since first contact For bronchitis***(mean, SD)	5.87, 4.36	5.21, 4.17	1.04 (1.02-1.05)	1.03 (1.01-1.06)
Treatment-related				
Bronchodilator drug (%) (vs no bronchdilator)	18.3	74.6	0.08 (0.07-0.09)	0.12 (0.10-0.14)
Maintenance drug**** (%) (vs no prophylaxis drug)	3.6	45.2	0.05 (0.04-0.06)	0.09 (0.07-0.11)
Oral corticosteroid (%) (vs no oral corticosteroid)	4.9	17.1	0.25 (0.20-0.31)	0.51 (0.38-0.70)

*adjusted for other factors in table, **lowest income quintile, ***single-parent, income assistance household
**** inhaled corticosteroid, sodium cromoglycate, ketotifen and salmeterol

Chapter 3. Asthma Severity in Children

Asthma pharmacoepidemiologic research is commonly plagued by confounding due to asthma severity because asthma severity is related both to the utilization of asthma drugs and to asthma outcomes of hospitalization or mortality. Confounding by asthma severity is pertinent to the dissertation research evaluating the association between inhaled corticosteroid use, which is frequently prescribed in more severe asthma, and hospitalization for asthma, which is more common in severe asthma. Valid measures of asthma severity are required to diminish this bias. In this chapter various approaches to the measurement of asthma severity are assessed. A proposal is made for a drug treatment-based asthma severity measure which can be applied to health care administrative data, followed by a presentation of dissertation findings on the reliability and validity of the proposed instrument.

3.1 Conceptual basis of asthma severity instruments

Asthma can manifest as a disease of mild and intermittent symptoms to one of life-threatening disease. [1] For lack of a better classification scheme, an international pediatric asthma consensus group has categorized the continuum of asthma symptoms as mild, moderate or severe asthma. This section synthesizes the literature on measures of asthma severity, with the objective of proposing a measure which overcomes limitations in existing measures and can be applied to health care administrative data. The theoretical

and operational adequacy of three constructs of asthma severity is described: 1) functional status measures, 2) physiologic indices, and 3) acute health care utilization.

3.1.1 Functional status measures

Functional status measures of asthma severity in children include assessments of asthma symptoms such as symptom frequency, intensity or duration, and impact of the disease on the daily activities of children, such as play, sleep and school attendance. Common symptom-based instruments are derived from the ordinal ranking of the frequency of wheezing symptoms. [2] Other instruments denote the intensity of asthma attacks such as the frequency of speech-limiting attacks. The similarity in prevalence of severe asthma among different functional status constructs of severity reported in the literature, suggests that they may be measuring the same phenomenon.(Table 3.1) Moreover, functional status indicators of asthma severity, such as the number of school days missed and symptom frequency, have been found to be correlated with each other.[3;4] Salome and Pattemore have also reported a correlation between the frequency of wheezing or any respiratory symptoms, and degree of bronchial hyper-responsiveness in children.[5;6]

3.1.2 Physiologic indices

Physiologic assessments conducted to diagnose asthma such as lung function tests, have also been employed to evaluate asthma severity. The FEV_1 lung function test is linearly related to airway diameter, and the severity of airway obstruction is measured by the percent of predicted FEV_1.[7] The % predicted FEV_1 value has been used to grade asthma severity from mild (% predicted FEV_1 of 70-100) to severe (score of 35-49). Bronchial

Table 3.1. Prevalence of Severe Asthma in Children by Type of Outcome Measure

Study Population	Mild Asthma Definition	Mild Asthma Prevalence	Moderate Asthma Definition	Moderate Asthma Prevalence	Severe Asthma Definition	Severe Asthma Prevalence
Physiologic measures:						
422 Australian children 8-11 yo with bronchial reactivity (Salome 1987)	PC_{20}:0.8-7.8 umol histamine	78.9%	PC_{20}: 0.1-0.8 umol histamine	17.3%	PC_{20}:<0.1umol histamine	3.8%
142 children with asthma diagnosis		69.7%		33.1%		10.6%
Functional measures:						
740 American children ≤ 18 yo with asthma in last 12 months (Taylor 1992)	no limitation in major activity	57.6%	no limitation in major activity	32.4%	limitation in major activity	10%
250 German children 9-11 yo with asthma diagnosis (Mielck 1996)	1-4 asthma attacks per year	55.6%	5-10 asthma attacks per year	22.0%	>10 asthma attacks per year	22.4%
1143 Italian children 6-7 yo with wheezing (SIDRIA 1997)	1-3 wheezing attacks per year	75.4%	4-12 wheezing attacks per year	18.0%	>12 wheezing per year	6.6%
					speech-limiting wheeze	18.0%
					awakening > 1 night/week	9.8%
788 British children 5-17 yo with wheezing (Strachan 1994)	1-3 wheezing attacks per year	55.6%	4-12 wheezing attacks per year	29.2%	>12 wheezing attacks per year	15.2%
					speech-limiting wheeze	16.0%
					awakening ≥ 1 night/week	29.8%
Health Utilization Measures:						
740 American children ≤ 18 yo with asthma in last 12 months (Taylor 1992)					hospitalized in past year	7.4%
9027 Manitoban children ≤ 14 yo with a physician diagnosis of asthma					hospitalized in past year	4.8%
768 Italian children 6-7 yo with asthma (SIDRIA 1997)					hospitalized in past year	3.0-6.0%
1034 New Zealander children ≤ 14 yo admitted to hospital for asthma (Mitchell 1994)					3-month hospital readmission	23%

hyper-reactivity has also been used as an index of severity. The dose of histamine required to cause a 20% fall in FEV1 (PC_{20}) and the proportion of children with bronchial hyper-responsiveness have been found to be linearly related to the number of wheezing episodes.[5] Values for PC_{20} have also been used to develop asthma severity scales.[7] Salome et al reported a strong linear relationship between increasing asthma severity, classified according to the degree of bronchial hyper-responsiveness, and the proportion of schoolchildren experiencing wheezing symptoms or receiving asthma medications.[6] Similarly, Amaro-Galvez and colleagues reported a inverse relationship between the dose of provocative methacholine and grade of asthma severity, developed from symptom and drug-based measures in their cohort of children attending an asthma clinic.[8]

Other investigators have documented a correlation between pulmonary function parameters such as % FEV_1 predicted and peak flow variability, and functional status/health care use measures of asthma severity in adolescents, but none with bronchial hyper-responsiveness.[9] Moreover, as bronchial hyper-responsiveness can exist independently of wheezing symptoms, Toelle at al proposed a definition of "current" asthma which is based on the presence of bronchial hyper-reactivity and wheezing.[10] In their study, children with "current" asthma, aged 7-10 years, were more likely than those with either wheezing or bronchial hyper-reactivity to experience limitations in activity; ten years later, children with "current" asthma were more likely to have activity limitations and sleep disturbance, then children with a diagnosis of asthma.[11] The authors concluded that the presence of bronchial hyper-responsiveness and wheezing denotes children with more severe asthma, and with a poorer prognosis.

3.1.3 Acute health service utilization

Hospitalization for asthma has predicted recurrent hospitalization and emergency department use in children and adults,[12;13] and has been found to be correlated with functional status measures of severity. Data from the 1988 US National Health Interview Survey documented that children with severe asthma, as defined by activity limitation, bed days and school days missed, were hospitalized more often than children with mild asthma (27% vs 3%), and spent more days in hospital (mean=56.1 days vs 15 days) in the past year.[14] Lieu et al observed that children who were hospitalized for asthma were significantly more likely to have frequent symptoms, to have activity limitations and to miss a greater number of school-days, than children with asthma who were not hospitalized.[15] In a random survey of 100 children admitted to a Los Angeles hospital for status asthmaticus in 1988, 34% had compromised physical activities, 49% missed at least 10 days of school and 60% had sleep interference because of asthma.[16] An increased number of days with wheezing has also predicted increased usage of the emergency department by children.[17] However, poor lung function values have not predicted recurrent emergency service use among adults with asthma.[13]

3.2 Validity and reliability of asthma severity instruments

Much of the discussion on the operational adequacy of the physiologic and functional domains of a case definition for asthma is also relevant to this section. However, there are additional issues with respect to the validity and reliability of asthma severity instruments. The occurrence of asthma symptoms may be adequately recorded in medical

records, but there appears to be a lack of data on the magnitude of asthma symptoms which is required to determine asthma severity. A medical chart audit of 166 American pediatricians and family physician in the 1970's documented the absence or presence of interval symptoms in 70% of the charts, but the frequency of asthma attacks was noted in less than 50% of charts.[18] Another review of 271 inpatient and outpatient medical records conducted by trained nurse abstractors showed that asthma severity could not be classified based on the information recorded regarding symptom frequency and activity limitation in more than 40% of the records.[19] In a re-analysis of the beta-agonist and fatal asthma study, the poor performance of a severity score based on the presence of disability (school/work missed) and clinical symptoms, recorded for previous hospitalizations, was attributed to the paucity of data in the hospital medical record.[20]

Parental reports are a good source of data on the frequency of wheezing and impact of asthma on the child's activities, but may be strongly biased with respect to the extent of the burden of asthma and its treatment on the family.[21] In Lieu et al's study, parents of children who were hospitalized were more likely than parents of children with asthma who were not hospitalized to state that their child had severe asthma, than to report frequent symptoms or major limitations in activity. [15] There are also issues related to the validity of the school days missed measure, which due to the lack of specificity of school records, may represent all school days missed.[4]

Parental reports and physician records are reliable sources of hospitalization data;[19;22] because hospitals are required to submit data subject to legislation or conditions of

reimbursement, health administrative records are the most complete. [23] However, despite correlation with symptom-based measures of asthma severity, hospitalization for asthma is not a highly valid measure of disease severity. Population-based proportions of children hospitalized for asthma are lower than the prevalence of severe asthma derived from functional status measures.(Table 3.1) Geographic area variations in asthma hospitalization have not been explained by variations in symptom-based asthma severity measures.[24]The acuity of hospital admission for asthma is rarely described in research [25;26] and there is some suggestion that hospital admission, similar to hospital length of stay, is dependent on hospital policies or physician practice styles.[27] Inappropriate hospital admission for asthma/bronchitis, defined on the basis of severity at presentation and intensity of hospital services, has been found to be as high as 15% of admissions in some US hospitals.[28] In a comparison of asthma hospitalization rates among three US communities, the community with the highest hospitalization rate also had the highest proportion of children who were not severely asthmatic during the first 24 hours of the hospital stay.[29;30] These observations may explain the lack of success of asthma hospitalization measures in controlling for asthma severity in epidemiologic research, such as Spitzer at al's trial of beta-agonist exposure and fatal/near fatal asthma.[31;32]

3.3 Summary of physiologic, functional and acute health care utilization measures

The theoretical orientation of symptom-based severity measures is strong, but symptom data are more reliable if obtained from parental reports than medical records.(Table 3.2) However, the main limitation of symptom-based severity measures is their inability to

Table 3.2. Evaluation of Various Domains of an Asthma Severity Instrument

Domain	Theoretical Adequacy	Operational Adequacy		
		Data Source	Reliability	Validity
1) bronchial reactivity	++ (+++), correlated with symptoms, influenced by age and drug therapy	study record	+++	++
		physician medical record	+	+
		health administrative record	NA	NA
2) asthma symptoms	++, influenced by asthma drug therapy	parental report	+++	+++
		physician medical record	+	+
		health administrative record	NA	NA
3) hospital utilization	++, influenced by hospital policy	parental report	+++	+++
		physician medical record	++	++
		health administrative record	+++	+++
4) asthma drug therapy	++ (+++), dependent on compliance	parental report	+++	++ (+++)*
		physician medical record	++	++ (+++)*
		health administrative record	+++	++ (+++)*

+=fair, ++=good, +++=very good, * reported use is not equivalent to actual use of drug, NA=not available

distinguish between asthma severity and asthma control.[33;34] A child with mild asthma may experience the same amount of wheezing as a child with more severe, but well-controlled asthma. In Powell et al's evaluation of 336 schoolchildren with asthma, no significant differences were found between the frequency of symptoms among children receiving inhaled corticosteroids, sodium cromoglycate or no regular treatment.[35] The bronchial reactivity test has also been shown to be sensitive to changes in asthma control when corticosteroids are prescribed. [36-38] In addition, as bronchial reactivity testing is not commonly performed in clinical settings, medical records are not good sources for this data. The hospitalization measure of asthma severity has been commonly used to define asthma severity, especially when health care administrative databases are data sources, but has been met with limited success in research practice.

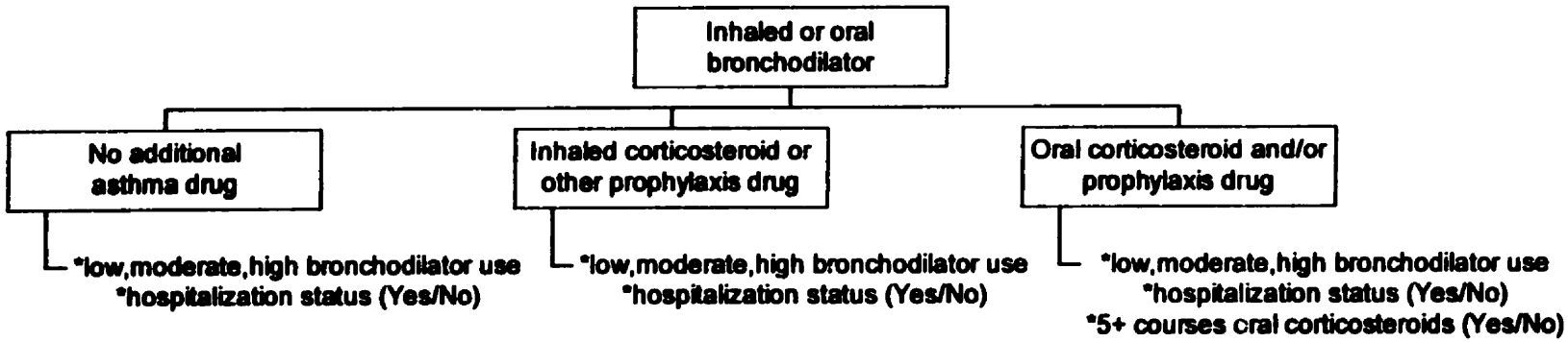
3.4 Drug regimen-based asthma severity instrument

Alternative measures of asthma severity are those based on drug treatment regimens. Drugs are prescribed in asthma following a step-wise approach, which represents the successive addition of asthma drugs to the drug therapy regimen, as asthma severity increases.[39;40] This approach begins with the use of "as needed" inhaled bronchodilator therapy for symptom relief in mild asthma. Mild asthma is defined as sporadic episodes of coughing or wheezing, usually less than 1-2 times weekly. Children with frequent, but episodic asthma, usually greater than 1-2 exacerbations per week are considered to have moderate asthma. Moderate asthma requires the initiation of daily treatment with an inhaled corticosteroid, sodium cromoglycate or ketotifen to prevent the

occurrence of symptoms. Children with severe, chronic asthma warrant more aggressive therapy. Higher doses of inhaled corticosteroid and/or concomittant therapy with long-acting bronchodilators are recommended at this stage. Short courses of oral corticosteroids are also recommended for the treatment of acute episodes.

Traditionally, markers of severe asthma such as greater intensity usage of bronchodilators or oral corticosteroids, have been utilized as measures of asthma severity in research. [31;41-43] Drug treatment-based scales are based on the step-wise approach to asthma pharmacotherapy, and assign higher severity scores with successive additions of asthma drugs to the drug regimen and/or with greater intensity use of drugs. [8;44-48] Amaro-Galvez and collegues categorized asthma severity according to use of bronchodilators, assigning non-users as mild asthmatics and daily users as severe asthmatics. [8] In other instruments, higher severity scores have been assigned with each successive addition of asthma drugs to an initial drug regimen of intermittent bronchodilators; children receiving oral corticosteroids are categorized as having severe asthma.[46;47] The scale developed by Richards et al also assigned a higher severity score to persons receiving multiple asthma drugs.[48] The asthma severity scales created by Walsh et al and Konig et al closely followed the stepwise approach to therapy and were applied to prescription data.[44;45] A prototype drug treatment-based asthma severity scale is presented in Figure 3.1.

Figure 3.1. Taxonomy for Asthma Severity Measure



Asthma severity markers such as high use of bronchodilators and oral corticosteroids, have been found more frequently among persons with more severe asthma, as defined by drug regimen asthma severity scales. [44] Drug treatment-based severity scales have also shown to be correlated with asthma symptom and bronchial reactivity measures of asthma severity.[8;47] Increasingly severe asthma according to Wahlgren et al's drug-based scale was significantly more likely in asthmatics with increased symptom severity, poorer lung function and greater limitations in activity.[46] Drug regimen-based scales have also been found to be correlated with health utilization measures and physician assessments of asthma severity.[48] They are common components of functional and health care use severity scales. [49] These types of scales have also been reported to be related to other functional status measures in children. In a cohort of 175 children attending an asthma clinic, school days missed were significantly higher among children with moderate asthma, on the basis of sodium cromoglycate use, than children with mild asthma, using only bronchodilators.[45]

The strength of drug treatment-based scales is that they can represent severe asthma in cases where more intense treatment has resulted in reduction of symptoms,[33;34] as was illustrated in Powell and Prinkham's evaluation of school-children with asthma.[35] Furthermore, a very useful application of the drug regimen-based asthma severity measure is the monitoring of asthma prognosis in children. Konig and Shaffer classified 175 children as having mild, moderate or severe asthma, following the stepwise approach to drug therapy, and followed them over an eight year period (range:2.2-16.8 years)[45] Ten percent of children with mild asthma were re-classified as having moderate-severe

asthma, while sixty percent of children with moderate-severe asthma remained in the same severity category at follow-up.

Critics of treatment-based scales point out that drug utilization is not a useful measure of asthma severity because it is influenced by physician prescribing patterns.[34;50] However, validity assessments can be performed to assess the influence of prescribing by different medical practitioners on the classification of asthma severity. [51] Another caveat to using drug-based scales is the potential exclusion of children with mild asthma because they are less are less likely than children with severe asthma to receive treatment with asthma medication.[6;11;52]

3.5 Proposed research and hypotheses

Research was undertaken to develop a drug treatment-based asthma severity instrument in children for application to population-based studies which utilize health care administrative data. The scientific merit of the asthma severity instrument in classifying asthma severity in children was assessed by tests of reliability, validity and responsiveness.

Study Hypothesis I:

The drug treatment-based asthma severity instrument is a reliable measure of asthma severity, as shown by high agreement on a test-retest of the classification of children into severity categories.

Study Hypothesis II-VI:

The drug treatment-based asthma severity instrument is a valid measure of asthma severity, such that children with severe asthma are more likely to:

i) have severe asthma at an early age,

ii) visit an asthma specialist,

iii) be high-intensity users of physician services,

iv) receive critical care while hospitalized, and

v) to live in low income neighbourhoods.

Study Hypothesis VII:

The drug treatment-based asthma severity instrument is responsive to changes in asthma severity over time, as documented by a higher prevalence of children with severe asthma who were re-classified with severe asthma two years later.

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NOT FOR CITATION

Development of a Drug Treatment-Based Asthma Severity Measure in Children

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ABSTRACT

Background: Valid measures of asthma severity are critical in asthma pharmaco-epidemiologic research to diminish confounding of associations between drug therapy and outcomes. This study was undertaken to develop and validate a drug treatment-based asthma severity measure in children for application to health care administrative data.

Methods: A drug treatment-based asthma severity measure was developed on the basis of stepwise addition of asthma drugs with increasing asthma severity and indicators of asthma exacerbations. The measure was applied to a cohort of 16,862 children meeting a diagnosis and drug-based case definition for asthma, and having at least one prescription for an asthma drug during January 1995-March 1996. The reliability of the measure was assessed using test-retest reproducibility, predictive and construct validity of the measure were ascertained through comparisons with other markers of severe asthma, and measure responsiveness was determined by assessment of changes to asthma severity over time.

Results: The drug treatment-based asthma severity measure classified 37% of children with mild asthma, 42% with moderate asthma, 19% with moderate-severe asthma and 2% with severe asthma. The weighted kappa score for agreement on asthma severity classification between two successive time periods was 0.82. Children classified with moderate-severe and severe asthma were significantly more likely to have previous asthma hospitalizations, to visit asthma specialists, to have 5 or more physician visits/15 month period and to require critical care upon hospitalization. These children were also twice as likely to be re-classified in the same severity category, two years following the end of the study period.

Conclusion: A drug treatment-based asthma severity measure in children was developed for application to health care administrative data. The measure was found to be highly reliable and valid, and responsive to changes in asthma over time.

INTRODUCTION

Asthma can manifest as a disease of mild and intermittent symptoms to one of life-threatening disease. [1] Children with the more severe form of the disease are more likely to have activity limitations and to be hospitalized.[2] Measurement of asthma severity is critical in asthma pharmacoepidemiologic research to diminish potential confounding of associations between drug therapy and asthma outcomes. Although previous hospitalization for asthma predicts future hospitalization,[3] hospitalization for asthma has not consistently been an effective measure of severity status.[4-7] Functional asthma severity measures such as symptom frequency, and physiologic measures such as pulmonary function tests, are constrained by the paucity of data in the medical record.[8-10] Moreover, these measures are limited in their ability to discriminate between disease severity and disease control.[11-13]

Alternative measures of asthma severity are those based on drug treatment regimens. Centered on the step-wise approach to asthma drug therapy and markers of asthma exacerbations [14-20] drug treatment-based scales assign higher severity scores with successive additions of asthma drugs to the drug therapy regimen and with greater intensity use of drugs.[16,21-25] Drug treatment-based scales have shown to be

correlated with functional status and physiologic measures of asthma severity, and have the advantage of representing severe asthma in cases where more intense treatment has resulted in reduction of symptoms. [16, 22-25] They can also be combined with functional and health care use severity scales. [26,27] Critics of treatment-based scales point out that drug utilization is not a useful measure of asthma severity because it is influenced by physician prescribing patterns; [28,29] However, validity assessments can be performed to assess the influence of practitioner prescribing on the classification of asthma severity.[30] The objective of this research was to develop and validate a drug treatment-based asthma severity measure in children for application to population-based studies which utilize health care administrative data.

RESEARCH METHODS

Development of Asthma Severity Measure

A drug treatment-based asthma severity measure, categorizing children as having mild, moderate, moderate-severe and severe asthma, was developed for application to health care administrative data.[1] The measure was composed of two components, which assessed: 1) the profile of asthma drug categories, and 2) the frequency of asthma attacks, represented by proxy indicators such as asthma hospitalizations, and oral steroid and bronchodilator prescriptions. The latter was included as a component in the event that secondary asthma drugs were not prescribed or obtained for children with more severe asthma. The main features of the measure were as follows:

- utilization of asthma drugs, in addition to a bronchodilator or sodium cromoglycate, increased severity by one level (by two levels if oral corticosteroids),

- hospitalization for asthma, high bronchodilator use [19,21] and 5+ courses of corticosteroids/15 month period [17,21] increased severity by one level

High bronchodilator use corresponded to doses in the highest decile (90^{th}) of the distribution of bronchodilator use (total doses/15 month period) in the child cohort.[21] Hospitalization for asthma was a hospital admission with a primary ICD-9-CM diagnosis code of asthma or bronchitis, or with a primary code for respiratory infection and a secondary diagnosis of asthma.

Data Sources and Record Linkage

The asthma severity measure was applied to health care administrative records of Manitoba children, defined as having asthma. Data for this study were obtained from four computerized databases maintained by the Manitoba Health Services Insurance Plan (MHSIP): 1) registration files, 2) records of physician reimbursement claims, 3) records of hospital separation abstracts, and 4) records of prescriptions dispensed in retail pharmacies. The MSHIP registration file contains a record for every individual registered to receive insured health services and records birthdate, sex and geographic location. Records of physician reimbursement for medical care provided are submitted under a fee-for-service arrangement, and contain information on patient diagnosis at the 3-digit level of the ICD-9-CM classification system and physician specialty. Separation abstracts for hospital services provided include information on 16 ICD-9-CM diagnostic codes, of which the first is the diagnosis which is most responsible for the hospital stay. Prescriptions dispensed which are submitted by retail pharmacies for reimbursement by provincial drug insurance plans or for drug utilization review purposes, contain data on the date of prescription dispensing, drug name, strength, and quantity, and a 9-digit drug

identification number. The reliability and validity of the MSHIP databases has been shown be high.[31-33] Record linkages among databases were achieved through the use of anonymous personal identifiers. Statistics Canada Census 1996 household income data, aggregated to the geographic unit of the enumeration area, were used to rank neighbourhood income quintiles from 20% of the population residing in the lowest income to 20% of the population residing in the highest income neighbourhoods.[34-36] A database characterizing Manitoba physicians was also utilized.

Study Population

A total of 174,208 children, aged 5-15 years as of January 1, 1995, living in households with adults and registered with Manitoba Health until March 31, 1996 were identified from the MSHIP registry. This time period was chosen to capture data prior to a major policy change in the provincial drug insurance program. Approximately 48,000 children met the following case definition for asthma: at least one diagnosis of asthma or bronchitis on a physician claim or hospital abstract record, or in the absence of these diagnoses, one prescription for an inhaled corticosteroid or sodium cromoglycate, or two prescription records for a bronchodilator, or one prescription for a bronchodilator and ketotifen during a 3+ year time period, January 1, 1995 - March 31, 1998. [37] A study cohort of 16,862 children was derived from this sample, representing children who had received a prescription for an asthma drug during the time period, January 1,1995 to March 31,1996. Asthma drug therapy was classified as follows [38]: 1) inhaled bronchodilators [eg. b-adrenergic agonist, ipratropium bromide], 2) oral bronchodilators [eg. b-adrenergic agonists, theophylline], 3) inhaled corticosteroids [eg. beclomethasone

dipropionate, budesonide, fluticasone propionate], 4) antiallergic agents [eg. sodium cromoglycate, ketotifen], and oral corticosteroids [eg.prednisone, prednisolone].

Reliability of Asthma Severity Measure

Psychometric assessments of the reliability of the asthma severity algorithm, such as the Cronbach alpha measure of internal consistency, were not undertaken because the severity algorithm was defined on clinical grounds and it was not expected that individual components of the scale would consistently be correlated in the same direction.[24,38] For example, the correlation between receipt of 5+ courses of oral corticosteroids and hospitalization among individual children could be positive or negative, depending on the degree of asthma control. An alternative measure of reliability, test-retest reproducibility, which assessed the stability of the asthma severity measure over time was employed.[40] The study period was divided into two equal time periods. The asthma severity measure was applied to July 16, 1995 - March 31, 1996 prescription and hospital abstract data, and the resultant frequency distribution of asthma severity categories was compared to those based on January 1,1995 - July 15, 1995 data for the 6,187 children who received prescriptions for asthma drugs in both time periods. The weighted kappa statistic was calculated to describe the percent agreement on the asthma severity categories between the two time periods. [40,41]

Predictive and Construct Validity of the Asthma Severity Measure

The predictive validity of the asthma severity measure was assessed by examining the relationship between the asthma severity scale and future outcomes which are associated with asthma severity such as increased likelihood of critical care during hospitalization, of high intensity physician use and of consultation with asthma or pediatric specialists,

over the time period January 1995-March 1996. [2,23,30,39] The ability of the measure to predict previous outcomes such as asthma severity at a younger age, was also assessed.[42,43] Requirement for critical care was defined as the transfer to a critical care unit, or ICD-9-CM procedure or diagnosis codes for ventillatory support during hospitalization for asthma. Consultation with an asthma or pediatric specialist was defined as contact with hospital or ambulatory care physician classified as an allergist, respirologist or other pediatric specialist. High intensity physician use represented the highest decile (90^{th}) of the distribution of physician visits per child in the cohort, which was equivalent to 5 or more physician visits over the 15 month period. Asthma severity at a younger age was measured as the annual number of hospital admissions for asthma from birth to beginning of study period. For the predictive validity analyses, the moderate-severe and severe categories were combined to form the severe asthma category. We hypothesized that children with severe asthma were more likely to have severe asthma at an early age, to visit an asthma specialist, to be high-intensity users of physician services, and to receive critical care while hospitalized.

Predictive validity was assessed by determining the likelihood of the predicted outcome, as represented by the odds ratio (OR) for the outcome among children with severe asthma versus those without severe asthma. Another test of predictive validity involved the linear regression of the number of events for the outcome on the category of severe asthma. The outcome variable was log transformed if distribution characteristics did not follow a normal distribution. To control for the potential influence of physician prescribing on the

asthma classification system, these analyses were also conducted in children stratified by asthma specialist status (ever seen asthma specialist versus not).

In addition, the construct validity of the asthma severity scale was determined by assessing the relationship between asthma severity and residence in a low income neighbourhood. Consistent with the literature, we hypothesized that children with more severe asthma were more likely to live in low income neighbourhoods.[44] To test this hypothesis, children were placed into neighbourhood income quintiles according to the postal code location of their home. The likelihood (odds ratio) of severe asthma in lower versus higher income neighbourhoods was determined, and a Mantel-Haenszel chi-square trend test was conducted to assess the distribution of asthma severity across income quintile neighbourhoods. All statistical tests were conducted at the 95% level of confidence.

Responsiveness of Asthma Severity Measure

The responsiveness of the asthma severity measure or its ability to detect change in severity over time was assessed. [23,40] The magnitude of decreased asthma severity in children with mild to moderate asthma versus children with moderate-severe asthma between the time period January 1995-March 1996, and April 1996-March 1998 was described by the odds ratio, and 95% confidence interval. Decreased asthma severity was defined as: 1) discontinuation of asthma drugs and 2) decreased level of severity from moderate-severe asthma to mild-moderate asthma. To enable comparisons across time, the severity algorithm was applied to prescription and hospitalization data for the time

period April 1, 1996 to March 31, 1998, and adjustments were made for the longer evaluation period (ie. severe asthma if 8 courses of oral corticosteroids over 24 months).

RESULTS

The study cohort was composed of 16,862 children who met the case definition for asthma and had a prescription for an asthma drug during January 1,1995 to March 31,1996. Excluded were 15,377 children with health care contacts for asthma-like diagnoses, but no asthma drug prescriptions during the study period, of which 75 (0.5%) had been hospitalized during the study period, and 12,341 (80%) had received an asthma drug prescription during April 1996-March 1998, but not January 1995-March 1996. Sixty percent of the 16,862 cohort children were aged 5-10 years, 76% were children from urban areas, and 33% lived in the 2 lowest neighbourhood income quintiles. Half of the children had a physician diagnosis of asthma, 25 % had concurrent diagnoses of bronchitis, 15% of children only had diagnoses of bronchitis, and 11% had prescriptions for asthma drugs, but no health care visits during the study period. Eighty-three percent of cohort children had received bronchodilators, 45% had received inhaled corticosteroids, 9% had received prophylaxis drugs other than inhaled corticosteroids, and 18% had received oral corticosteroids. Over fifty percent of children were treated with asthma drugs in addition to inhaled bronchodilators or sodium cromoglycate, 7% of children were high users of bronchodilators, 2.2% of children were hospitalized for asthma, and <1% of children had received 5 or more courses of oral steroids.

Following the application of the asthma severity measure to prescription and hospitalization data, 37% of children had mild asthma, 42% had moderate asthma, 19% had moderate-severe asthma, and 2% had severe asthma. The distribution of asthma severity in children with selected medication profiles is shown in Table 3.7.1 to illustrate how the severity measure was applied. The majority of children treated only with bronchodilators were categorized as mild asthmatics, those treated with inhaled corticosteroids were mostly classified as moderate asthmatics, and children treated with oral corticosteroids were mainly defined as moderate-severe asthmatics.

Thirty-six percent of cohort children had no prescriptions for asthma drugs during January 1,1995-July 15,1996 and 28% had no asthma prescriptions during the second time period, leaving 6,187 children or 37% of the original cohort in the test-retest assessment of the reliability for the asthma severity algorithm. Application of the asthma severity measure to the July 16,1995-March 31,1996 time period showed that a substantial proportion of children were re-classified into the same asthma severity category, as in the first time period (Table 3.7.2). The weighted kappa score for agreement on asthma severity categories between the first and second time periods was 0.82, which is considered excellent agreement. [45]

Severe asthma (excluding moderate-severe asthma) was significantly more likely to be present in asthmatic children living in the two lowest income quintile neighbourhoods (OR=1.31, 95%CI:1.05-1.63), and a negative income gradient was present with increased severity of asthma (Mantel-Haenszel chi-square, p=0.001).The likelihood of

severe asthma at an earlier age, hospital admission for severe asthma, and high physician utilization and asthma specialist use was significantly greater among children with severe asthma (Table 3.7.3). Similarly, results from regression analysis documented that the number of events for each severe asthma outcome were significantly higher in children with severe asthma (Table 3.7.4). Similar relationships between critical care and high intensity physician use, and asthma severity were observed among children who had seen an asthma specialist and among children who had not.

Seven percent of cohort children received no prescriptions and 34% of children had no prescription records for asthma drugs from April 1, 1996 to March 31, 1998. Children classified with moderate to severe asthma in 95/96 were twice as likely (95% CI:1.8-2.2) as children with mild to moderate asthma to continue to receive prescriptions for asthma drugs in 96/98. Among 10,918 children who continued to receive asthma drug prescriptions, children with moderate to severe asthma were 5.3 times more likely (95% CI:4.9-5.8) than children with mild to moderate asthma to be classified as having moderate to severe asthma in 1996-1998.

DISCUSSION

The reliability of the asthma severity measure, assessed by the test-retest measure, was found to be excellent. This reliability rating is much higher than that reported by Richards et al who used the Cronbach alpha coefficient to evaluate the internal consistency of their asthma severity scale.[24] Their findings support our a priori belief that individual

components of an asthma severity scale would not be well correlated, and our decision not to use the test of internal consistency. The asthma severity algorithm was also responsive to changes in asthma severity over a three year period. Natural history studies of asthma show that 30-80% of school-age children will have decreased asthma-like symptoms by the time they reach adulthood.[46] As the cohort aged two years, 40% of the children ceased to receive prescriptions for asthma drugs. Children with moderate to severe asthma in 95/96 were more likely than children with mild-moderate asthma to continue to be treated with asthma drugs, and to experience severe asthma. Our observations are consistent with the literature which reports that prognosis and severity of childhood asthma is related to severity at an earlier age.[42,43] Similar findings have been documented with other drug treatment-based measures.[23]

The asthma severity measure has face validity because it was founded on clinical practice guidelines for asthma drug therapy. The distribution of children by asthma severity was similar to that obtained from other asthma severity scales [16,23] and the proportion of children categorized with severe asthma was similar to that reported by population-based studies.[2,47,48] We have also shown that the asthma severity measure has construct and predictive validity. The association between asthma severity and socioeconomic status was reproduced using the asthma severity scale.[44] The predictive validity of the measure was evident in its ability to predict asthma severity outcomes of increased need for hospital critical care, of increased ambulatory physician care and of increased consultation with asthma or pediatric specialists. Other empiric evidence shows that drug regimen-based asthma severity measures are related to severity measures such school-

days missed and unscheduled physician visits, [23] and indirect markers of severity, such as high intensity use of bronchodilator and oral corticosteroid drugs.[21] The likelihood of seeing an asthma specialist and the number of specialist visits was significantly higher children with severe asthma, suggesting that higher severity classification by the asthma severity measure was representing physician prescribing, as has been described by others.[30] However, the asthma severity scale continued to have predictive validity for the other outcomes independent of physician specialty.

A limitation of the asthma severity measure is that it may be vulnerable to bias associated with the employment of health care utilization data. The literature reports that as much as 30% of children with asthma symptoms have not seen a physician. [49] However, almost all children with a diagnosis of asthma will receive drug therapy at some point, and a high proportion of children experiencing current asthma symptoms are treated with drug therapy. [48,50] Our drug regimen-based asthma severity measure had the potential to classify an additional 12,341 children who eventually received a prescription for an asthma drug, but we selected the 15 month time period prior to a major change to pharmaceutical policy, believing that it would impact on drug utilization. In addition, the caveat to using longer evaluation periods are changes to asthma severity over time, as we have shown. Finally, the asthma severity measure would not classify children with mild asthma, who never see a physician, and children with severe asthma who receive asthma drug therapy only while hospitalized. In our study, the latter accounted for 75 children during the study period.

In conclusion, we have developed a severity measure for childhood asthma which can be applied to health care administrative data. Our asthma severity measure was found to be highly reliable and valid, and responsive to changes in asthma severity over time. As such, it should prove to be a useful measure of asthma severity in epidemiologic research.

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Table 3.7.1. Frequency Distribution (%) of Asthma Severity Categories by Asthma Drug Profiles

Asthma Category	Mild	Moderate	Mod-Severe	Severe
All children (n=16,862)	36.6	42.2	19.2	2.0
Bronchodilators only (n=6674)	94.8	5.1	0.01	
Low use	8.4	0.1		
Moderate use	86.4	0.3		
High use		4.7	0.01	
Inhaled corticosteroids + other asthma drugs (6053)		90.5	9.3	0.2
Low bronchodilator use*		33.4	0.1	
Mod bronchodilator use		57.1	0.8	
High bronchodilator use			8.4	0.2
Oral corticosteroids + other Asthma drugs (n=2974)			89.0	10.6
Low bronchodilator use*			30.6	1.5
Moderate bronchodilator use			49.1	6.3
High bronchodilator use			9.3	2.8

* includes children with no bronchodilators

Table 3.7.2. Frequency Distribution (%) of Asthma Severity Categories in 1/95-7/95 and 7/95-3/96

		7/95 – 3/96			
Asthma Category		Mild	Moderate	Mod-Severe	Severe
1/95 – 7/95					
Mild	24.3	22.5	1.8	0.02	0.0
Moderate	46.4	0.8	44.1	1.5	0.02
Mod-severe	24.0	0.0	1.9	20.9	1.2
Severe	5.3	0.0	0.0	0.8	4.5
All children (n=6187)		23.3	47.8	23.2	5.7

Table 3.7.3. Likelihood of Critical Care, High Physician Utilization, Specialist Use by Severity Status

Predicted factor	% children	Odds Ratio (95% CI)
Previous hospital admission for asthma (> 1/year)		
Severe asthma (n=3570)	25.8	3.3 (3.0-3.6)
Not severe asthma (n=13292)	9.5	
Hospital admission for severe asthma (transferred to ICU and/or required ventillatory support)*		
Severe asthma (n=3071)	0.6	--
Not severe asthma (n=9871)	0.0	
High Physician Utilization (5+ visits/15 months) **		
Severe asthma (n=3570)	32.2	5.1 (4.6-5.5)
Not severe asthma (n=13292)	8.6	
Ever seen by specialist (asthma or other pediatric) *		
Severe asthma (n=3071)	23.1	1.9 (1.7-2.1)
Not severe asthma (n=9871)	13.7	
Controlling for specialist use=yes		
Transferred to ICU and/or required ventillatory support		
Severe asthma (n=709)	1.7	--
Not severe asthma (n=1356)	0.0	
High Physician Utilization (5+ visits/15 months)		
Severe asthma (n=709)	67.7	3.7 (3.1-4.5)
Not severe asthma (n=1356)	36.1	
Controlling for specialist use=no		
Transferred to ICU and/or required ventillatory support		
Severe asthma (n=2362)	0.3	--
Not severe asthma (n=8515)	0.0	
High Physician Utilization (5+ visits/15 months)		
Severe asthma (n=2362)	28.4	4.7 (4.3-5.3)
Not severe asthma (n=8515)	7.7	

* no physician utilization in 3920 children, ** includes children with no physician utilization

Table 3.7.4. Number of Critical Care Admissions, Physician and Specialist Visits by Severity Status *

Predictive factor	Number of Events Per 100 children	p value
Previous hospital admissions for asthma per year		
Severe asthma	0.41	0.0001
Not severe asthma	0.16	
Hospital admissions for severe asthma (transfer to ICU and/or required ventillatory support)		
Severe asthma	0.104	0.0001
Not severe asthma	0.100	
Physician Visits		
Severe asthma	104	0.0001
Not severe asthma	27	
Specialist visits (asthma or other pediatric)		
Severe asthma	48	0.0001
Not severe asthma	22	
Controlling for specialist use=yes		
Hospital admission for severe asthma (transfers to ICU and/or required ventillatory support)		
Severe asthma	0.105	0.0001
Not severe asthma	0.102	
Physician Visits		
Severe asthma	123	0.0001
Not severe asthma	40	
Controlling for specialist use=no		
Hospital admission for severe asthma (transfers to ICU and/or required ventillatory support)		
Severe asthma	0.102	0.0001
Not severe asthma	0.099	
Physician Visits		
Severe asthma	72	0.0001
Not severe asthma	23	

*derived from regression of predictive factor on asthma severity status (1=severe, 0=not severe)
ICU = intensive care unit

Chapter 4. Socioeconomic Status and Inhaled Corticosteroid Utilization in Children with Asthma

In the previous two chapters, the reader became acquainted with the methods for defining childhood asthma and measuring asthma severity. The discussion now turns to the research area of interest, related to the utilization of inhaled corticosteroid drugs in children. This chapter presents background data on the efficacy and effectiveness of inhaled corticosteroid drugs in children, and observations on how these drugs are used in practice. The chapter is concluded with the findings of the dissertation research on socioeconomic status and utilization of inhaled corticoteroid drugs.

4.1 Asthma pharmacotherapy

Drug therapy is the cornerstone of asthma management; nonpharmacologic measures are adjunct measures. [1] Beta$_2$-agonist drugs stimulate B_2 receptors to relax airway smooth muscle and are administered for symptomatic relief of airway obstruction. [2;3] In addition to having excellent bronchodilator properties, this class of drugs provides a bronchoprotective effect, by preventing the bronchoconstriction which occurs immediately after allergen challenge. The beta-agonist, salbutamol, is most often administered as an inhaled drug on as needed basis to treat acute episodes, but can be administered on a daily basis in its oral form to provide prolonged bronchodilatation. Oral preparations are also of use in some children who cannot master proper inhalation technique. The newer long-acting, inhaled beta-agonist salmeterol has an extended

duration of action and is indicated for maintenance treatment of asthma, but not for acute symptomatic relief or as monotherapy. [4] Long acting formulations of theophylline, a bronchodilator, were the mainstay of chronic asthma therapy in the early 1980's, but have fallen into disfavour.

Considerable evidence has accumulated to show that airway inflammation is a major factor in the pathogenesis of asthma.[5] Subsequently, airway inflammation has become the target of drug therapy. Corticosteroids alter the underlying inflammatory processes by inhibiting the recruitment of inflammatory cells such as eosinophils, into the bronchi, and preventing or decreasing airway mucosal edema and mucous secretion. [2;3] Inhaled corticosteroid administration has resulted in the reduction of bronchial inflammatory cells, and repair of bronchial epithelium.[6] The latter suggests that inhaled corticosteroids can reverse structural changes in the lung which occur following chronic airway inflammation and leave the airway hyperresponsive. [7] Other anti-inflammatory drugs such as sodium cromoglycate, nedocromil sodium or ketotifen, also inhibit the activation of inflammatory cells, but corticosteroids are the most potent anti-inflammatory agents. Leukotriene pathway modifiers are the newest class of asthma drugs, which decrease the influx of inflammatory cells into airways.[8]

4.1.1 Efficacy and effectiveness of inhaled corticosteroid drugs

The prescription of inhaled corticosteroid medications represents a secondary prevention intervention for which there is an abundance of evidence regarding efficacy in improving

asthma symptoms. [9-12] A systematic review of 15 randomized controlled trials of inhaled coricosteroids in comparison to placebo in childhood asthma showed that inhaled corticosteroids significantly decreased asthma symptoms, decreased concomittant beta-agonist or oral corticosteroid use, and improved lung function tests. [12] A recently conducted randomized controlled trial compared an inhaled corticosteroid with a long-acting inhaled beta-agonist drug, as well as placebo, in children with stable asthma. [9] The inhaled corticosteroid was associated with significantly less airway hyper-responsiveness and need for salbutamol as rescue therapy than the long-acting beta-agonist. The effect of the inhaled corticosteroid is limited to the treatment period, and most studies report that the effect of inhaled corticosteroids on bronchial reactivity and symptoms are lost 2-4 weeks after discontinuation of treatment.[9;13;14]

The effectiveness of corticosteroids in reducing hospital admissions for asthma have been demonstrated in several ecological and observational studies. [15-18] Communities with lower hospitalization rates for asthma have been observed to have higher inhaled anti-inflammatory drug or corticosteroid use.[16;19-21] The odds of fatal and near fatal asthma in persons using inhaled corticosteroids on a regular basis was significantly reduced in comparison to non-users, in Ernst et al's cohort of 12,301 persons, aged 5-54 years, receiving asthma drug prescriptions. [18] In a cohort of 2,059 hospitalized asthmatic patients, aged 5-54 years, subjects treated regularly with inhaled corticosteroids for 16 days to 6 months were 40% less likely to be readmitted to hospital for asthma. [22] Similarly, a case-control study of newly treated asthma documented that subjects initiated on regular inhaled corticosteroids therapy were 40% less likely to be hospitalized, than

those treated with theophyliine therapy.[23] Inhaled corticosteroids in Donahue et al's evaluation of 6,562 children decreased the risk of asthma hospitalization to one-third.[15]

Continuous administration of inhaled corticosteroid therapy is a common goal of treatment, but intermittent treatment for the deterioration of asthma due to upper respiratory tract infections has also been evaluated in several randomized, double-blind, controlled trials using a crossover design. Svedmyr J et al administered high dose inhaled corticosteroids over a 9-day period to children with asthma, aged 3-10 years, at the first sign of an upper respiratory tract infection.[24] In comparison to placebo, the number of hospitalizations and emergency room visits was reduced, and peak expiratory flows were increased in the treatment group, although there were no differences in the frequency of symptoms. These findings have been replicated in younger children.[25]

4.1.2 Optimal chronic management of asthma

Current recommendations for asthma management include a stepwise approach to asthma pharmacotherapy which represents the successive additions of asthma drugs.[1;26] This approach begins with the use of "as needed" inhaled bronchodilator therapy for symptom relief in mild asthma. Mild asthma is defined as sporadic episodes of coughing or wheezing, usually less than 1-2 times weekly. In children with mild asthma, prophylactic agents such as sodium cromoglycate or ketotifen, are administered in advance of a known precipitating event such as exercise or exposure to cold asthma air, animals or pollen. Children with frequent, but episodic asthma, usually greater than 1-2 exacerbations per

week are considered to have moderate asthma. Moderate asthma requires the initiation of daily treatment with an inhaled corticosteroid, sodium cromoglycate or oral ketotifen to prevent the occurrence of symptoms. Subsequent to concerns regarding the inhibitory effect of inhaled corticosteroids on the growth of children, [27] a trial of sodium cromoglycate or ketotifen prior to inhaled corticosteroids is recommended.

Children with severe, chronic asthma warrant more aggressive therapy. Higher doses of inhaled corticosteroid and/or concomittant therapy with long-acting inhaled or oral bronchodilators are recommended at this stage. [1;26] The increase in dose of inhaled corticosteroid can be limited to the occurrence of an acute exacerbation of asthma or a time period of anticipated worsening of symptoms. A short course of oral corticosteroids is also recommended for the treatment of acute episodes. As in mild asthma, treatment with bronchodilators is recommended on a need to use basis among children with more severe asthma. Once control of asthma symptoms is reached and sustained, a step-down reduction in therapy is considered, so that children receive the minimum therapy required to achieve control.

In addition to pharmacotherapy, environmental control is an important component of asthma management. [1;26] In the presence of demonstrated hypersensitivity to allergens such as house dust mites or pollen, avoidance measures are recommended. These can include the removal of pets, and the introduction of bedroom dust-proofing and household dehumidification. Parents are also strongly advised to stop smoking cigarettes,

or at the very least to minimize the child's exposure to tobacco smoke. The value of hyposensitization to decrease allergen sensitivity is controversial.[1;26]

4.2 Utilization of inhaled corticosteroid drugs in children

Large population-based studies conducted in the UK report that 40-45% of children, aged 4-17 years, receiving asthma drug prescriptions, were prescribed inhaled corticosteroids in the early 1990s.[28;29] A similar proportion of use has been reported in several other smaller cohorts of children with asthma in the UK and New Zealand. [30;31] Inhaled corticosteroids are utilized less frequently in children less than 5 years old (13%).[31] Data from a large health maintenance organization in the United States indicated that 24% of children less than 17 years old, receiving asthma medications, were prescribed inhaled corticosteroids over the time period 1991-1994.[15] The utilization of individual inhaled corticosteroid drug entities depends on the time period of market availability. In New Zealand, high potency beclomethasone dipropionate inhaler usage rates were highest in the mid-1990s, followed by budesonide.[32] On average, children aged 6-18 years, used 400 micrograms per day, but this varied with the potency of the inhaled corticosteroid.

The outcome of reserving inhaled corticosteroid drugs for more severe asthma in children is a higher prevalence of bronchodilator utilization (typically,80%) [28;31] and delay in initiation of inhaled corticosteroid therapy, on average 6.5 years from onset of disease. [33] Asthma drug therapy guidelines in the 1990's recommended that maintenance

therapy with inhaled corticosteroids be initiated in the earlier stages of asthma to prevent symptom occurrence.[26;34] Inhaled corticosteroid drug utilization has increased over the last decade. [28;35;36] Children in the 1990's are 6 times more likely to receive a prescription for an inhaled corticosteroid than children in the 1980's. [37] Despite trends in increased utilization, inhaled corticosteroids are reported to be underutilized, from the perspective that utilization of inhaled corticosteroids remains low among persons with more severe asthma, among persons recently hospitalized with asthma and among high users of bronchodilators.[38-42]

4.2.1 Factors affecting utilization

a) Asthma severity

Current asthma drug therapy guidelines recommend that treatment with inhaled corticosteroids be initiated in children with more severe asthma, (see above) although recent literature suggests that children with more mild forms of the disease would also benefit from inhaled corticosteroids.[9] Not surprisingly, evaluations of drug utilization among children with asthma show that those with severe asthma are treated more often with inhaled corticosteroids. In Togias et al's evaluation, 37% of adolescents with severe asthma received inhaled corticosteroids, in contrast to 14% with mild to moderate asthma. [43] Children with severe asthma were more likely to use anti-inflammatory drugs in Lieu et al's study of asthma hospitalization. [44] Limitation in activity was significantly more likely among children prescribed inhaled corticosteroids, than children prescribed bronchodilators in Wahlgren et al's randomized controlled trial of an asthma intervention.[45]

b) Physician prescribing practices

Variations in anti-inflammatory drug use have been found in association with physician utilization patterns of the child. Evaluations of children hospitalized for asthma have documented that children whose medical care provider was an allergist were more likely to be treated with an inhaled corticosteroid or sodium cromoglycate than children seeing a pediatrician, family physician or an emergency room physician.[46] Similarly, thirty percent of children with continued attendance at a hospital-based allergy clinic had received a prescription for an inhaled corticosteroid, in comparison to 8% of those who did not remain active clients.[47] Among 600 health maintenance organization clients with asthma in the 1990's, those in the care of an allergist were significantly more likely than those in the care of a generalist to receive a prescription for an inhaled corticosteroid.[48] These differences remained following the stratification of persons by asthma severity.

Moreover, current treatment with an anti-inflammatory drug is significantly more likely among asthmatic adults and children who had seen a physician in the last year.[49-51] Hospitalization for asthma has been reported to double previous utilization of inhaled corticosteroid drugs.[23] Among 300 schoolchildren with asthma in the UK, those who had attended a hospital as a regular source of care for asthma were slightly more likely to be prescribed an inhaled corticosteroid, than those seeing a general pediatrician. [30] However, children without a regular source of care were significantly less likely to receive prophylaxis with an inhaled corticosteroid. Similarly, inhaled corticosteroid treatment were more common among US inner-city children with asthma, if a physician

was identified as a primary source of care than if they received most of their care from the emergency department. [52;53]

c) Adherence to drug therapy

Unfortunately, non-adherence with asthma drug therapy is common. It is estimated that fifty percent of children with asthma do not adhere to their treatment regimen.[54] Non-adherence with an inhaled corticosteroid is characterized as the omission of a time of administration of a dose, which has been reported to occur as often as 50% of the time. [55;56] Adherence with an inhaled corticosteroid decreases if frequent daily administration is required, and if additional maintenance drugs are added to the drug therapy regimen.[56;57] The end results of non-adherence are greater morbidity and mortality. Non-continuous use of inhaled corticosteroids has not decreased the risk of asthma hospitalization [23] and children who are non-adherent with inhaled corticosteroid therapy are much more likely to require courses of oral corticosteroids for the treatment of asthma exacerbations.[58]

Many of the factors which are associated with an increased likelihood of non-adherence to drugs are present in asthma: long-term treatment, delayed consequence of treatment cessation, medication expense and skill requirements in using medication.[54;55] The high potency corticosteroid inhalers are expensive, and are prescriptions which are typically not collected if there are payment problems.[2;59] Persons with mild asthma are less likely to obtain prescriptions for asthma drug prescriptions than those with severe asthma.[60] Under-utilization of inhaled corticosteroids may also be the outcome of

parental knowledge regarding how asthma drugs work, which has been observed to be inadequate.[61-63] Persons with asthma are more likely to be adherent with asthma drugs which they perceive to be most useful; the perceived usefulness of inhaled corticosteroids is low.[64] Compliance is lower with inhaled drug therapy than with oral therapy [65] and the majority of patients using metered dose inhalers have difficulties with coordination. [66] Spacer devices, which are extension chambers added onto mouthpieces of pressurized metered dose inhalers, are used in children to facilitate delivery of the drug to the lung. Poor parental knowledge of asthma treatment is potentially related to limited knowledge of health professionals in areas such as proper inhaler technique, [67] or the inability of health professionals to communicate this knowledge to their patients. [68]

4.3 Utilization of inhaled corticosteroid drugs among lower income children

Children living in impoverished environments are less likely to be treated with drug therapy.[69;70] Asthma drug therapy is no exception. The use of prophylactic drugs has been reported to be 7-22% less frequent among children living in lower, than higher socioeconomic status families surveyed in the UK, Australia and the US. [43;49;71] Prescriptions for inhaled corticosteroid drugs have been documented in 35% of asthmatic children living in income assistance households in a Canadian province,[72] but a prevalence as low as 3% has been reported among inner-city children in the US.[52] There are many barriers to the use of inhaled corticosteroids in low income children. The literature tells us that utilization of inhaled corticosteroids is more frequent among children with a regular source of care or among children visiting an asthma specialist.

Lower income asthmatic children are less likely to see a physician and more likely to receive care from an emergency department. [73;74] In the Canadian setting of universal health care, physician office visits are more frequent among children living in lower income neighbourhoods, but referrals to specialists are less common.[75] In addition to health care insurance issues, lack of transportation in lower income families may affect utilization of health services. [76]

While it is difficult to ascertain whether lower utilization of inhaled corticosteroids in lower income children represents less frequent prescription of inhaled corticosterids or non-adherence once prescribed, non-adherence with asthma management regimens in this population is a significant factor.[77] Lower income asthmatics are less likely to fill their prescriptions [60] or to respond to inhaled corticosteroids once prescribed.[78] In an evaluation of 34 US inner-city children with asthma, many of whom were receiving income assistance, 44% of prescribed inhaled corticosteroid doses were taken and only 12% of children had adherence rates greater than 75%.[79] Low income parents report difficulties in being able to pay for their children's asthma medication, an issue which is especially relevant to use of the high potency inhaled corticosteroids.[59;80-82] Drug prescription expense is also a barrier to the use of drugs in Canada because universal health insurance in Canada does not cover prescription drugs.[83]

However, lower socioeconomic status have been observed to predict non-adherence among adults with asthma who have been supplied inhaled corticosteroids free of charge in a clinical trial setting.[84] In an observational study, one quarter of asthmatic children

receiving free prescription drugs through income assistance benefits did not have asthma prescriptions. [52] Non-adherence may be related to decreased knowledge about asthma among lower income parents, [85] which may stem from poor communication with the physician.[84] In addition, persons with asthma from low income environments are more likely to express a disbelief in the effectiveness of drugs in preventing asthma symptoms. [86] Parental doubts regarding the usefulness of asthma drugs are more common among low income parents who report non-adherence with drug therapy, or who are repeated users of the emergency department for their child's asthma. [87;88] In addition, adherence to treatment may be more difficult among low income, single-parent families, subsequent to time constraints, or among dysfunctional, low income households.[89-92]

4.4 Proposed research and hypotheses

A study of the utilization of inhaled corticosteroid drugs in children with asthma was undertaken, with the following objectives: 1) to describe the proportion of children with an inhaled corticosteroid drug according to neighbourhood income, level of asthma severity and physician specialist use, and 2) to determine the "risk" of a new prescription for an inhaled corticosteroid by household income status, adjusting for asthma severity, physician specialty and other factors which influence the use of inhaled corticosteroids.

Study Hypothesis I:

Lower income children are significantly less likely to receive a prescription for an inhaled corticosteroid drug than higher income children. A positive gradient in the proportion of

children with inhaled corticosteroid prescriptions across neighbourhood income quintile will be documented.

Study Hypothesis II:

The relative risk for a new prescription for an inhaled corticosteroid prescription is decreased in lower versus higher income children, following adjustment for disease severity, physician specialty and other risk factors.

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Socioeconomic Status and Inhaled Corticosteroid Utilization Among Children with Asthma

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ABSTRACT

Background: Asthma hospitalization can be prevented with the use of prophylaxis drugs, such as inhaled corticosteroids. There is limited evidence that asthmatic children living in lower income households are more likely to underutilize inhaled corticosteroids. A study was undertaken to determine whether the utilization of inhaled corticosteroid drugs in Manitoban children with asthma was related to their socioeconomic environment.

Methods: Using population-based prescription and health care utilization data, a cohort of 16,862 children, aged 5-15 years, was identified on the basis of a diagnosis and drug-based case definition for asthma, and at least one prescription for an asthma drug during January 1995-March 1996. The proportion of children with an inhaled corticosteroid prescription by neighbourhood income, with adjustments for asthma severity and physician specialist use, was ascertained. A longitudinal assessment of the likelihood of a new prescription for an inhaled corticosteroid by household income, defined on the basis of drug insurance plan membership, was also conducted.

Results: Forty-five percent of children had at least one prescription for inhaled corticosteroid drug during January 1995-March 1996. The proportion of inhaled corticosteroid users increased with successive increases in neighbourhood income quintile. Adjustment for asthma severity and specialist use, eliminated the gradient in inhaled corticosteroid utilization among children with severe asthma, but among children with mild or moderate asthma, the income trend in utilization was present among children who had not seen an asthma specialist. A new prescription for an inhaled corticosteroid was documented in 41% of 12,481 children without a prescription for an inhaled

corticosteroid during the first six months of study. The relative risk for a new inhaled corticosteroid prescription, adjusted for asthma severity and specialist use, was 0.9 among low income or income assistance children, in comparison to higher income children. This risk was further reduced in income assistance children to 0.82 (95%CI:0.76-0.88) following adjustment for factors, such as frequency of upper respiratory tract infection.

Conclusions: Low income children with asthma are significantly less likely to be prevalent or incident users of inhaled corticosteroid drugs.

INTRODUCTION

Children living in impoverished environments are more likely to experience morbidity.[1-5] Despite this increased burden of illness, lower income children are less likely to be treated with drug therapy.[6,7] Inhaled corticosteroids are prophylaxis drugs in asthma therapy which have been shown to reduce hospitalization for asthma.[8-11] While the use of inhaled corticosteroids has increased over the past 10 years, studies show that these drugs continue to be underutilized, [12-16] and there is limited evidence that children living in lower income households are more likely to underutilize inhaled corticosteroid drugs. [17-20] Therefore, this study was undertaken to determine whether the utilization of inhaled corticosteroid drugs in Manitoban children with asthma was related to their socioeconomic environment. Our hypothesis was that low income children with asthma, independent of confounding factors such as asthma severity and prescribing by asthma specialists, would be less likely to receive a prescription for an inhaled corticosteroid than their higher income counterparts.

RESEARCH METHODS

Data for this study were obtained from four computerized databases maintained by the Manitoba Health Services Insurance Plan (MHSIP): 1) registration files, 2) records of physician reimbursement claims, 3) records of hospital separation abstracts, and 4) records of prescriptions dispensed in retail pharmacies. The MSHIP registration file contains a record for every individual registered to receive insured health services and records birthdate, sex and geographic location. Records of physician reimbursement for medical care provided are submitted under a fee-for-service arrangement, and contain information on patient diagnosis at the 3-digit level of the ICD-9-CM classification system and physician specialty. Separation abstracts for hospital services provided include information on 16 ICD-9-CM diagnostic codes, of which the first is the diagnosis which is most responsible for the hospital stay. Prescriptions dispensed which are submitted by retail pharmacies for reimbursement by provincial drug insurance plans or for drug utilization review purposes, contain data on the date of prescription dispensing, drug name, strength, and dosage form, and a 9-digit drug identification number. Record linkages between these databases were achieved by the use of anonymous personal identifiers. Statistics Canada Census 1995 household income data, aggregated to the geographic unit of the enumeration area, were used to rank neighbourhood income quintiles from 20% of the population residing in the lowest income to 20% of the population residing in the highest income neighbourhoods.[21-23] A database characterizing Manitoba physicians was also utilized.

A total of 174,208 children, aged 5-15 years as of January 1, 1995 and registered with Manitoba Health until March 31, 1996, were identified from the MSHIP registry. This time period was chosen to capture data prior to a major policy change in the provincial drug insurance program. Approximately 48,000 of these children met the following case definition for possible, probable or definitive asthma: 1) at least one diagnosis of asthma or bronchitis on a physician claim or hospital abstract record, or 2) in the absence of these diagnoses, one prescription for an inhaled corticosteroid or sodium cromoglycate drug, or two prescription records for a bronchodilator drug, or one prescription for a bronchodilator and ketotifen during a 3+ year time period, January 1, 1995 - March 31, 1998. A study cohort of 16,862 children was derived from this sample, representing children who had received a prescription for an asthma drug during the time period, January 1, 1995 to March 31, 1996. Asthma drug therapy was classified as follows [24]: 1) inhaled bronchodilators [eg. b2-adrenergic agonist, ipratropium bromide], 2) oral bronchodilators [eg. b2-adrenergic agonists, theophylline], 3) inhaled corticosteroids [eg. beclomethasone dipropionate, budesonide, fluticasone propionate], 4) antiallergic agents [eg. sodium cromoglycate, nedocromil sodium, ketotifen], and oral corticosteroids [eg. prednisone, prednisolone].

The analysis was divided into two parts: 1) a 15-month cross-sectional view (January 1, 1995 - March 31, 1996) of the proportion of children with an inhaled corticosteroid prescription by neighbourhood income, and 2) a 39-month longitudinal assessment (January 1, 1995 - March 31, 1998) of the likelihood of a new prescription for an inhaled corticosteroid by household income. For the cross-sectional description,

children were placed into income quintile neighbourhoods according to the 6-digit postal code of the household in which they lived. [21-23] They were further categorized by level of asthma severity (mild, moderate, moderate-severe, severe), using a drug regimen-based asthma severity instrument which had been developed to assign asthma severity on the basis of prescription and hospitalization records. The instrument was found to have good reliability and validity.[25] Children with moderate-severe and severe asthma were grouped together to form the severe asthma category; children with mild or moderate asthma were defined as not having severe asthma. To disentangle the effects of physician practice styles and the socioeconomic environment on utilization of inhaled corticosteroids, [26-28] a dichotomous measure was created to categorize children on the basis of seeing at least one physician specialist for asthma care during the time period, January 1, 1995 to March 31, 1996. An asthma care visit was defined as a physician visit or hospitalization in which the primary diagnosis was asthma or bronchitis, or a primary diagnosis for respiratory infection co-existed with a secondary diagnosis of asthma. Asthma specialists were defined as allergists, respirologists or other pediatric specialists; physicians which did not fall into these categories (ie. family practitioners, general pediatricians) were defined as non-asthma specialists. Children were also categorized according to whether the diagnoses recorded in their health care contacts over an extended time period, January 1,1995 to March 31,1998 were: 1) solely asthma diagnoses, 2) solely bronchitis diagnoses, and 3) a combination of asthma and bronchitis diagnoses. [15,29-31]

The study cohort was described in terms of the proportion of children with at least one prescription for an inhaled corticosteroids during the time period, January 1995 to March 1996, across neighbourhood income quintiles and by other sociodemographic variables. Results were presented in terms of unadjusted proportions, and proportions adjusted for asthma severity and physician specialist use (at least one visit to a specialist for asthma care versus none). Statistical differences in proportions were determined with the chi-square test for two group comparisons, and with the Mantel-Haenszel chi-square trend test for multi-group comparisons. All analysis were conducted at the 95% level of confidence.

The longitudinal assessment of the risk of a new prescription for an inhaled corticosteroid involved assembling a sub-cohort of children with no inhaled corticosteroid prescriptions for at least six months from study entry. Household income was derived from the prescription benefit status of the child and neighbourhood income as follows: 1) income assistance children included children receiving prescription benefits from Manitoba Family Services, Winnipeg and other municipal Social Services, and Medical Services Branch which provided benefits to Treaty Status Indians, 2) low income, but not income assistance children included children receiving Pharmacare prescription benefits and living in the lowest neighbourhood income quintile, and 3) higher income, but not income assistance children included children receiving Pharmacare prescription benefits not living in the lowest neighbourhood income quintile. In addition to asthma severity and asthma specialist use, five explanatory variables were evaluated: 1) age at study entry,[32] 2) hospitalization for asthma from birth to study onset, [33-35] 3) duration of

time from the first health care contact for asthma from birth to study onset, [33,35] 4) continuity of physician care prior to prescription, defined as at least 90% of physician visits made to one non-asthma specialist and/or one asthma specialist,[36,37]) and 5) presence of a high number of respiratory infections prior to prescription.[38,39] The latter variable encompassed all physician visits and hospitalizations for respiratory infections or bronchitis, and for asthma if followed by a prescription for an antibiotic within 7 days of the visit. Children with a high number of respiratory infections were those in whom the respiratory infection contact rate over time prior to prescription fell into the 90^{th} percentile or greater.

The relative risk of a first prescription for an inhaled corticosteroid was determined from Poisson regression modelling after ensuring that the proportion of inhaled corticosteroid use followed a Poisson distribution (mean number of prescriptions = variance). [40] The relative risk, and not the odds ratio, was selected as the likelihood measure because inhaled corticosteroid use is not a rare event and the odds ratio would not be a good approximation for the relative risk. Explanatory variables were retained in the model by comparing the difference in deviance between nested models to the chi-square statistic for the difference in degrees of freedom between two models at a 95% level of confidence. Sample size calculations showed that 723 children in the income assistance group and 578 low income children were minimally required to detect a relative risk for a new inhaled corticosteroid prescription of 0.85 in comparison to high income children. Sample size determinations were made assuming a power index of 2.96 (Bonferroni corrected alpha=0.05/3, one sided and beta=0.20), an incidence of 0.45 inhaled corticosteroid

prescriptions over a 3-year period, and a sample size ratio of 0.11 for low versus high income children and 0.24 for income assistance versus high income children.

RESULTS

The asthma cohort was comprised of 16,862 children, aged 5-15 years, who met the case definition and had at least one prescription for an asthma drug in the time period, January 1,1995 to March 31,1996. Overall, the proportion of children with at least one prescription for an asthma drug was found to be 83% for inhaled or oral bronchodilators, 45% for inhaled corticosteroids, and 18% for oral corticosteroids. The proportionate use of other asthma drug categories was less than 10%. The proportion of children with a bronchodilator prescription did not differ by age or gender, but prescriptions for inhaled corticosteroids were significantly more likely among children aged 10 years or less (47%), and among male children (46%). Inhaled corticosteroids prescriptions were documented in 50% of children with an asthma, or asthma and bronchitis diagnoses recorded in administrative records, significantly higher than the proportion (16%) found in children with solely bronchitis diagnoses.(Table 4.6.1) The presence or absence of an asthma diagnoses did not differentiate the proportion of children utilizing bronchodilators. The likelihood of a prescription for an inhaled corticosteroid was significantly greater in children with severe, than mild to moderate asthma, and in children who had seen at least one asthma specialist for asthma care, in comparison to those who had not. Again, the likelihood of bronchodilator use was more similar across these categories. Children with severe asthma were twice as likely to see an asthma

specialist than children with mild to moderate asthma. When stratified by asthma severity, the difference in the proportion of children with inhaled corticosteroid prescriptions between children seeing and not seeing an asthma specialist diminished slightly in children with severe asthma.

Lower neighbourhood income children were significantly less likely to receive an inhaled corticosteroid prescription than their higher income counterparts, and the trend in increased proportion of inhaled corticosteroid users with successive increases in neighbourhood income quintile was significant.(Figure 4.6.1) In contrast, the proportion of children utilizing bronchodilators marginally decreased with each successive increase in income quintile. Adjusting for asthma severity eliminated the gradient in inhaled corticosteroid utilization among children with severe asthma, but the gradient was more pronounced in children with mild or moderate asthma.(Figure 4.6.2) Further adjustments for physician specialty for asthma care diminished the slope of the gradient in inhaled corticosteroids use across neighbourhood income.(Figures 4.6.3 & 4.6.4) Among children with mild or moderate asthma, the income trend in utilization was significant among children who had not seen an asthma specialist, or who had not seen a physician during the study period. Among severely asthmatic children, a gradient in inhaled corticosteroid utilization across income was observed only among children who had not seen a physician during the study period.

From the original cohort of 16,862 children with asthma, 12,481 children did not have a prescription for an inhaled corticosteroid for at least six months from study entry date. A

new prescription for an inhaled corticosteroid was documented in 5,104 (40.9%) of children from 01/95-03/98. Income assistance and low income children were significantly more likely to have frequent respiratory infections and previous hospitalizations for asthma, than higher income children. (Table 4.6.2) However, they were less likely to have a new inhaled corticosteroid prescription or health care contact for asthma. Unadjusted relative risks showed that a new prescription for an inhaled corticosteroid was significantly less likely in low income versus higher income children, and significantly more likely in children with severe versus mild asthma, in children with a previous hospitalization or health care visit for asthma, and in children with numerous respiratory infections.(Table 4.6.3) Children with continuous physician care were at decreased risk of receiving a new prescription for an inhaled corticosteroid. The relative risk for a new inhaled corticosteroid prescription, adjusted for asthma severity and asthma specialist use, among low income or income assistance children, in comparison to higher income children was 90%. This risk was further reduced in income assistance children to less than 90% following adjustment with the other explanatory variables.

DISCUSSION

Almost 50% of Manitoban children, aged 5-15 years old, with asthma drug therapy and/or asthma-related diagnosis, had received a prescription for an inhaled corticosteroid in 1995/96. This finding is not dissimilar to the prevalence reported in a population-based study in the United Kingdom. [14] Children who at some point, had received a diagnosis of asthma were significantly more likely to obtain an inhaled corticosteroid prescription,

than children with bronchitis diagnoses only. A correlation between the prevalence of asthma drug treatment and of physician-diagnosed asthma has been documented by others.[15,29-31] However, fifteen percent of children with bronchitis, but not asthma diagnoses received these drugs. Bronchitis diagnoses may represent viral-associated wheezing, which can be treated with a trial of inhaled corticosteroids. [41-43] However, this finding also illustrates the potential extent to which asthma may be under-diagnosed and the importance of including bronchitis diagnoses in a case definition.[30,31,44]

Despite asthma management guidelines in the 1990's which recommended the administration of inhaled corticosteroids in mild to moderate asthma, [45,46] the prevalence of inhaled corticosteroid utilization was higher in our cohort children with more severe asthma, as has been reported by others.[18,47] Also consistent with the literature, was our finding that a higher proportion of inhaled corticosteroid use was observed among children who were seen by an asthma specialist during the study period, than those who had not. [26-28] Children seeing an asthma specialist were almost twice as likely as those not visiting a specialist to receive a prescription for an inhaled corticosteroid. Similar to findings by Vollmer and colleagues, stratifying for asthma severity did not substantially diminish this difference, suggesting that differences in inhaled corticosteroid prescription by physician specialty are due to physician practice styles and not disease characteristics.[26] The outcome of receiving care from an asthma specialist versus a generalist has been observed to be a significant decrease in emergency department visits and hospitalizations. [26,28] It is not clear whether the more favourable

outcomes of seeing an asthma specialist can be attributed to increased use of inhaled anti-inflammatory drugs or to outpatient management of acute asthma.

Our finding of a progressive decline in utilization of inhaled corticosteroid drugs in children with asthma with decreasing neighbourhood income contributes to the literature on socioeconomic status and use of asthma prophylaxis drugs.[17-20] Inhaled corticosteroid drug utilization decreases the risk of asthma hospitalization [8-11] and one can speculate that a negative income gradient in inhaled corticosteroid utilization contributes, among other factors, to the same gradient in asthma severity and hospitalization observed in children.[48-52] As hospitalization for asthma and associated costs continue to rise among children, this finding has major health care policy implications.[53-56] Moreover, hospitalization contributes to poor quality of life of children with asthma.[57] According to our observations, lower and higher neighbourhood income children with severe disease, not in the care of an asthma specialist, would equally be at risk for poor outcomes associated with decreased utilization of inhaled corticosteroid drugs. However, lower income children with mild to moderate asthma, not seeing an asthma specialist or any physician for asthma care, would be at a disproportionate greater risk for poor outcomes.

Our cross-sectional description of inhaled corticosteroid drug utilization by socioeconomic status had the potential to be biased because it described prevalent use and did not take into account differences in the time course of asthma. Inhaled corticosteroid use is more likely among children with previous inhaled corticosteroid

prescriptions, in children previously hospitalized and in children with a history of numerous respiratory infections. [39,46,58,59] These factors are not equally distributed across household income status. [48-52, 60] Evaluating the longitudinal risk of a new prescription for an inhaled corticosteroid drug and adjusting for some of these factors, diminished this bias. As anticipated, we found that new use of inhaled corticosteroid was significantly more likely in children with previous evidence of asthma or hospitalization for asthma, and among children with numerous respiratory infections. Contrary to the literature, we found that a regular source of medical care was associated with a decreased likelihood of inhaled corticosteroid use. [37,59] This discrepancy in findings is likely a function of the definition of regular source of medical care, which in the literature is based on parental report of receiving asthma care from a primary care physician, in contrast to an emergency room. Adjustment for factors which predicted receipt of inhaled corticosteroid prescriptions, did not alter the reduced likelihood of utilization in lower income and income assistance children.

Policy initiatives to improve the utilization of inhaled corticosteroid drugs need to take into consideration our findings of income differences in utilization which were relative to each other, placing higher income children also at risk for under-utilization.[61] However, the income quintile measure does not distinguish whether barriers to the utilization of inhaled corticosteroid drugs in low income households are related to cost of the prescription or to asthma management practices.[62-64] Low income families report payment problems in acquiring asthma medication, [65,66] but independent of cost barriers low income persons with asthma are less likely to be adherent to their drug

regimen.[67] By defining household income on the basis of drug insurance plan membership in our longitudinal assessment of children, we found a lower likelihood of inhaled corticosteroid utilization in income assistance children who were recipients of free prescription drugs. Personal beliefs regarding asthma management are also issues in non-adherence. [35,68] Parental disbelief in the effectiveness of asthma medication in preventing symptoms has been reported to be associated with recurrent emergency department utilization by low income children.[69,70] In addition to ensuring that health professionals are well prepared to discuss asthma with their patients, [71,72] asthma education should address patient belief systems. Moreover, pharmaceutical policy which encourages the utilization of drugs which prevent the morbidity associated with asthma and other chronic diseases in children should be advocated.[73-74]

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Table 4.6.1.The Proportion of Children with at Least One Prescription for a Bronchodilator or Inhaled Corticosteroid Drug by Asthma Severity, and Physician Diagnosis and Specialty, 01/95-03/96

Characteristic	% Utilizing Bronchodilators	% Utilizing Inhaled Corticosteroids
Physician diagnoses		
Asthma only (n=8368)	84.7, p<0.001*	52.3, p<0.001
Asthma/bronchitis (n=4247)	86.3	49.4
Bronchitis only (n=2472)	76.1	15.7
No diagnosis** (n=1775)	75.8	43.2
Asthma severity level		
Severe asthma (n=3570)	76.8, p<0.001	60.3, p<0.001
Not severe asthma (n=13292)	84.6	41.2
Physician specialist use for asthma care		
One+ visits to asthma specialist (n=2064)	85.9, p<0.001	72.5, p<0.001
No visits to asthma specialist (n=10878)	84.6	43.8
No physician visits*** (n=3920)	76.7	34.9
Mild-moderate asthma		
One+ visits to asthma specialist (n=1356)	83.3, p<0.001	66.5, p<0.001
No visits to asthma specialist (n=8515)	86.1	39.6
No physician visits*** (n=3421)	81.4	35.1
Moderate-severe, severe asthma		
One+ visits to asthma specialist (n=709)	91.0, p<0.001	83.9, p<0.001
No visits to asthma specialist (n=2362)	79.3	59.1
No physician visits*** (n=499)	44.5	32.9

*comparison within categories, ** no physician visits for asthma/bronchitis 01/95 – 03/98, *** no physician visits for asthma/bronchitis diagnoses January 1995 – March 1996

Table 4.6.2. Distribution (%) of New Inhaled Corticosteroid Utilization and Related Factors, 01/95-03/98, By Household Income Status

	High Income (n=9227)	Income Assistance (n=2175)	Low Income (n=1079)
New Inhaled Corticosteroid	41.7	38.4	39.3,p<0.01*
Severe asthma	1.7	2.1	3.2
Mod-severe asthma	18.6	16.5	19.6
Mild-mod asthma	79.7	81.4	77.3, NS
Asthma specialist consultation	9.4	6.8	9.4, NS
Regular source of physician	51.8	47.3	52.8, NS
Previous asthma hospitalization	10.3	14.3	12.7, p<0.001
Previous visit for asthma	62.1	56.5	59.2, p<0.001
Frequent upper respiratory tract infections**	8.6	15.4	10.3, p<0.001

*Mantel Haenszel trend test, **frequent was defined as rates in the 90th percentile

Table 4.6.3.Relative Risk of a New Prescription for an Inhaled Corticosteroid Drug, Jan/95-Mar/98

Explanatory factor	New ICS Prescriptions	Person-days	Rate/ 1000	RATE RATIO Crude	Adjusted[a] Model A	Adjusted[b] Model B
Income assistance	835	1967759	0.42	0.89 (0.83-0.96)	0.90 (0.83-0.9)	0.82 (0.76-0.88)
Low income	424	964063	0.44	0.92 (0.83-1.02)	0.90 (0.81-0.99)	0.88 (0.80-0.97)
High income	3845	8066894	0.48	BASELINE		
Severe asthma	186	122270	1.52	3.68 (3.17-4.26)	3.68 (3.17-4.26)	2.59 (2.21-3.03)
Moderate-severe	1191	1864121	0.64	1.54 (1.45-1.65)	1.53 (1.43-1.64)	1.42 (1.33-1.52)
Mild-moderate	3727	9012325	0.41	BASELINE		
Asthma specialist visit	538	961697	0.56	1.23 (1.12-1.34)	1.17 (1.07-1.28)	1.10 (1.00-1.20)
No specialist visit	4566	10037019	0.45	BASELINE		
Continuous MD care	2102	5994833	0.35	0.58 (0.55-0.62)		removed from model[c]
No continuous care	3002	5003883	0.60	BASELINE		
Prior hospitalization[d]	698	982824	0.92	2.18 (2.02-2.34)		1.54 (1.42-1.67)
No hospitalization	4206	10015892	0.42	BASELINE		
Prior asthma visit	3635	6321478	0.57	1.83 (1.72-1.95)		1.64 (1.54-1.75)
No prior visit	1469	4677238	0.31	BASELINE		
Frequent URI[e]	828	785321	1.05	2.52 (2.34-2.71)		2.53 (2.35-2.73)
Few URI	4276	10213395	0.42	BASELINE		
Age 5-6 years	1162	2408288	0.48	1.05 (0.98-1.12)		
Age 7+ years	3942	8590428	0.46	BASELINE		

ICS= inhaled corticosteroid
a=adjusted for factors listed in Model A, b=adjusted for factors listed in Model B,
c=addition of variable altered significance of physician specialty measure, so decision made to retain physician specialty,
d=hospitalization for asthma, e=upper respiratory tract infection rate in the 90th percentile

Figure 4.6.1. Frequency (%) of Children with One or More Prescriptions for Selected Asthma Drugs by Neighbourhood Income Quintile

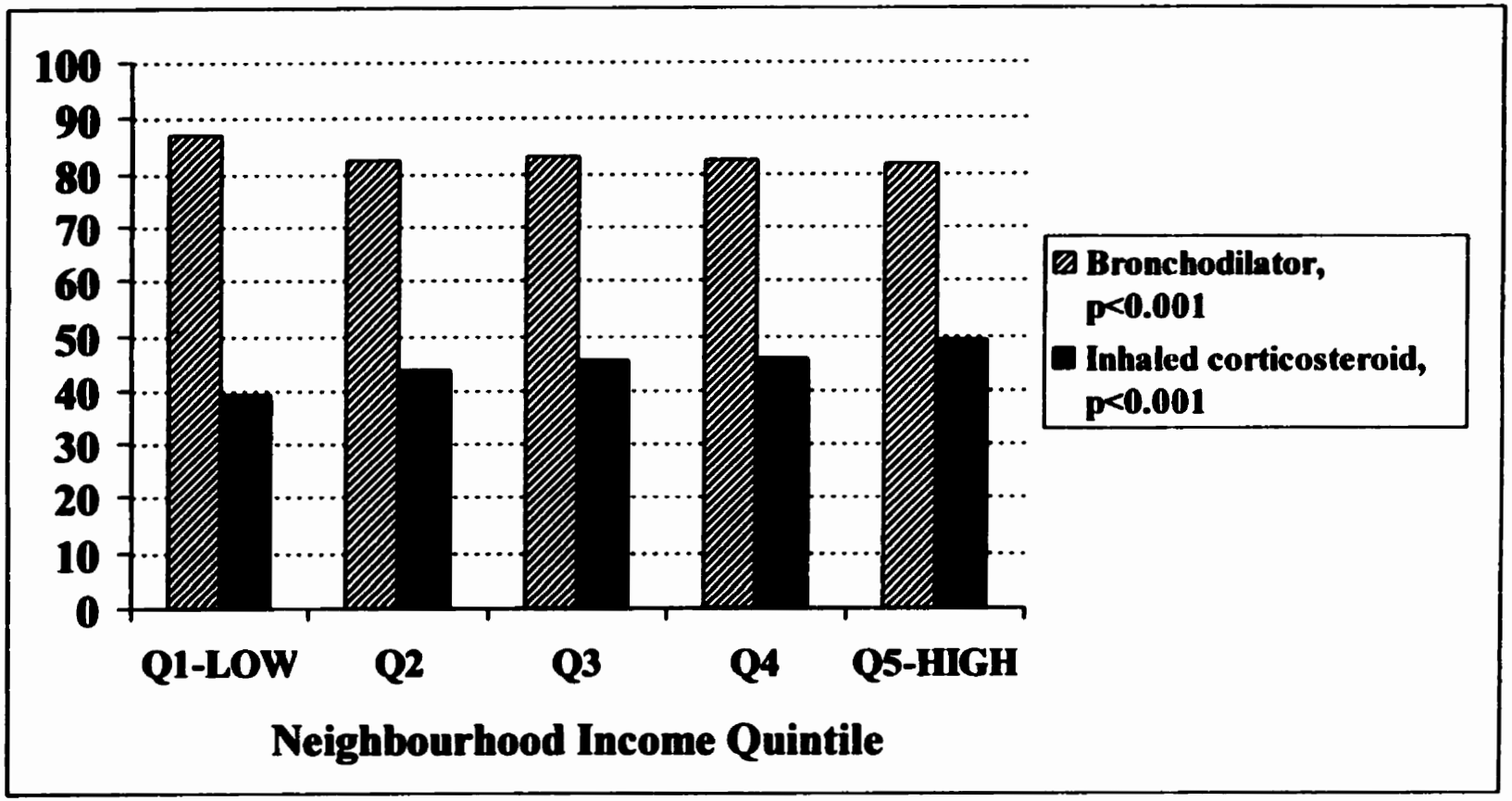


Figure 4.6.2. Frequency (%) of Children with One or More Prescriptions for Inhaled Corticosteroid Drugs by Asthma Severity and Neighbourhood Income Quintile

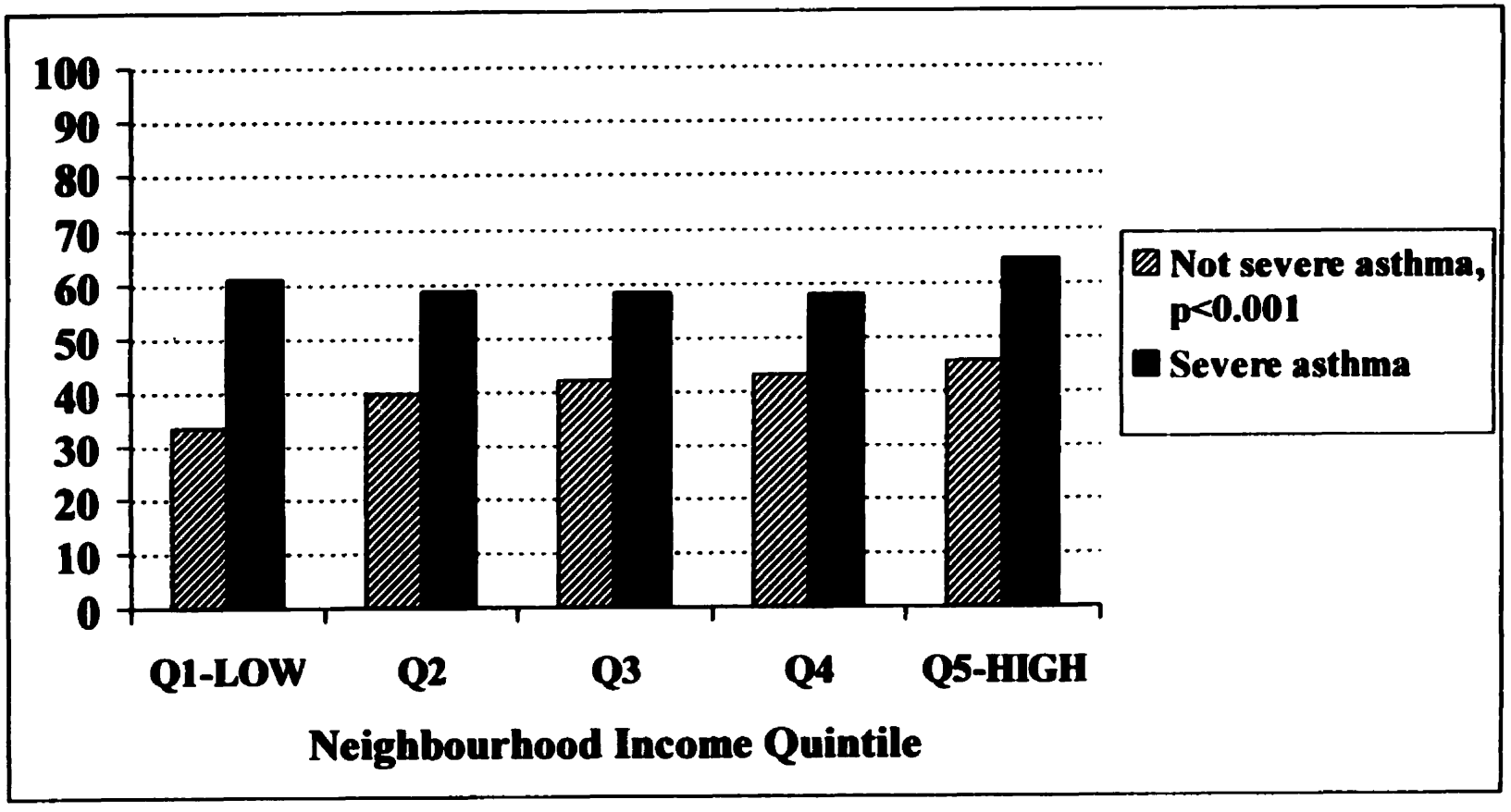


Figure 4.6.3. Frequency (%) of Children with Mild to Moderate Asthma and One+ Prescriptions for Inhaled Corticosteroid Drugs by Physician Specialty and Neighbourhood Income Quintile

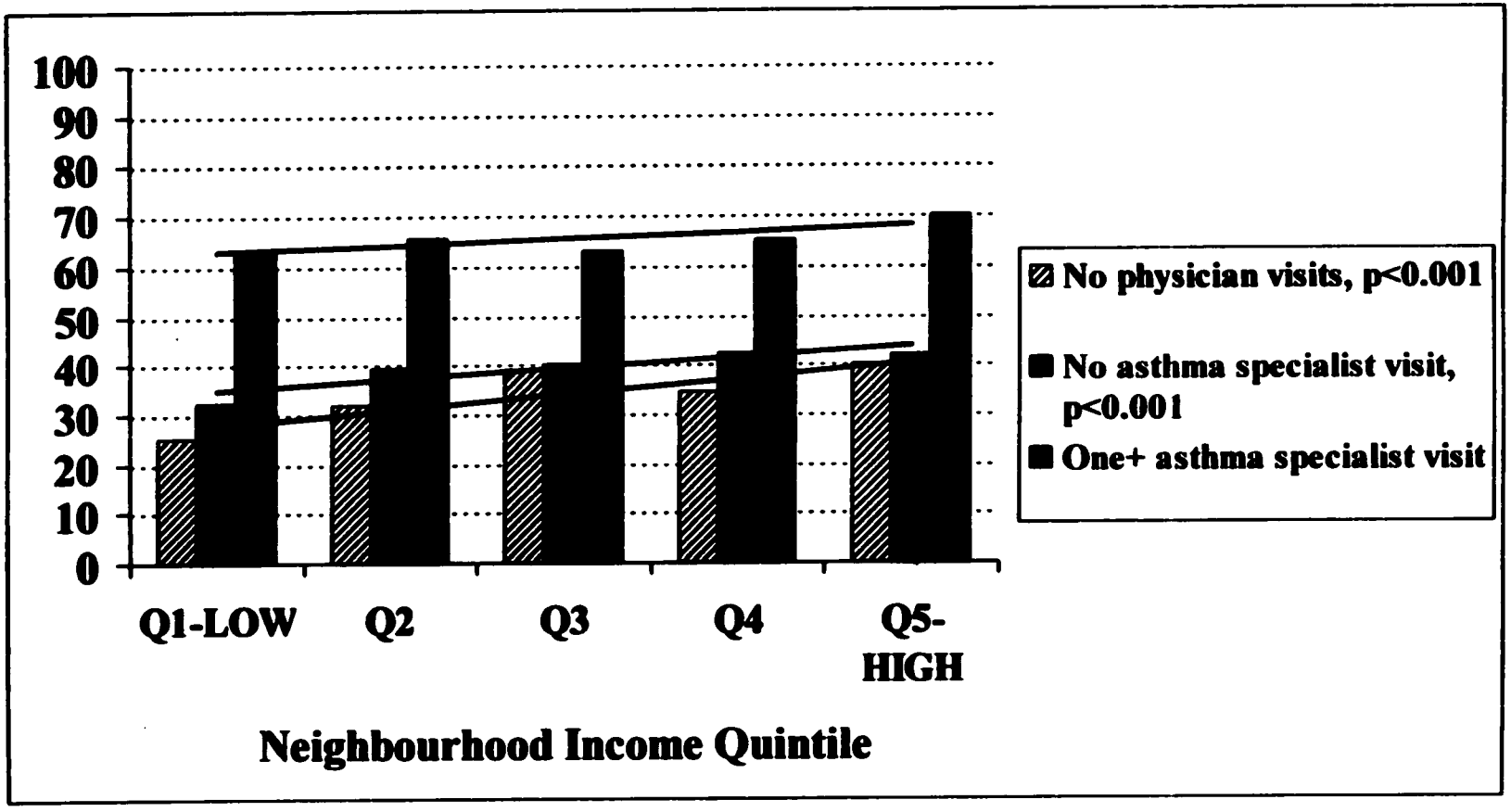
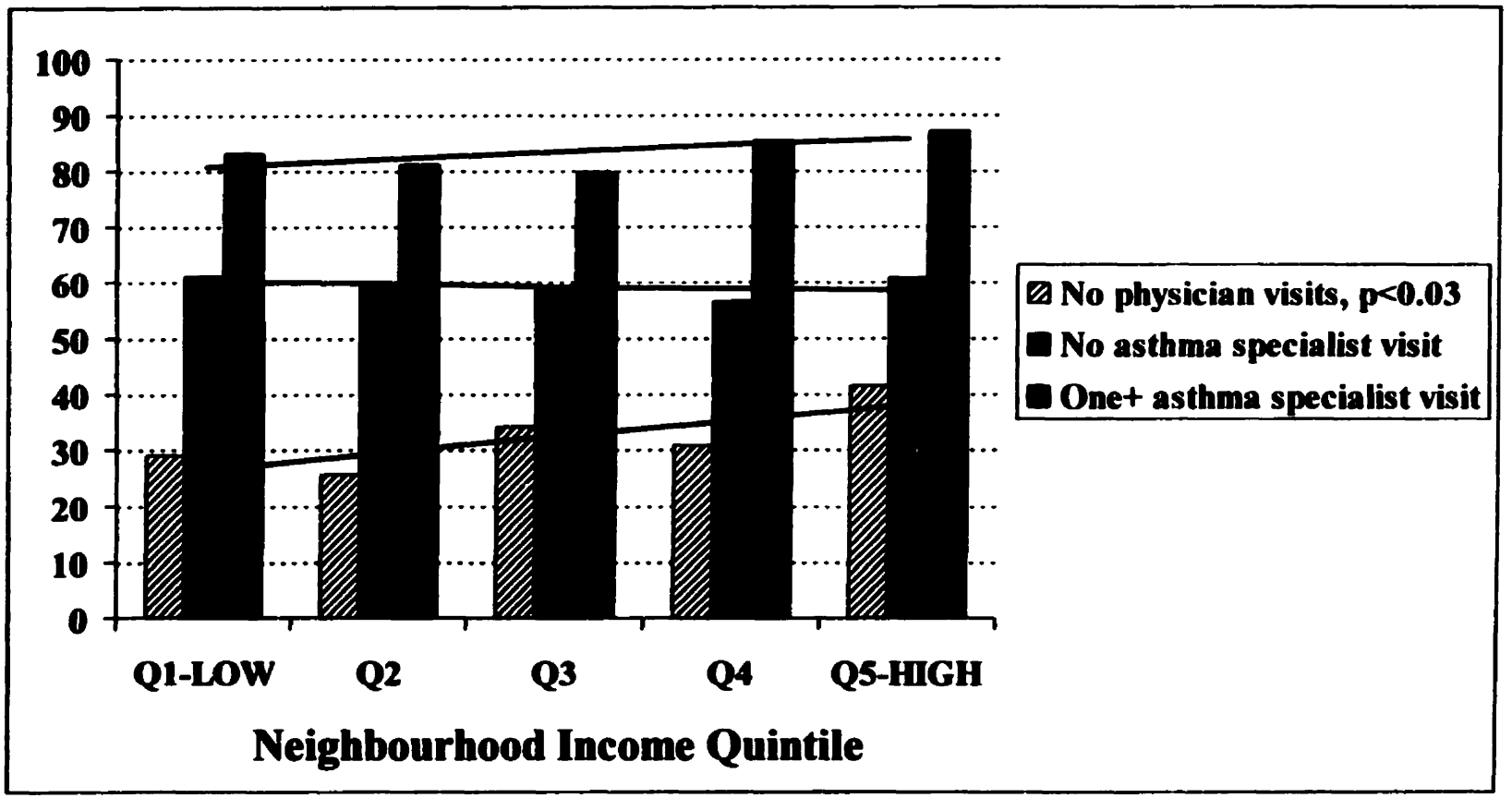


Figure 4.6.4. Frequency (%) of Children with Moderate-Severe to Severe Asthma and One+ Prescriptions for Inhaled Corticosteroid Drugs by Physician Specialty and Neighbourhood Income Quintile



Chapter 5. Pharmaceutical Insurance Policy and Inhaled Corticosteroid Utilization in Children with Asthma

Factors affecting the utilization of inhaled corticosteroid drugs in children were identified in the previous chapter. The reader learned from a review of the literature that asthmatic children living in low income households were less likely to receive inhaled corticosteroid drugs. The dissertation research reported in Chapter 4 yielded similar findings, adding to this body of literature data on Canadian children. These findings were based on a 15-month period prior to the introduction of a income-based drug reimbursement policy in Manitoba because it was anticipated that the new policy would impact utilization. This chapter explores the literature evaluating the influence of pharmaceutical policy on drug utilization. It is concluded with an evaluation of the impact of Manitoba's income-based pharmaceutical policy on the utilization of inhaled corticosteroid drugs in the study cohort of children with asthma.

5.1 Pharmaceutical reimbursement policy and prescription utilization

Pharmaceutical reimbursement policy plays an important role in determining a population's access to pharmaceuticals. Policies may expand drug utilization by removing cost barriers to the acquisition of prescription drugs, or may restrict use by imposing cost barriers to curtail utilization.[1] The introduction of drug insurance programs in populations without previous insurance, or of income-based policies are examples of

expansive policies. Over the past two decades there has been a growth in restrictive pharmaceutical policy, a growth which can be attributed to: 1) rapid increases in drug expenditures, and 2) accumulating evidence which suggests that drugs are not being appropriately utilized and contribute to iatrogenic disease.[2] The conventional wisdom is that restrictive pharmaceutical policies promote cost-effective and optimal utilization of pharmaceuticals, but many policies are implemented with little evidence about their true impact on drug utilization or health.

5.1.1 Administrative restrictions on drug reimbursement

There are two types of restrictive drug reimbursement policies: 1) administrative restrictions such as the listing of eligible drugs in a formulary, or the requirement of prior authorization to receive reimbursement for specific drugs, and 2) patient cost sharing, including restrictions on the number or value of prescriptions for which a recipient is eligible to receive reimbursement.[2] Administrative restrictions such as the withdrawal of reimbursement for less efficacious drugs also have had unintended effects on drug therapy. The discontinued reimbursement by Medicaid in 1982 of 141 drugs designated as ineffective by the US Drug Efficacy Study resulted in increased prescription of substitute drugs, some of which were not improvements over existing therapy.[3] In the case of persons with asthma however, withdrawing reimbursement for irrational drug combinations such as theophylline and sedatives products, led to increased prescription of non-sedative containing theophylline products and thus, potentially improved drug therapy options. In addition, it was speculated that this policy had far-reaching beneficial

effects by accelerating the decline in prescription of combination theophylline products for non-Medicaid recipients.[4] Other benefit restriction policies such as a priori authorization requirements for certain drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) not generically available, have been reported to increase the prescription of generic NSAIDS, but not substitute analgesics.[5]

5.1.2 Patient cost-sharing

Cost sharing can take the form of deductible payments, coinsurance, or co-payments at time of prescription dispensing, or limits on the number or total value of prescriptions which are reimbursed.[2] The few quasi-experimental studies which have evaluated patient cost sharing policies show that imposing a limit on the number of reimbursable prescriptions has a negative impact on the number of prescriptions filled for discretionary and essential drugs.[6-8] The abrupt introduction by New Hampshire Medicaid of a three-drug payment limit resulted in a 30% decrease in prescriptions for insulin and diuretics, and a 45% drop in prescriptions for digoxin.[6] Similarly, the outcome of a five-prescription limit implemented by Georgia Medicaid was a 5% reduction in prescriptions for cardiovascular and pulmonary drugs. [7] Out-of-pocket costs for drugs increased temporarily, then decreased in successive months after the prescription limit. The introduction of a $1.50 copayment per prescription in a health care maintenance organization, which previously had no copayment requirements, resulted in a 10% decrease in the number of prescriptions filled for essential drugs.[8] Further increases to copayments over time resulted in additional reductions in prescription utilization.

Johnson and colleagues have also shown that increases in copayment and coinsurance for health maintenance organization members have diminished annual increases in prescriptions dispensed per capita.[9]

A recent example of the impact of a pharmaceutical cost-sharing policy in Canada comes to us from the province of Quebec. With the implementation of a universal drug insurance program in Quebec in August 1996, cost-sharing was introduced among social assistance recipients who had previously received prescription drugs free of charge, and prescription copayment charges were increased among seniors.[10] During the 10-month period which followed, the elderly and social assistance recipients significantly reduced their prescription utilization in comparison to pre-policy utilization. Reductions were greatest among the heaviest prescription drug users (16-19%), and among persons using essential drugs (13-17%), high cost drugs (27%), or drugs to treat mental illness or chronic disease (17-30%).

Post-policy evaluations of increasing user charges for prescriptions in New Zealand documented that 1.5% of persons presenting prescriptions to pharmacies could not pay for them, of which 20% did not return for their prescription.[11] Prescriptions for children were more likely to be associated with payment problems. The impact of this policy on persons with asthma was that 0.75% did not collect their asthma drug prescriptions.[12]With no comparisons with a control group, or to the pre-policy period, the impact of the policy on prescription utilization is difficult to ascertain. However, Watt et al did document that inhaled corticosteroid drugs were asthma drugs most frequently

not collected.[12] Change to pharmaceutical program policy in Quebec has impacted upon the utilization of asthma drugs. A significant decrease in consumption of inhaled corticosteroid drugs was observed in social assistance recipients, who previously had received free prescription benefits and were now required to pay a deductible payment.[13]

Conversely, pharmaceutical policy which introduces or expands first-dollar coverage for prescription drugs, increases prescription drug utilization. Among individuals enrolled in a large health maintenance organization in the United States, drug utilization was higher among those with extended benefits packages.[9] It is unclear whether the increased utilization was proportional to health status, a question which is addressed by Grootendorst and colleagues. Utilizing data from the 1990 Ontario Health Survey on self-reported drug use in persons 55-75 years old, they found that the provision of first-dollar prescription coverage at age 65 years was associated with an increase in drug use.[14] Increases in utilization were concentrated among individuals with lower health status. Income-based reimbursement policies, which require lower deductible payments among persons with lower income, have shown to have a protective effect on drug utilization in lower income persons. The outcome of Quebec's new pharmaceutical policy, which also introduced income-based deductible payments, was a reduction in prescription utilization among higher income seniors, not receiving guaranteed income supplements, but no changes to utilization in lower income seniors receiving guaranteed income supplements.[10]

Cost-sharing pharmaceutical policies do not affect everyone equally; those with lower incomes and poorer health status are more likely to reduce utilization. The imposition of these policies on Medicaid populations with chronic diseases was followed by 40% decreases in utilization of prescription drugs. [15,16] On the basis of this evidence it is estimated that low income persons are sensitive to prescription copayments as low as 50 cents to one dollar.[2] In an evaluation of 121 adults attending a walk-in clinic in a low income area, persons with Medicaid or other drug insurance were six times more likely (OR=6.3, 95%CI:1.6-25.0) than those uninsured, to report that cost was not a barrier to purchasing antihypertensive prescriptions.[17] The Medicare plan in the United States provides medical care insurance to the elderly and the disabled, but only covers drugs prescribed in inpatient settings. Low income Medicare enrollees without drug insurance have significantly lower drug expenditures than members with private drug insurance.[18] However, drug utilization in Medicare enrollees without drug insurance approaches utilization rates among enrollees with drug insurance at higher incomes.

Manitoba has a universal drug insurance program which is administered through prescription cost-sharing. Prior to April 1996, an annual, standard deductible payment per family was required; an income-based deductible payment has since been implemented. Families with an annual income of $15,000 or less are required to pay a deductible equivalent to 2% of their net income, while those with higher annual incomes paid a 3% deductible. Once the deductible was reached, the province paid 100% of all prescription costs. A recent evaluation of the utilization of pharmaceuticals by Manitobans documented an increase in the proportion of persons utilizing pharmaceuticals and in the

intensity of use with successive decline in neighbourhood income.[19] However, as this analysis provided no information on health status and excluded low income persons receiving free prescription benefits, we are unable to determine whether higher utilization in the low income group was appropriate relative to health status. Williamson et al's comparison of low income individuals receiving and not receiving social assistance effectively illustrates the extent of differences in drug utilization between lower income individuals receiving free prescription benefits and lower income persons enrolled in prescription cost-sharing programs.[20] Sixty-percent of the later group did not have at least one prescription filled in the past year, in comparison to 30% of persons receiving social assistance. Moreover, not being able to afford the prescription was reported as a reason in 93% of persons receiving subsidized prescription benefits.

5.2 Pharmaceutical reimbursement policy and health outcomes

The impact of pharmaceutical cost-sharing policy on prescription utilization has been suggested to translate into impacts on health status. Soumerai et al observed that decreases in prescription utilization were greatest in the elderly and the disabled.[6] Two follow-up evaluations were conducted to determine the impact of the New Hampshire Medicaid cap on prescription reimbursement on health outcomes. A clear effect of the payment cap on a cohort of low income, elderly persons being treated for chronic illnesses was a doubling of the rate of nursing home admissions.[15] The authors could not distinguish whether increased nursing home admission was subsequent to a deterioration in health status or a mechanism to obtain needed medications. In a cohort of

persons with schizophrenia, the cap resulted in significant increases in emergency department utilization.[16] In both evaluations, no changes to nursing home admissions or emergency department utilization were observed in control populations of Medicaid beneficiaries. The change to pharmaceutical program policy in Quebec made newspaper headlines, with claims that it had cost lives.[21] Increases in hospitalization and long-term care institutionalization were observed in the elderly following implementation of the Quebec policy, but no control groups were available for comparison.[10] A closer link between pharmaceutical policy and health status was observed in Ahluwalia et al's research. In their study, low income adults attending a walk-in clinic who reported that cost was not a deterrent in obtaining antihypertensive drugs, a factor which was related to their insurance status, had significantly better blood pressure control.[17]

5.3 Proposed research and study hypotheses

An income-based pharmaceutical policy has the potential to improve the acquisition of prescription drugs by lower income households, yet be a cost barrier to higher household incomes. A study was undertaken to determine the impact of this income-based pharmaceutical benefit policy in Manitoba on the utilization of inhaled corticosteroid drugs among children with asthma of different socioeconomic backgrounds.

Study Hypothesis I

The proportion of children using inhaled corticosteroid drugs, and the mean dose of inhaled corticosteroid was increased post income-based policy among lower income children with asthma, in comparison to a control group of children.

Study Hypothesis II

The proportion of children using inhaled corticosteroid drugs, and the mean dose of inhaled corticosteroid was decreased post income-based policy among higher income children with asthma, in comparison to a control group of children.

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Income-Based Pharmaceutical Benefit Policy: Impact on Utilization of Inhaled Corticosteroid Drugs in Children With Asthma

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ABSTRACT

Background: Pharmaceutical reimbursement policy plays an important role in determining a population's access to prescription drugs. A study was undertaken to determine whether the introduction of an income-based reimbursement policy by Manitoba's Pharmacare drug insurance program resulted in change to inhaled corticosteroid drug utilization in children with asthma.

Methods: Using population-based health care utilization data, a cohort of 10,918 children, aged 5-15 years, was identified according to a diagnosis and drug-based case definition for asthma, and the presence of one or more asthma drug prescriptions during a 15-month period before and a 24-month period after the income-based policy. Children were categorized by drug insurance program: 1) non-Pharmacare, 2) low income Pharmacare, and 3) higher income Pharmacare. Low income Pharmacare children represented children living in the lowest neighbourhood income quintile. Non-Pharmacare children constituted the control group because no change to pharmaceutical reimbursement policy had occurred in this group. The impact of the income-based pharmaceutical reimbursement policy was evaluated by the monthly likelihood of a prescription for an inhaled corticosteroid, and by the mean number of inhaled corticosteroid doses among children receiving these drugs.

Results: Changes to inhaled corticosteroid prescription utilization in the post income-based policy period corresponded to changes in asthma severity, and were similar among Pharmacare and control children, with one exception. Among children with severe

asthma, inhaled corticosteroid use did not change in control and low income Pharmacare groups, but was significantly less likely in higher income Pharmacare children (OR=0.82, 95%CI:0.77-0.88). Moreover, among higher income Pharmacare children utilizing inhaled corticosteroid prescriptions, the mean number of doses decreased significantly in the post policy period. The mean number of inhaled corticosteroid doses was lowest among low income Pharmacare children and remained unchanged post policy.

Conclusion: The introduction of an income-based drug reimbursement policy in Manitoba was associated with decreased utilization of inhaled corticosteroid prescriptions in higher income children with severe asthma, and did not improve utilization in low income children.

INTRODUCTION

Pharmaceutical reimbursement policy plays an important role in determining a population's access to pharmaceuticals. Policies can be viewed as being expansive, by removing cost barriers to the acquisition of prescription drugs, or restrictive, by imposing cost barriers to curtail drug utilization.[1] The conventional wisdom is that pharmaceutical policies promote cost-effective and optimal utilization of pharmaceuticals. However, well-intended pharmaceutical reimbursement policies may have unintended effects on the utilization of drugs in a population. [2] For example, benefit policies which withdraw reimbursement for less efficacious drugs may achieve their intended objectives, [3;4] but also result in increased prescription of substitute drugs. [5] Patient cost sharing policies which impose a limit on the number of

reimbursable prescriptions, may decrease the number of prescriptions filled for discretionary and essential drugs.[6-8] Negative health outcomes of cost-sharing policies have been documented, including increases in acute mental health services by mentally ill persons and in admission of the elderly to nursing homes.[9;10] Recently, a change to pharmaceutical program policy in Quebec has made newspaper headlines, with claims that it has cost lives. [11] The outcome of this policy change which required social assistance recipients, who previously received free prescription benefits, to pay a deductible payment,[12] was a significant decrease in their consumption of inhaled corticosteroid drugs.

In April 1996, the provincial drug insurance program in Manitoba, Pharmacare, changed the annual deductible payment for prescriptions from a standard amount of $350.00 per family to one based on family income. [13] Families with an annual income of $15,000 or less were required to pay a deductible equivalent to 2% of their net income, while those with higher annual incomes paid a 3% deductible. Once the deductible was reached, the province paid 100% of all prescription costs. A hypothetical benefit of this reimbursement policy, which was intended to distribute benefits more equitably, was decreased cost barriers to low income individuals who are more likely to have chronic conditions and require drug treatment. [13;14] Interviews with low income Canadians reveal that persons receiving free prescription benefits are much more likely to receive a prescription, than persons receiving prescription benefits with fixed deductible rates.[15] While there are many classes of drugs used in the management of chronic disease, one would anticipate that drugs which are expensive to acquire, would be especially sensitive

to pharmaceutical reimbursement policies. One such class of drugs is inhaled corticosteroid drugs, administered in persistent asthma to prevent acute exacerbations.[16] Quebec's experience has shown us how drug reimbursement policy can affect utilization of these drugs.[12] Therefore, this study was undertaken to determine if change to an income-based pharmaceutical remibursement policy in Manitoba resulted in change to inhaled corticosteroid drug utilization in children with asthma. Our hypothesis was that in comparison to children for whom there was no change to drug reimbursement policy, utilization would increase among children living in low income households receiving Pharmacare benefits, due to decreases in deductible payments. We also hypothesized that utilization of inhaled corticosteroid drugs would decrease in children living in higher income families, which would face increases in deductible payment obligations.

RESEARCH METHODS

Data for this study were obtained from four computerized databases maintained by the Manitoba Health Services Insurance Plan (MHSIP): 1) registration files, 2) records of physician reimbursement claims, 3) records of hospital separation abstracts, and 4) records of prescriptions dispensed in retail pharmacies. The MSHIP registration file contains a record for every individual registered to receive insured health services and records birthdate, sex and geographic location. Records of physician reimbursement for medical care provided are submitted under a fee-for-service arrangement, and contain information on patient diagnosis at the 3-digit level of the ICD-9-CM classification

system and physician specialty. Separation abstracts for hospital services provided include information on 16 ICD-9-CM diagnostic codes, of which the first is the diagnosis that is most responsible for the hospital stay. Prescriptions dispensed which are submitted by retail pharmacies for reimbursement by provincial drug insurance plans or for drug utilization review purposes, contain data on the date of prescription dispensing, drug name, strength, and dosage form, and a 9-digit drug identification number. Record linkages between these databases were created by the use of anonymous personal identifiers. Statistics Canada Census 1995 household income data, aggregated to the geographic unit of the enumeration area, were used to rank neighbourhood income quintiles from 20% of the population residing in the lowest income to 20% of the population residing in the highest income neighbourhoods. [17;18]

From a total of 174,208 children, aged 5-15 years as of January 1, 1995, identified in the MSHIP registry, 48,146 children were registered until March 31, 1998 and met the following case definition for asthma: 1) at least one diagnosis of asthma or bronchitis in any diagnosis field on a physician claim or hospital abstract record, or 2) in the absence of asthma/bronchitis diagnoses, one prescription for an inhaled corticosteroid or other prophylaxis drug, or one prescription for ketotifen concomittant with a bronchodilator, or two prescription records for a bronchodilator during the time period January 1, 1995 – March 31, 1998. To identify children in treatment with asthma drugs, children were further selected on the basis of at least one prescription for an asthma drug in the 12 month period prior to and the 24 month period following the policy change to the Pharmacare program in April 1,1996. Subsequently 10,918 children constituted the study

cohort of children with asthma. The study was broken down into three evaluation periods: 1) a 12 month period prior to policy change, 2) the first 12 month period following policy change and 3) the second 12 month period following policy change.

Children were placed into income quintile neighbourhoods according to the 6-digit postal code of the household in which they lived, excluding 2 children who could not be classified. The cohort of children was then categorized into three drug program groups: 1) non-Pharmacare children (control group), 2) Pharmacare children who lived in the lowest neighbourhood income quintile, with an average annual income of approximately $15,000 ("low income Pharmacare"), and 3) Pharmacare children who did not live in the lowest neighbourhood income quintile ("high income Pharmacare"). Non-Pharmacare children represented children living in households receiving free prescription benefits from social assistance or treaty status Indian benefits programs. Non-Pharmacare children had been selected as a control group because there had been no change to pharmaceutical reimbursement policy for this group during the study period.

In order to disentangle policy-induced changes in inhaled corticosteroid use from alterations in asthma severity over the three year study period, children were classified according to level of asthma severity. An asthma severity instrument had been developed to assign asthma severity on the basis of prescription and hospitalization records, and was found to have had good reliability and validity. Four groups of asthma severity were created for the analysis: 1) children with mild to moderate asthma in the three evaluation periods, 2) children with severe asthma before change in policy, but in whom asthma had

decreased in severity during the two years after change, 3) children with mild to moderate asthma before change in policy, but in whom asthma had increased in severity in the two years after change, and 4) children with moderate-severe and severe asthma in the three time periods.

The impact of the change to the income-based pharmaceutical reimbursement policy was evaluated in all cohort children, as the monthly likelihood of a prescription for an inhaled corticosteroid, and among children receiving inhaled corticosteroid drugs, as the mean number of inhaled corticosteroid doses. The monthly likelihood of a prescription for an inhaled corticosteroid was evaluated one year before and the first year after, and one year before and the second year after the new policy. For each of the two comparisons, a Mantel-Haenszel likelihood ratio and 95% confidence interval were reported per program and asthma severity group, stratified by month to adjust for seasonal variations. In cases where there was significant month-to-month heterogeneity, month-specific odds ratios were examined. The mean number of inhaled corticosteroid doses per child-year among users was derived from the prescription quantity recorded in the database and the standard unit sizes of inhalers. A split-unit analysis was conducted to determine whether the mean inhaled corticosteroid dose in the pre and post policy time periods was related to the program group, and whether there existed an interaction between the program group and asthma severity. Results of the split-unit analysis were reported in terms of least square means and 95% confidence intervals.

RESULTS

Forty-five percent of the study cohort, aged 5-15 years, had received a prescription for an inhaled corticosteroid during the time period April 1995-March 1996. In the month of April 1995, approximately 10% of children had received a prescription for an inhaled corticosteroid. Overall, the monthly proportion of children utilizing inhaled corticosteroids decreased in the following three years to 8% in March 1998, with peaks in use reported for March, May, September and December. (Figures 5.5.1-5.5.5) Peaks in March were observed among Pharmacare children, but not control group children. The proportion of inhaled corticosteroid use over time varied by level of asthma severity. In the control group, this proportion decreased over the study period for children with stable, mild or with decreasingly severe asthma. Among control group children with stable severe asthma utilization remained the same, and in those with increased asthma severity, the proportion increased over time.

Adjusting for asthma severity, the likelihood of an inhaled corticosteroid prescription in the first year following policy change, in comparison to the previous year, was dependent on the program group. (Table 5.5.1). Among children with stable, mild-moderate asthma the likelihood of inhaled corticosteroid use was unchanged in the control and low income Pharmacare groups, but was significantly decreased in the higher income Pharmacare group. The likelihood of inhaled corticosteroid use was significantly decreased in all children with decreasingly severe asthma. Increased asthma severity over the time period was associated with a significant increase in likelihood of inhaled corticosteroid use in all

groups. Among children with stable severe asthma, inhaled corticosteroid use remained unchanged in the control and low income Pharmacare groups, but was significantly less likely in high income Pharmacare children. Similar patterns in likelihood ratios for inhaled corticosteroid use were observed in the second year after change to policy, with the exception that the likelihood of use among children with mild-moderate asthma was significantly decreased in all children. Significant heterogeneity in the monthly likelihood of inhaled corticosteroid use was observed only in the high income Pharmacare group. Closer inspection of monthly odds ratios for high income Pharmacare children with increased asthma severity, showed a significantly increased likelihood of inhaled corticosteroid in the months of September, October, November, January and March.(Table 5.5.2)

A total of 7,221 children had received at least one prescription for an inhaled corticosteroid during the 3-year study period. Consumption of inhaled corticosteroid doses remained constant for the control group pre and post-policy, but decreased among low and high income Pharmacare children. (Figures 5.5.6-5.5.11) Children with severe asthma received a significantly higher number of doses of inhaled corticosteroid than children with mild asthma. The average dose of inhaled corticosteroid was not significantly different among control and low income Pharmacare children with stable, mild-moderate asthma in the pre and post policy periods, but decreased significantly in high income Pharmacare children. Among children with a decline in asthma severity, the mean dose of inhaled corticosteroid significantly decreased pre and post policy, but this finding was not significant in the low income Pharmacare group. Similarly, the mean

dose increased with greater asthma severity post policy, but this increase reached statistical significance only in the control and high income Pharmacare groups. However, among high income Pharmacare children with stable severe children, the mean number of doses of inhaled corticosteroid decreased significantly in the post policy period. The mean number of doses remained unchanged for both low income Pharmacare and control children, but was significantly lower in the low income Pharmacare than the control group. In the pre-policy period the mean dose of inhaled corticosteroid was not significantly different among control and high income Pharmacare children, but in the second year post-policy the mean dose in high income Pharmacare children was significantly decreased.

DISCUSSION

Over all, the proportion of children utilizing inhaled corticosteroid drugs decreased over the three year study period, consistent with the natural history of wheezing symptoms in children.[19;20] Observations of monthly peaks in utilization of inhaled corticosteroid drugs were also compatible with reports of seasonal variations of asthma symptoms or hospitalization. Peaks observed in May and September have been attributed to seasonal exposure to allergens, [21;22] and peaks in December to increased exposure to respiratory viruses.[21;23] Inhaled corticosteroids are not effective in the symptomatic treatment of asthma attacks,[16] but parents anticipating seasonal worsening of symptoms may be prompted to obtain an adequate supply of prophylactic inhalers. In addition, some treatment regimens recommend a doubling of inhaled corticosteroid dose during periods

of increased symptoms.[24] The peak observed in March among Pharmacare-eligible children was likely the outcome of parents obtaining prescriptions before the annual deductible payment was reset for the upcoming fiscal year.

Adjusting for asthma severity and monthly variation, the most notable finding was a significantly decreased likelihood of an inhaled corticosteroid prescription post income-based policy in higher income Pharmacare children with severe asthma. Among higher income Pharmacare children with severe asthma continuing to receive inhaled corticosteroid prescriptions, utilization decreased from a mean of approximately one dose of inhaled corticosteroid per day to about 300 doses per year. These findings are not dissimilar to other reports of a decline in utilization of essential prescription drugs following changes to pharmaceutical policies which impose increased costs on its recipients. [6-8;12] The finding of heterogeneity in monthly use of inhaled corticosteroid among higher income Pharmacare, but not control group children is also noteworthy, suggesting that Pharmacare recipients had changed their prescription acquisition behaviour to accommodate the new policy. Under the new policy of 100% reimbursement following payment of the annual deductible, parents were potentially further motivated to obtain their prescriptions in March before the end of the fiscal year. Moreover, an increased likelihood of inhaled corticosteroid use in children with increasing asthma severity only during months which are associated with increased prevalence of asthma symptoms (ie October, January), suggest that parents were delaying their prescription refills to high need periods. Payment problems for prescriptions frequently have resulted in requests that drug items on a prescription not be filled at first presentation of the

prescription; [25] corticosteroid, but not bronchodilator inhalers are examples of drugs which are not collected.[26]

Prior to the income-based policy, the mean number of doses of inhaled corticosteroid per child with severe asthma was significantly lower among low income Pharmacare than control children, and this difference widened post policy. Control group children also lived in low income households, but as part of social assistance benefits provided to their families, their parents obtained their prescription drugs free of charge. These findings point to a further outcome of the new Pharmacare policy: the income-based policy did not improve drug utilization among low income Pharmacare children, despite diminishing cost barriers to acquiring these drugs. Low income adults report problems in being able to pay for their children's asthma prescriptions,[27] and are less likely to fill prescriptions for asthma drugs. [28] A very high deductible level relative to inhaled corticosteroid prescription may explain why higher income families would decrease their use of these drugs. Moreover, it also potentially explains why low income families failed to increase utilization of these drugs. The annual deductible of approximately $300.00 for families earning less than $15,000.00 was not much different from the pre-policy deductible amount, and would require out-of-pocket payments for an annual supply of corticosteroid inhalers.

Threats to internal validity were minimized in this study through the use of multiple measurement endpoints pre and post policy in a well defined population at risk, in comparison to a well-chosen control population.[2] Furthermore, this study has illustrated

the importance of controlling for changes to asthma severity when describing trends in inhaled corticosteroid utilization in children over time. One would expect inhaled corticosteroid use to decrease in a cohort of "asthmatic" children with age, subsequent to the cessation of transient wheezing syndromes later in childhood.[19;20] As asthma severity is greater in lower income children,[29] the inclusion of an asthma severity measure would be especially important in comparisons across income. Nonetheless, trends in inhaled corticosteroid use pre and post change to pharmaceutical policy were potentially confounded by the asthma severity measure. Children with mild or moderate asthma were grouped together, as were children with moderately severe or severe asthma. It is possible that higher income Pharmacare children with severe asthma in both time periods decreased their use of inhaled corticosteroid because they had experienced decreased severity which was not captured by the present asthma severity classification. Furthermore, the potential existed for a Type II error in the pre and post policy comparisons of inhaled corticosteroid use in low income Pharmacare children with severe asthma, such that inhaled corticosteroid use may have also been decreased post policy in this group, as well as higher income Pharmacare children.

Cost barriers to the use of prescription drugs in the management of chronic disease impose increased morbidity among those affected. [10;30;31] Lower utilization of inhaled corticosteroids has been associated with increased hospitalization for asthma. [30;32] Hospitalization for asthma contributes substantially to the costs of managing this disease.[33-35] and affects the quality of life of asthmatic children.[36] Despite an increase in use of inhaled corticosteroid over the last ten years, [37-39] inhaled

corticosteroids remain underutilized.[40-43] It is therefore, imperative that pharmaceutical reimbursement policy not be a deterrent to the utilization of these drugs, especially in children, among whom prescription payment problems are more common.[25;26] In our era of cost containment, income-based pharmaceutical benefit policies appear to be good choices for equitably distributing the burden of prescription costs.[44] However, the impact of these policies on prescription utilization requires evaluation and if necessary, as done in other jurisdictions, readjustments need to be made to levels of patient cost sharing.[25]

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Table 5.5.1.Likelihood of a Prescription for an Inhaled Corticosteroid Drug Before and After Income-Based Policy by Drug Program Group,Adjusting for Monthly Variation*

	High income Pharmacare household	Low income Pharmacare household	Control group**
A. One Year Before and One Year After Change to Income-Based Policy			
Mild-Moderate asthma before and after policy	0.81 [0.77-0.85]	0.86 [0.73-1.01]	0.95 [0.85-1.06]
Decreased asthma severity after policy	0.68 [0.63-0.74]	0.69 [0.53-0.90]	0.65 [0.53-0.79]
Increased asthma severity after policy	1.16 *** [1.06-1.27]	1.55 [1.18-2.03]	1.69 [1.40-2.03]
Severe asthma before and after policy	0.83 [0.77-0.89]	0.8 [0.64-1.00]	1.03 [0.90-1.17]
B. One Year Before and Second Year After Change to Income-Based Policy			
Mild-Moderate asthma before and after policy	0.68 *** [0.65-0.71]	0.68 [0.57-0.80]	0.87 [0.78-0.97]
Decreased asthma severity after policy	0.55 *** [0.50-0.60]	0.45 [0.33-0.60]	0.58 [0.47-0.71]
Increased asthma severity after policy	1.22 *** [1.11-1.33]	1.35 [1.02-1.79]	1.76 [1.46-2.11]
Severe asthma before and after policy	0.82 [0.77-0.88]	0.86 [0.69-1.08]	1

*Mantel-Haenszel OR and 95% confidence intervals, ** Non-Pharmacare households

*** Breslow-Day test for heterogeneity of monthly OR's indicating that they should not be combined

Table 5.5.2. Monthly Likelihood of an Inhaled Corticosteroid Prescription in High Income Pharmacare Children with Increased Asthma Severity Before/After Income-Based Policy

Month	First Year After Policy		Second Year After Policy	
April	0.78	[0.57-1.08]	0.77	[0.56-1.07]
May	1.03	[0.78-1.37]	1.01	[0.76-1.34]
June	1.2	[0.86-1.66]	1.21	[0.88-1.68]
July	0.96	[0.70-1.33]	1.22	[0.90-1.65]
August	0.75	[0.53-1.05]	1.21	[0.89-1.64]
September	1.28	[0.97-1.68]	1.45	[1.11-1.90]
October	1.42	[1.07-1.89]	1.23	[0.91-1.65]
November	1.64	[1.18-2.28]	1.71	[1.23-2.38]
December	1		0.88	[0.66-1.17]
January	1.5	[1.04-2.15]	1.71	[1.20-2.43]
February	1.39	[0.98-1.97]	1.3	[0.91-1.85]
March	1.44	[1.08-1.94]	1.39	[1.03-1.87]

Figure 5.5.1. Proportion of All Asthma Cohort Children Receiving an Inhaled Corticosteroid Prescription on a Monthly Basis by Drug Program and Income Status, 01/95-03/98

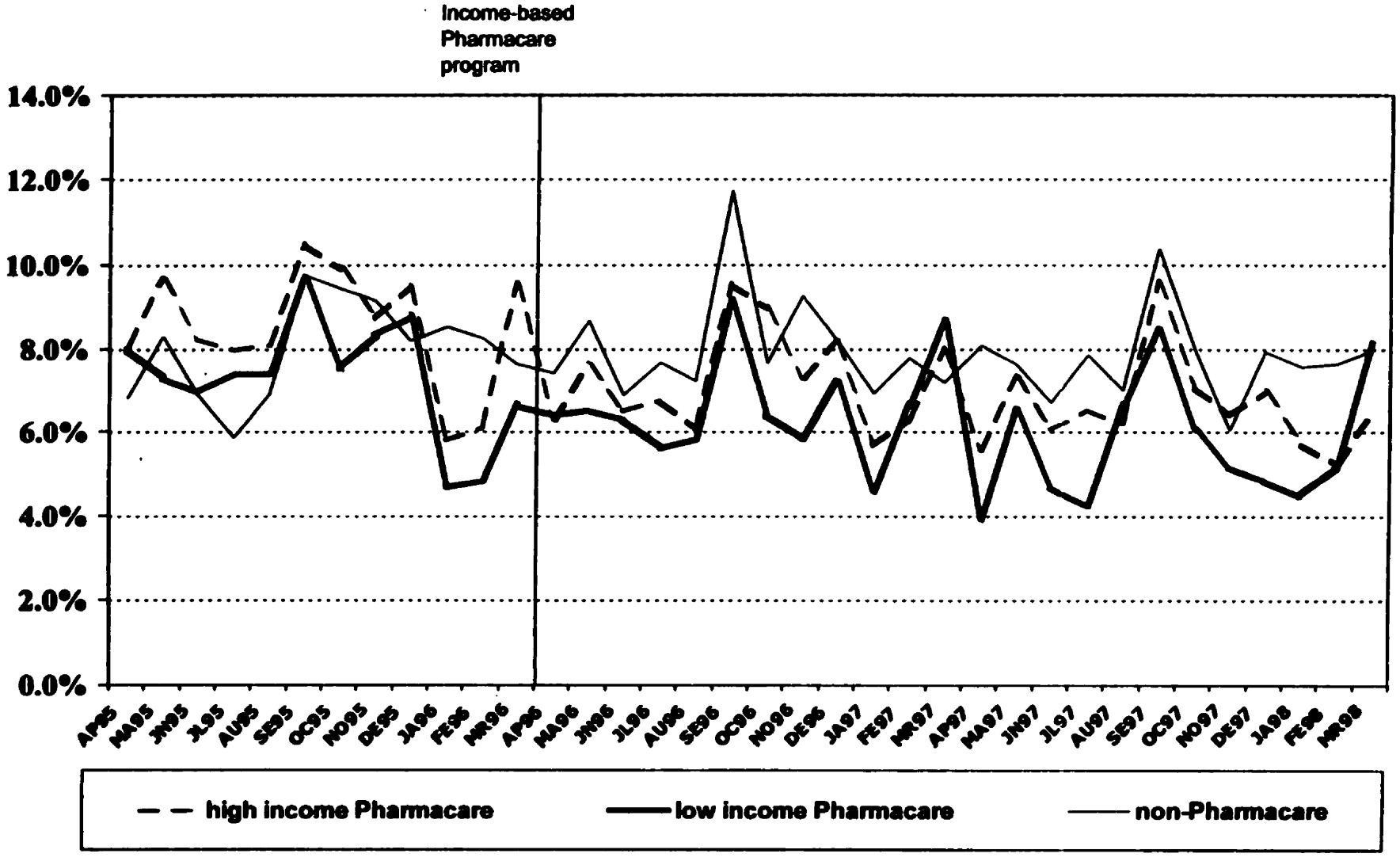


Figure 5.5.2. Proportion of Asthma Cohort Children with Stable Mild/Moderate Asthma Receiving an Inhaled Corticosteroid Prescription on a Monthly Basis by Drug Program and Income Status, 01/95-03/98

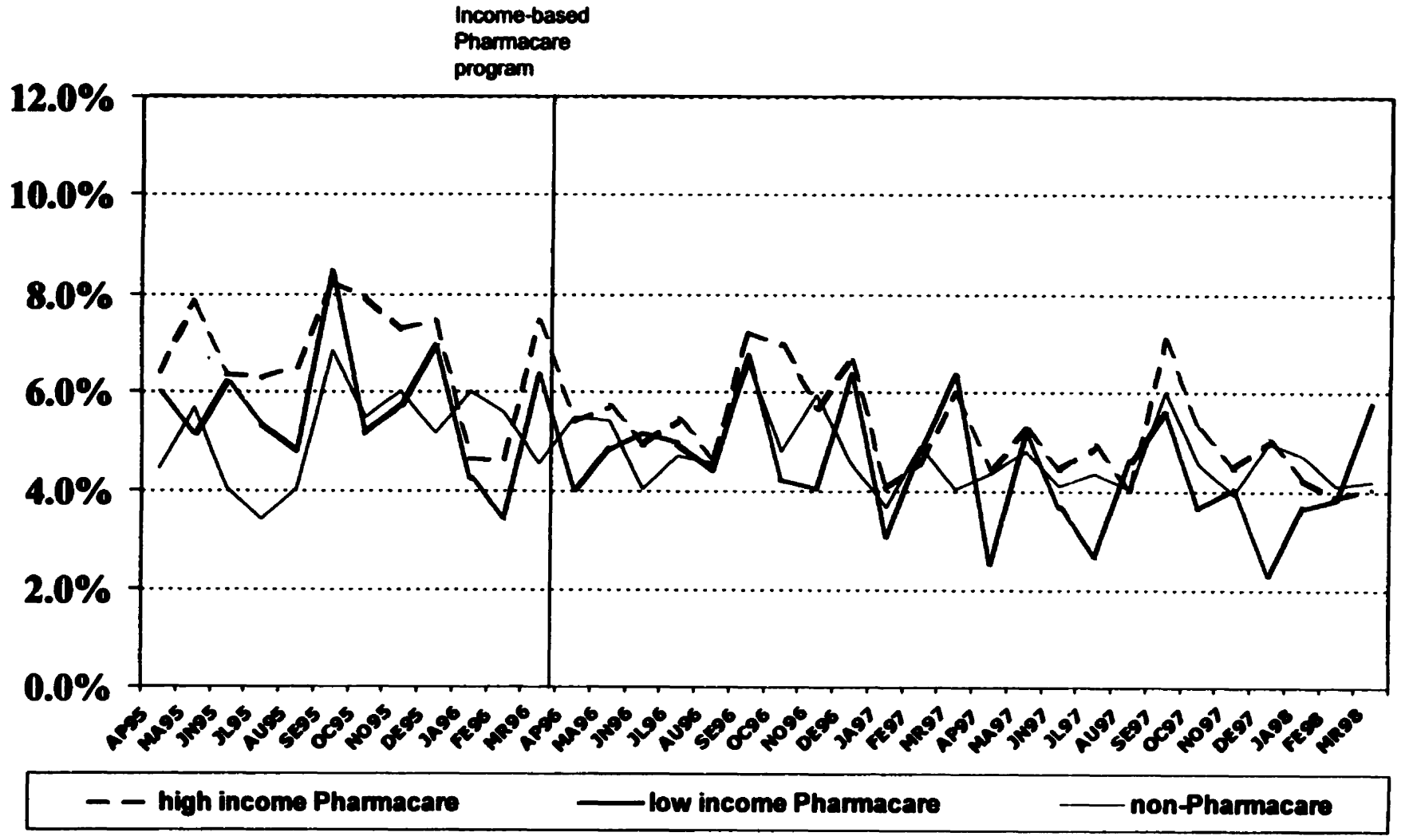


Figure 5.5.3. Proportion of Asthma Cohort Children with Decreasingly Severe Asthma Receiving an Inhaled Corticosteroid Prescription on a Monthly Basis by Drug Program and Income Status, 01/95-03/98

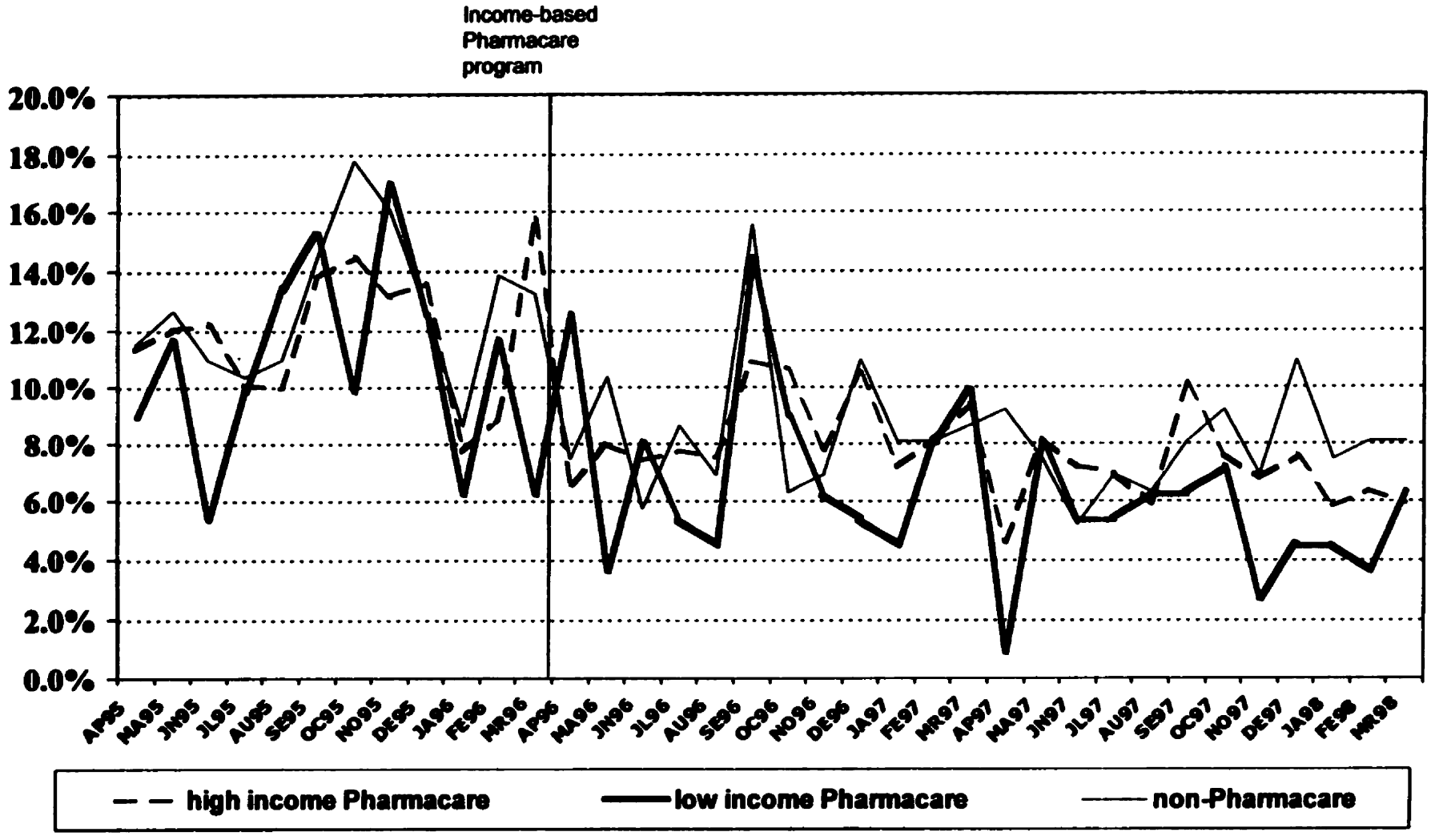


Figure 5.5.4. Proportion of Asthma Cohort Children with Increasingly Severe Asthma Receiving an Inhaled Corticosteroid Prescription on a Monthly by Drug Program and Income Status, 01/95-03/98

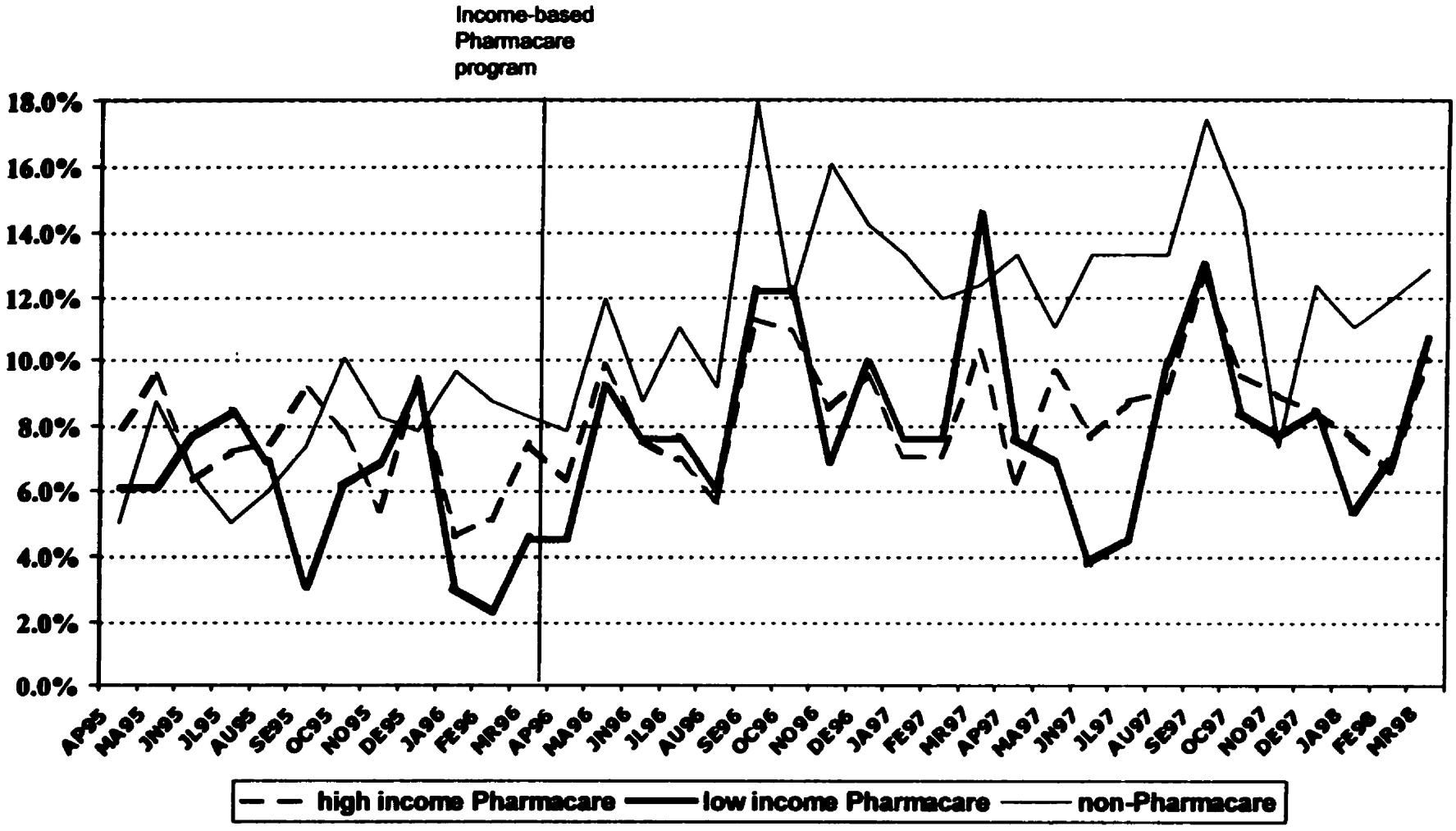


Figure 5.5.5. Proportion of Asthma Cohort Children with Stable, Severe Asthma Receiving an Inhaled Corticosteroid Prescription on a Monthly Basis by Drug Program and Income Status, 01/95-03/98

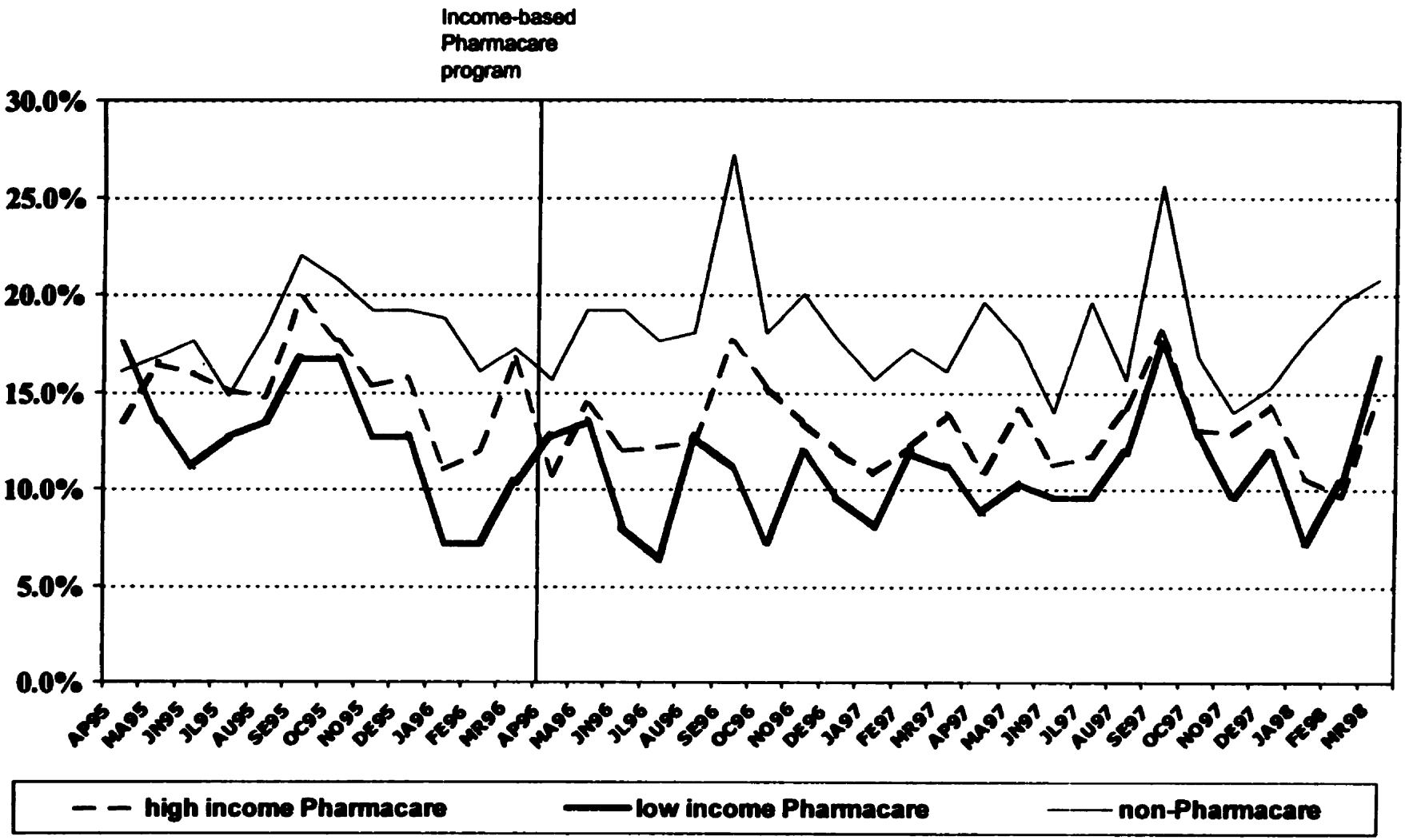


Figure 5.5.6. Mean Number of Inhaled Corticosteroid Doses (95% CI) in Children with Asthma Before and After Income-based Policy by Drug Program and Income Status

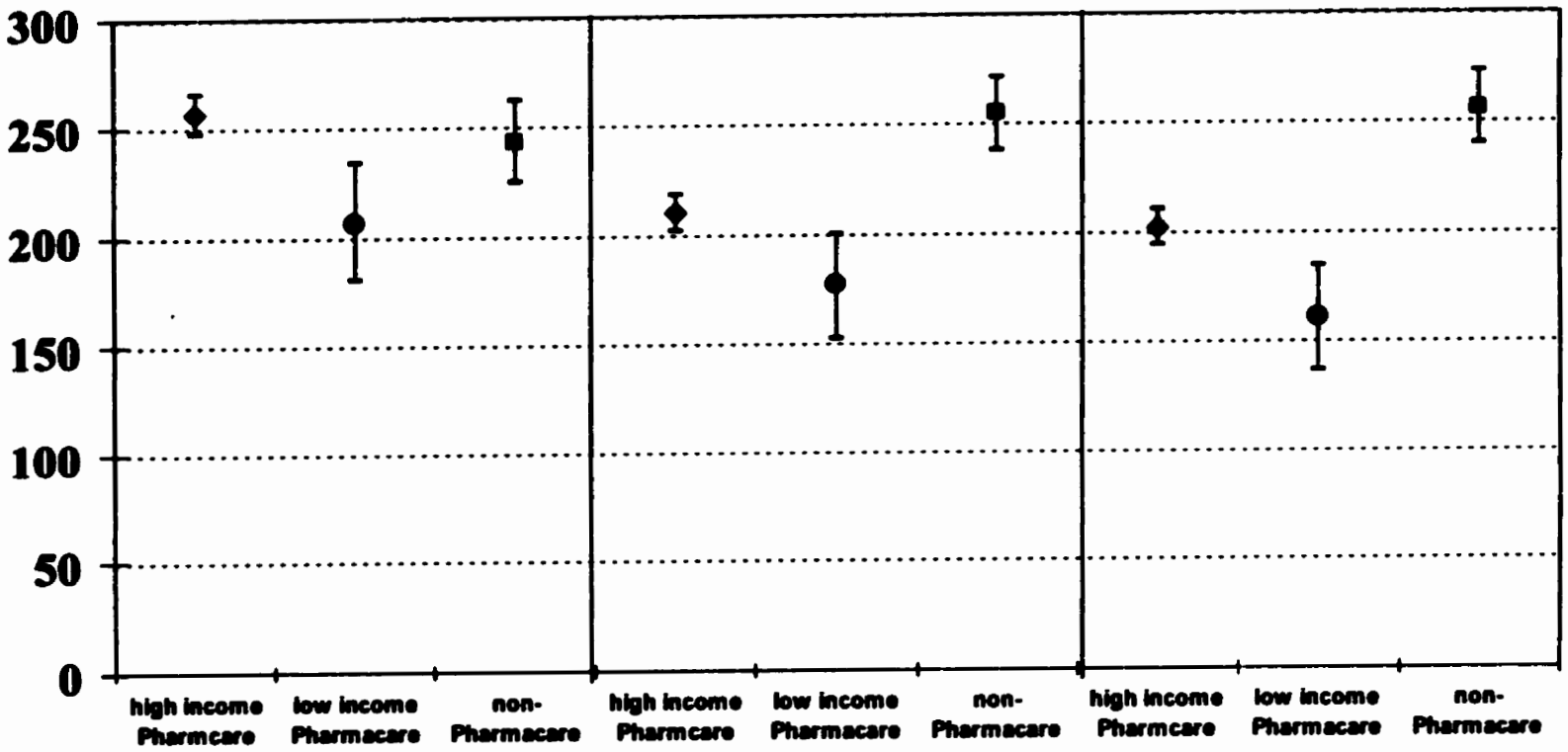


Figure 5.5.7. Mean Number of Inhaled Corticosteroid Doses (95% CI) in Children with Asthma Before and After Income-based Policy by Asthma Severity

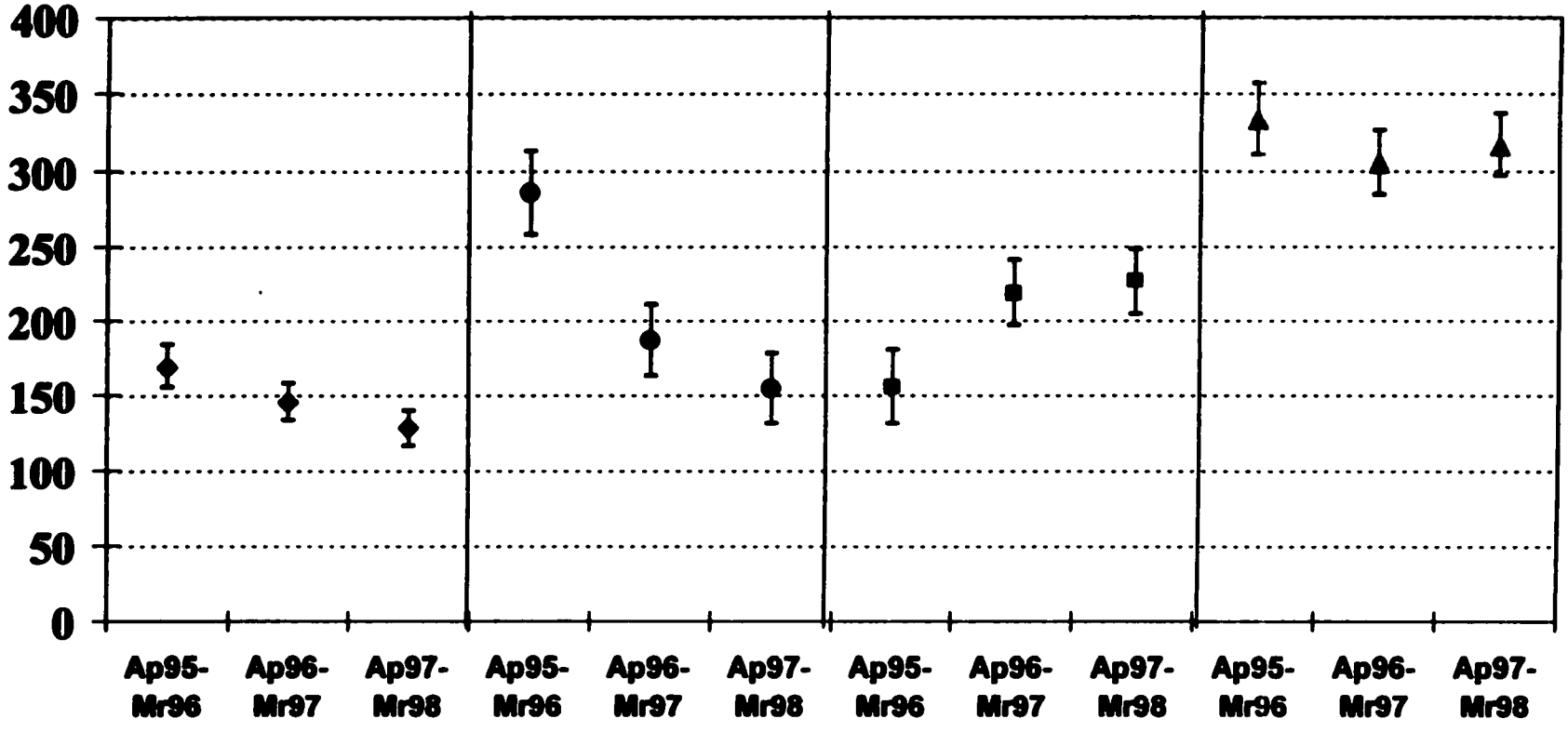


Figure 5.5.8. Mean Number of Inhaled Corticosteroid Doses (95% CI) in Children with Stable, Mild Asthma Before and After Income-based Policy by Drug Program and Income Status

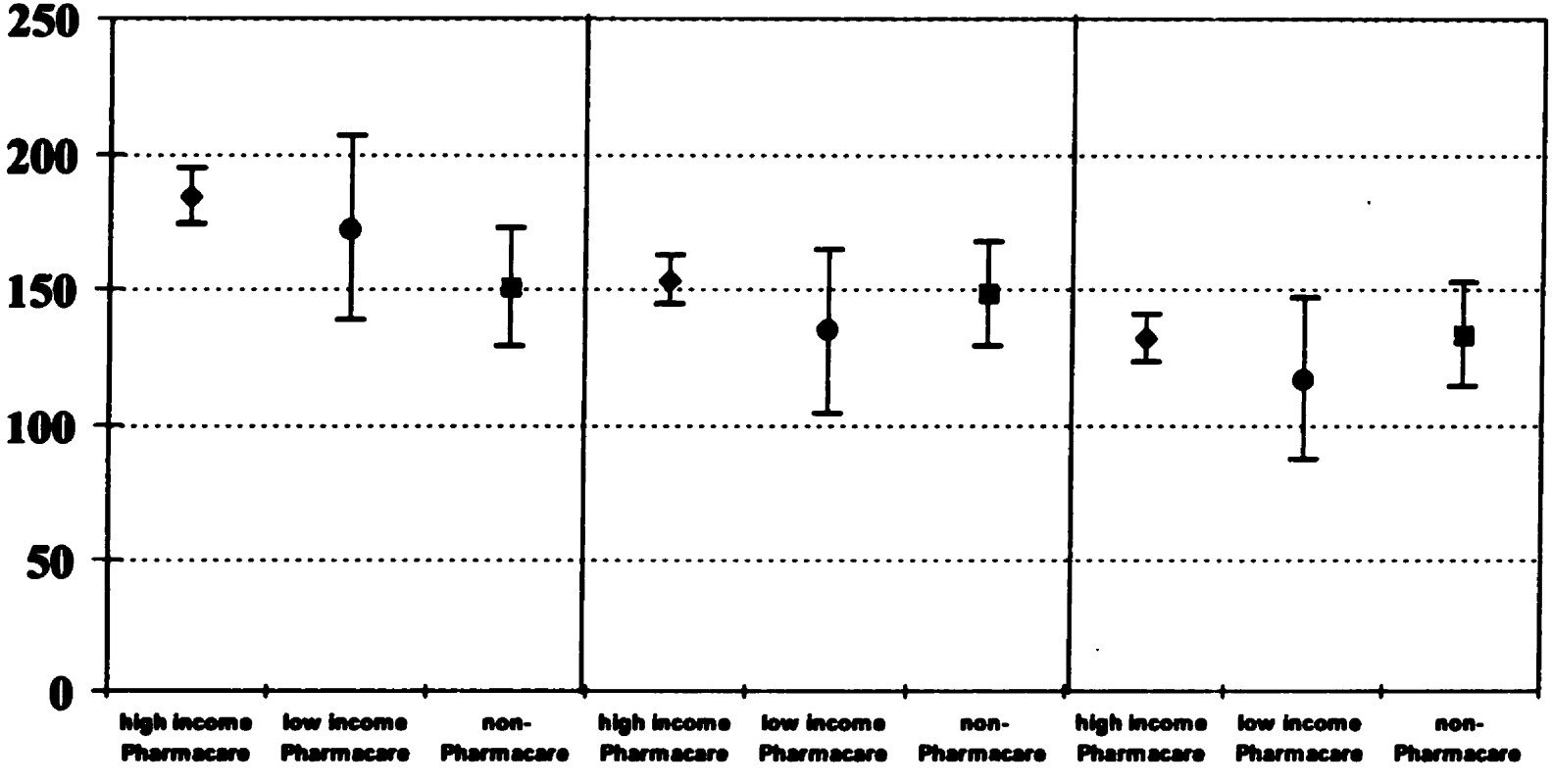


Figure 5.5.9. Mean Number of Inhaled Corticosteroid Doses (95% CI) in Children with Decreased Asthma Severity Before and After Income-based Policy by Drug Program and Income Status

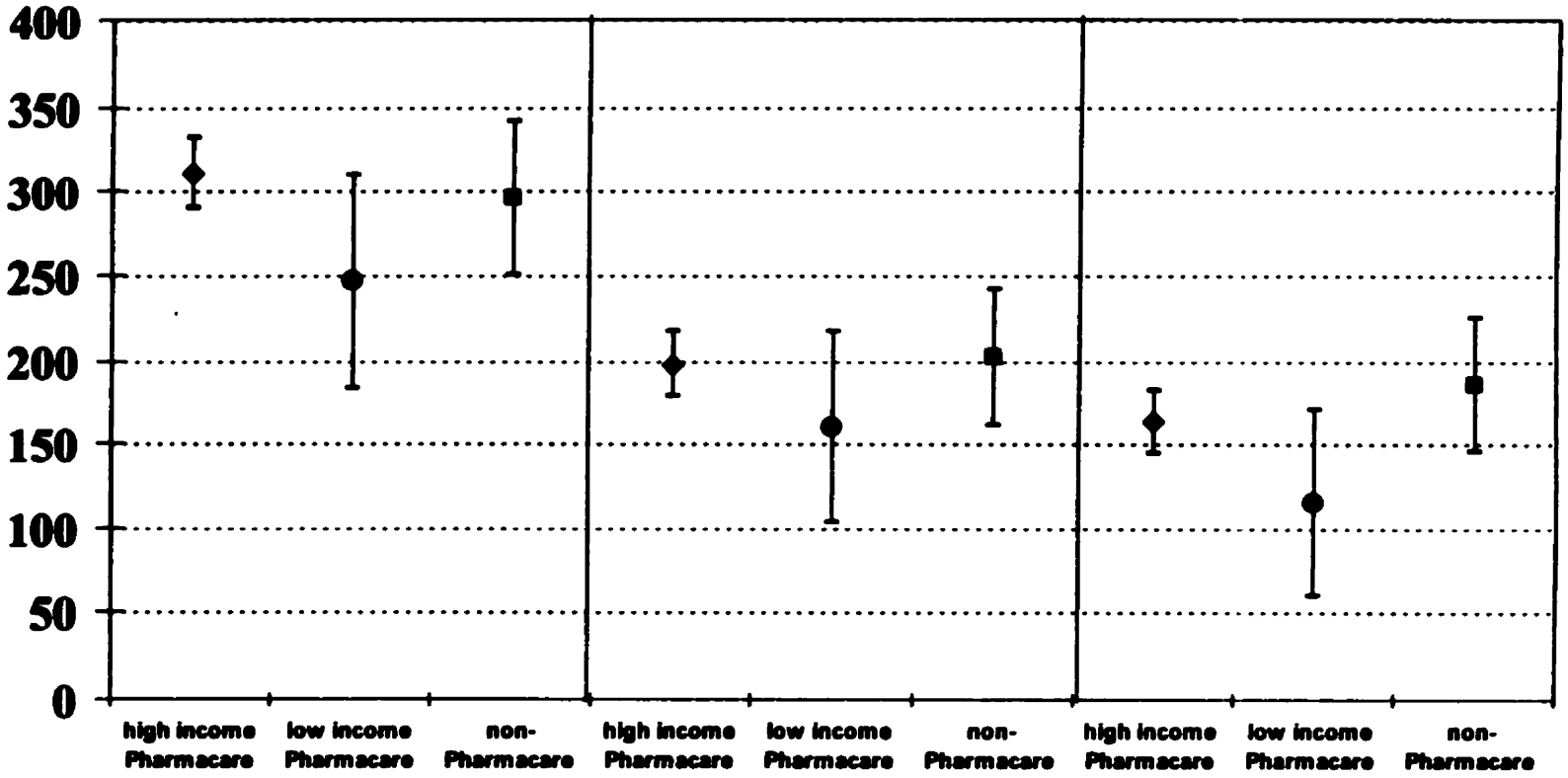


Figure 5.5.10. Mean Number of Inhaled Corticosteroid Doses (95% CI) in Children with Increased Asthma Severity Before and After Income-based Policy by Drug Program and Income Status

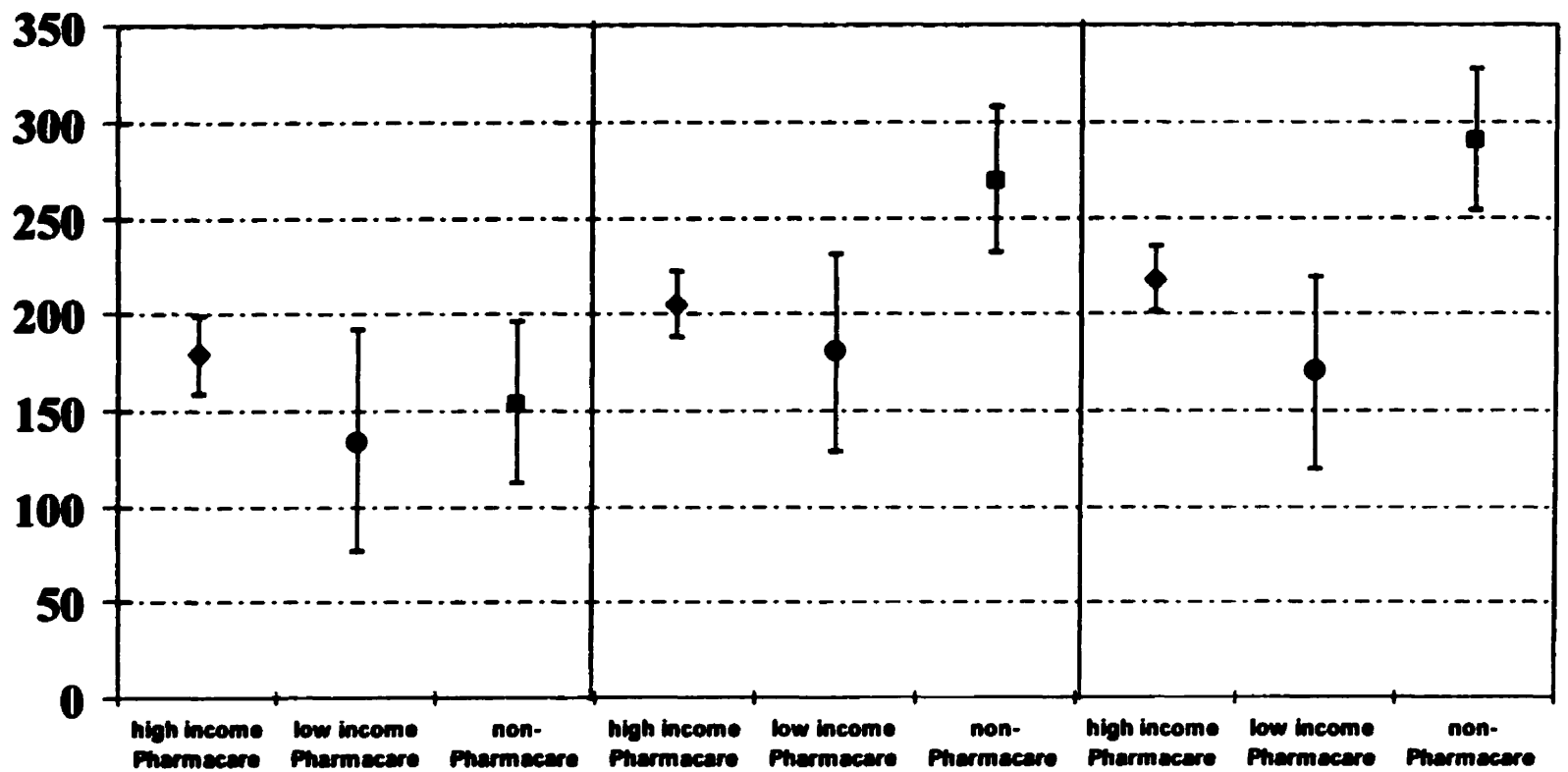
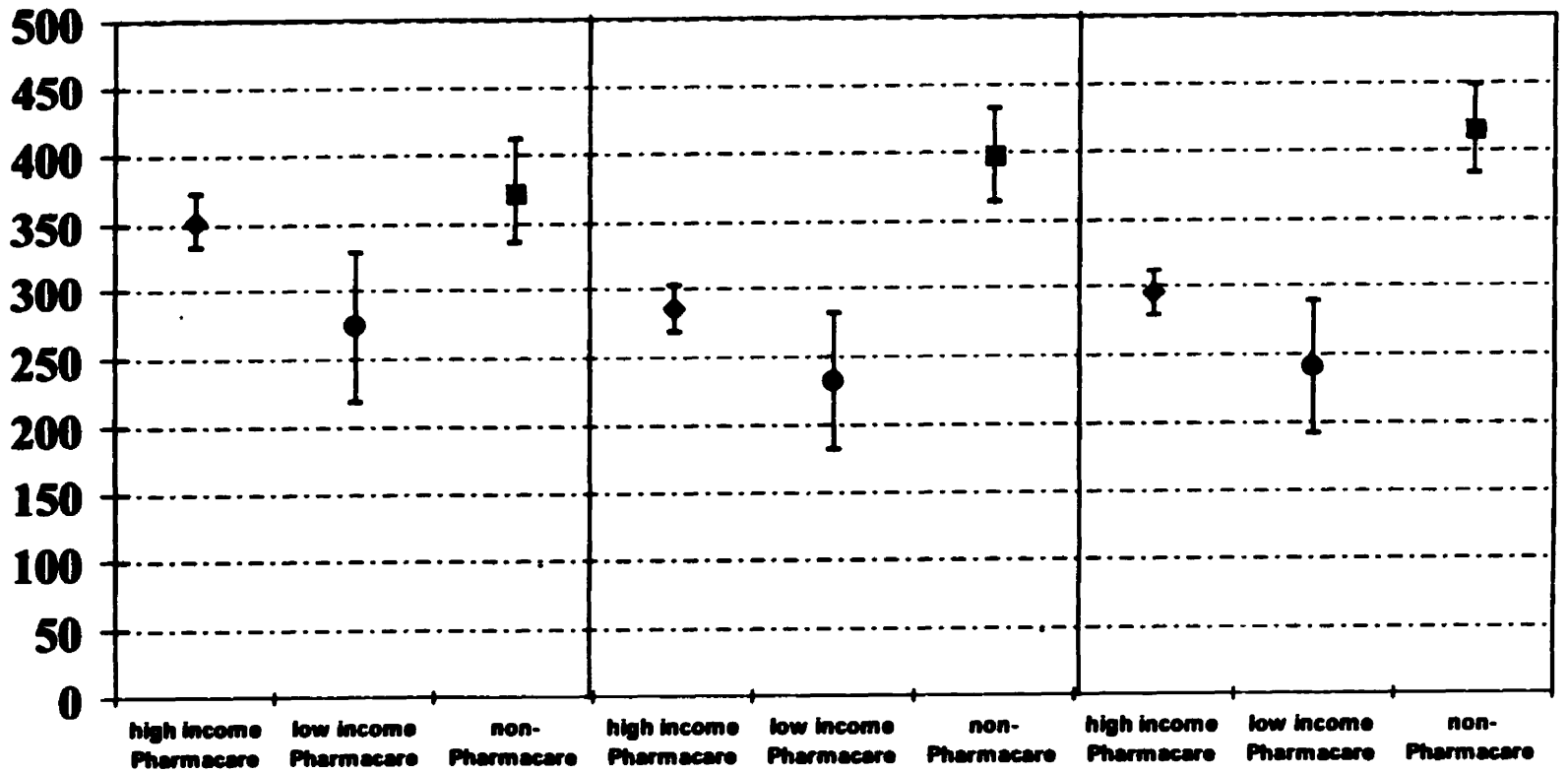


Figure 5.5.11. Mean Number of Inhaled Corticosteroid Doses (95% CI) in Children with Stable, Severe Asthma Before and After Income-based Policy by Drug Program and Income Status



Chapter 6. Socioeconomic status, inhaled corticosteroid utilization and asthma hospitalization in children

The reader was introduced to the literature on the effect of household income and pharmaceutical policy on the utilization of inhaled corticosteroid drugs in asthmatic children in the previous two chapters. The dissertation research has documented that asthmatic children living in low income households were less likely to receive prescriptions for inhaled corticosteroid drugs, and that an income-based pharmaceutical policy did not improve utilization in low income children. Does sub-optimal utilization of inhaled corticosteroid drugs contribute to the increased risk of asthma hospitalization observed in low income children? This question is addressed in the current chapter. Initially a review of the empiric literature on socioeconomic status and asthma hospitalization is presented. Thereafter, dissertation findings on the association between household income and asthma hospitalization in children, and on whether the association can be explained by inhaled corticosteroid utilization, are presented.

6.1 Epidemiology of asthma hospitalization in children

From recent population-based surveys of Canadian children it is estimated that 11% of children less than 14 years old, have asthma [1] and that 13% of school-children, aged 5-19 years have current asthma, defined as a physician-diagnosis of asthma, or recent symptoms of wheezing, asthma attacks or asthma medication use.[2] A 1995/96 school-based survey reported that 20% of students had visited an emergency department in the last year and 4 % were hospitalized for

asthma. Similar asthma hospitalization rates have been reported in Manitoba and other jurisdictions.[3;4] Asthma hospitalization rates in children had increased by 40 to 50% over the last two decades, but rates have begun to plateau in the 1990s, more so in school-age than preschool children. [1;5-8] The hospital readmission rate among Canadian children with asthma has remained stable in the early 1990's; the one-year readmission rate for asthma among children, 5-17 years old, has been reported to be 17%. [6]

The burden of hospitalization for asthma is unevenly distributed among children. Several small area analysis and survey-based studies have drawn linkages between low socioeconomic status and hospitalization for asthma. Wissow et al found asthma hospitalization rates among Maryland children in 1979/82 to be highest among Medicaid children. [9] Area poverty rates explained 30% of the variation in asthma hospitalization. Targonski et al documented higher asthma hospitalization rates among Chicago children living in low socioeconomic status households in 1987/89.[10] The median household income explained 30% of the variation in asthma hospitalization. Data from the 1988 US National Health Interview Survey showed that children living below the poverty index were 40% more likely to be hospitalized for asthma, than children living above the poverty line.[11] Higher socioeconomic status, as measured by family income or education level, was associated with a decreased risk of hospitalization in Lieu et al's study of 1,498 children, enrolled in a US health maintenance organization in 1995.[12]

An association between hospitalization for asthma and lower socioeconomic status has also been documented in Canada and Europe, including several universal health care insurance settings. In the 1994/95 Italian Studies on Respiratory Disorders in Childhood and the Environment study,

hospitalization for asthma among Italian children was negatively correlated with household socioeconomic status.[13] Watson and colleagues found a strong association between socioeconomic status, as measured by the Townsend index, and asthma hospitalization rates in UK children.[14] Erzen et al's evaluation of Manitoba children, <14 years, documented that children living in low income quintiles were hospitalized almost twice as often than those in higher income quintiles, in 1988 and 1992.[3] Furthermore, asthma hospitalization rates have increased disproportionately in lower income children over the past decade. [3;15]

6.2 Asthma hospitalization in lower income children

Asthmatic children who have more frequent symptoms are more likely to be hospitalized or visit the emergency department.[12;16] In the 1988 US National Health Interview Survey, children with severe asthma were hospitalized 10 times as often as children with mild disease. Numerous studies have reported more frequent asthma symptoms among children of lower, than higher socioeconomic status. [17-19] Children with asthma living in lower socioeconomic status households are more likely to experience limitations in activity such as absence from school or confinement to bed, than asthmatic children living in higher income household.[4;20] It is however, difficult to ascertain whether increased symptom frequency in low income children represents greater inherent asthma severity or poor control of asthma symptoms.[21] Children with asthma which is well-controlled with drug therapy experience fewer exacerbations than children with poorly controlled asthma.[22] However, despite optimal drug treatment, children with severe asthma experience more symptoms than children with mild asthma.[23]

Several hypothesis have been proposed to explain the higher asthma hospitalization rates among low income children: 1) greater inherent asthma severity, 2) poor symptom control subsequent to increased exposure to environmental allergens and 3) poor symptom control subsequent to decreased treatment with prophylactic medication, such as inhaled corticosteroids.

6.2.1 Inherent asthma severity

Little is known about the risk factors determining the inherent severity of asthma in an individual and/or influencing the progression of mild asthma to more severe forms of the disease. Several factors have been postulated as contributing to asthma severity, including inflammatory, structural, hereditary/congenital and environmental factors.[24] Prematurity is a congenital factor which increases the likelihood of asthma, [25;26] and the prevalence of prematurity is higher in lower income populations.[27] Children at risk for asthma because of a positive family history have been reported to be significantly more likely to develop asthma by age 11 years if they were exposed to high levels of dust mite allergens at one year of age. [28] In this study, children with exposure to higher levels of house dust mite allergens were more likely to wheeze at an earlier age. Lower income children have been reported to have greater exposure to indoor allergens, such as house dust mite and cockroach debris, [29-32] to household smoke, [33;34] and to respiratory infections [35] Greater exposure to allergens may increase the likelihood of early onset asthma and longer-standing airway inflammation in lower income children, leading to structural changes in the bronchial wall and more severe asthma.[36]

Greater exposure to multiple allergens may further increase the likelihood of severe asthma in low income children.[24] Asthma severity, determined on the basis of asthma drug utilization

and symptom measures, and pulmonary function tests have been found to be related to the degree of sensitization to individual allergens, or to the total number of positive skin tests to different allergens.[29;30] A positive gradient in the proportion of asthmatic children exposed or sensitized to indoor allergens has been documented with decreasing household socioeconomic status.[31] There is some preliminary evidence that allergen sensitization among low income children increases the likelihood of asthma morbidity upon exposure to allergens. Rosenstreich et al's evaluation of low income, inner-city children showed that exposure to high levels of cockroach allergen increased asthma hospitalizations and school-days missed to a greater extent if there was prior sensitization to the cockroach allergen.[37] Furthermore, the ability of sensitization to individual allergens to predict asthma severity is dependent on household income status. In Togias et al's study, the strength of the association between asthma severity and cockroach sensitization was strongest among adolescents from the lowest income households, while the association with exposure to tobacco smoke was strongest in higher income adolesecents. [29] A greater number of positive skin tests was as likely to be predictive of severe asthma in low, as in high income children.

6.2.2 Asthma control and exposure to environmental allergens

Greater exposure to indoor allergens such as tobacco smoke, house dust mite and cockroach debris, and community allergens such as viruses and pollutants, has worsened asthma symptoms and lung function, and increased hospitalization in children with asthma. Household dampness, mould growth or mattress dust mite levels have been found to be positively related to the frequency of wheezing, medication requirements or pulmonary function tests in asthmatics. [38;39] Similarly, in a sample of 151 adolescents living in the US, positive skin tests for the

cockroach and dust mite allergen, which are correlated with allergen exposure, were related to increased symptom frequency, school or work days lost, activity limitation and health care use. [29;31] The US National Cooperative Inner-city Asthma Study documented that children with high exposure to cockroach allergen were significantly more likely than children with low allergen exposure to miss school, loose sleep, wheeze and be hospitalized. [37] As noted previously, this finding was only apparent in children with sensitization to cockroach allergen.

Frequent wheeze has been found to be significantly more common among children exposed to household tobacco smoke in two studies conducted in the UK.[40;41] Greater exposure to household smoking, as measured by urine cotinine levels in 199 children with asthma in the US, was also associated with an increased number of acute exacerbations.[34] The same authors found that % predicted FEV_1 decreased with increasing exposure to household smoking and urinary cotinine levels. Togias and colleagues documented an association between exposure to smoke and asthma severity in adolescents. [29] Passive smoking has increased emergency room visitation rates in asthmatic children. [42] Asthma symptom frequency in children was not found to be associated with air pollution in Finland; [43] however, higher emergency department use and hospitalization has been reported in preschool children with asthma, living in localized areas with high pollutants levels.[44;45]

Respiratory tract viruses such as influenza and rhinovirus, have been detected in 80-85% of asthma exacerbations in a group of children, aged 7-9 years, living in the UK.[46] A strong correlation between upper respiratory infection rates in children and hospitalization for asthma has also been reported.[47] Among environmental precipitants of asthma exacerbations, upper

respiratory tract infections appear to be the strongest trigger. Sarafino and colleagues reported that respiratory infections had the greatest impact on asthma severity in children. [48] From a list of asthma triggers reported by school-children in Canada, colds/chest infections accounted for 86% of triggers, followed by tobacco smoke or dust (55%) and then air pollution (32%).[2] Interventions to decrease exposure to indoor allergens, such as tobacco smoke have been successful in decreasing asthma symptoms in children.[49] Some studies suggest that despite allergen-avoidance measures, asthma exacerbations will continue to be triggered by respiratory tract infections.[50]

Greater exposure of lower income children to indoor allergens, [29;31;32] to household smoke [33;34], to respiratory infections [35] and to outdoor pollutants [51] increases their risk for poor asthma control. The effect of indoor allergen levels on asthma symptoms may be dependent on prior sensitization to the allergen.

6.2.3 Asthma control and prophylactic drug therapy

The prescription of inhaled corticosteroid medications represents a secondary prevention intervention for which there is an abundance of evidence regarding effectiveness in improving asthma symptoms.[52-55] The benefits of inhaled corticosteroids in reducing hospital admissions for asthma have been demonstrated in several small area analyses and observational studies. Communities with lower hospitalization rates for asthma have been observed to have higher inhaled anti-inflammatory drug or corticosteroid use.[56-59] The odds of fatal and near fatal asthma in persons using inhaled corticosteroids on a regular basis was significantly reduced in comparison to non-users, in Ernst et al's cohort of 12,301 persons, aged 5-54 years, receiving

asthma drug prescriptions. [60] In a cohort of 2,059 hospitalized asthmatic patients, aged 5-54 years, subjects treated regularly with inhaled corticosteroids for 16 days to 6 months were 40% less likely to be readmitted to hospital for asthma.[61] Similarly, a nested case-control study of newly treated asthma documented that subjects initiated on regular inhaled corticosteroids therapy were 40% less likely to be hospitalized, than those treated with theophyliine therapy.[62] Inhaled corticosteroids in Donahue et al's evaluation of 6,562 children decreased the risk of asthma hospitalization to one-third. [63]

The use of preventative drugs has been reported to be 7-22% less frequent among children living in lower, than higher socioeconomic status families surveyed in the UK, Australia and the US.[29;64;65] There are many barriers to the use of inhaled corticosteroids in low income children, which have been described at length in Section 3. In summary, the social environment of low income children places them at increased risk of not receiving an inhaled corticosteroid prescription. Low income children are less likely to be prescribed inhaled corticosteroid drugs because they are less likely to have a regular source of physician care or to consult with an asthma specialist. Non-adherence to inhaled corticosteroid therapy is not uncommon, but low income children appear to be especially non-adherent.[66] Greater medication non-adherence may be related to the decreased ability of low income households to obtain prescriptions for the high potency inhaled corticosteroids which are expensive, or to inadequate knowledge or misconceptions of parents regarding asthma management.

It is difficult to disentangle the contributions of under-treatment with inhaled corticosteroids versus increased allergen exposure in explaining higher hospitalization rates for asthma in lower

socioeconomic status children. A higher prevalence of more severe asthma was documented in low income children in the early 1970's, prior to the introduction of inhaled cortciosteroids as asthma prophylaxis therapy.[17] This historical evidence suggests that household socioeconomic status differences in asthma control are related to environmental factors, independent of drug therapy. Multivariate studies documenting an association between socioeconomic status and poor asthma control which cannot be explained by allergen exposure, suggest that other factors, which may include decreased use of inhaled corticosteroids, affect asthma control.[17;67] Observations of an interaction between the effect of socioeconomic status and allergen exposure on asthma morbidity suggest that low income children may not be benefiting from the protective effects of inhaled corticosteroids. [29;68] In Lieu et al's case-control of asthma hospitalization in children, family income, asthma severity and twice-monthly bedsheet washing (as a marker for allergen exposure) predicted hospitalization, but utilization of anti-inflammatory drugs did not. [12] Although these findings suggest a stronger relationship between asthma hospitalization and environmental allergen control, than with anti-inflammatory drug use, an important consideration in multivariate analyses is that allergen avoidance and regular use of anti-inflammatory drugs are often correlated.[66;69]

6.2.4 Summary

Hospitalization for asthma has been referred to as a crisis in the care of the asthmatic child, the result of inadequate prophylaxis therapy and delay in seeking health care.[70] Children with asthma living in lower socioeconomic status households appear to be at increased risk for these events. They are also at increased risk of exposure to environmental risk factors and more severe

disease, factors which need to be incorporated into investigations of the inter-relationship between socioeconomic status, drug therapy in children with asthma and outcomes of hospitalization.

6.3 Proposed research and hypotheses

A population-based study was conducted to assess the influence of socioeconomic status on the inhaled corticosteroid utilization in children with asthma, and its impact on hospitalization for asthma. Study objectives were three-fold:

1. To describe the utilization of inhaled corticosteroid medication in children with asthma.
2. To determine the characteristics of the social environment which are associated with non-use or non-regular use of inhaled corticosteroids in children with asthma.
3. To determine whether the non-use or non-regular use of inhaled corticosteroids is associated with hospitalization for asthma in children.

Study Hypothesis I

Lower income children are significantly more likely to receive non-continuous prescriptions for inhaled corticosteroid drugs than higher income children.

Study Hypothesis II

Without adjustment for other risk factors, lower income children are at increased risk for asthma hospitalization than higher income children.

Study Hypothesis III

Adjustment for asthma severity, inhaled corticosteroid continuity and other risk factors, lower income children are at increased risk for asthma hospitalization than higher income children. This increased risk will be lower than the unadjusted risk.

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NOT FOR CITATION

Increased Risk of Asthma Hospitalization In Lower Income Children: Can it Be Explained by Suboptimal Utilization of Inhaled Corticosteroid Drugs?

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ABSTRACT

Background: Children with asthma, living in low income households, are at greater risk for asthma hospitalization than higher income children. Asthma hospitalizations are considered largely preventable through the utilization of prophylactic drugs for asthma, such as inhaled corticosteroids. A study was conducted to assess the impact of continuity of inhaled corticosteroid drug utilization on asthma hospitalization in children, and to determine whether continuity of inhaled corticosteroid drugs could explain increased hospitalization for asthma among children living in lower income households.

Methods: Using population-based health care utilization data, a cohort of children, 5-15 years old, meeting a case definition for asthma, and receiving one or more prescriptions for asthma drugs during the time period January 1995-March 1996 was selected. Limiting the cohort to new users or non-users of inhaled corticosteroid drugs, a cohort of 12,534 children was followed over a 3-year period to observe first hospital admission for asthma. Household status of children was categorized as: 1) income assistance, 2) low income area and 3) higher income area. On the basis of congruence between the prescription refill-interval and days supply, children were classified as continuous or discontinuous users of inhaled corticosteroid prescriptions. A drug treatment-based asthma severity measure was implemented. The likelihood of asthma hospitalization in income assistance and low income children was determined from proportional hazards regression modelling, adjusting for continuity of inhaled corticosteroid use and other risk factors for asthma hospitalization.

Results: Continuous utilization of inhaled corticosteroids in children was associated with a decreased risk of asthma hospitalization (RR=0.37, 95% CI:0.29-0.48, adjusted for asthma severity). Income assistance and low income children were less likely to receive continuous prescriptions for inhaled corticosteroid drugs. Independent of continuity of inhaled corticosteroid utilization, asthma severity and other risk factors for hospitalization, income assistance, but not low income children, were significantly more likely to be hospitalized for asthma (RR=1.30, 95%CI:1.03-1.64).

Conclusions: The increased risk of asthma hospitalization in low income children can be partially attributed to discontinuous use of inhaled corticosteroid drugs.

INTRODUCTION

Admission rates to hospital among children with asthma have risen by 40% in Canada from the early to late 1980's. [1] This increase in hospitalization has been attributed to changes in asthma prevalence, untoward effects of treatment, changes in environmental risk factors and diagnostic shift.[2-6] Asthma hospitalizations are considered largely preventable; utilization of prophylactic medication for asthma such as inhaled corticosteroid drugs, has been associated with lower hospitalization rates.[7-10] Furthermore, the benefits of lower asthma hospitalization rates are attained only through continuous utilization of inhaled corticosteroid drugs.[11;12] Research findings have been translated into present-day asthma treatment guidelines which place emphasis on the use of inhaled corticosteroid drugs for the long-term management of asthma. [13]

Although asthma hospitalization rates in school-age children began to plateau in the 1990's, [14;15] the asthma hospital readmission rate in this age group remains at 20%.

The burden of hospitalization for asthma is unevenly distributed among children. Low socioeconomic status children are at higher risk for asthma hospitalization, than their higher income counterparts. [16-21] There is evidence that asthmatic children in lower income families receive suboptimal drug treatment, either by not being prescribed inhaled corticosteroids, or by poor adherence to inhaled corticosteroid regimens.[22-25] Therefore, a population-based study was proposed to assess the influence of prophylactic treatment of asthma on the association between household socioeconomic status and hospitalization for asthma in children. Study objectives were two-fold: 1) to assess the impact of non-use or non-continuous use of inhaled corticosteroid drugs on asthma hospitalization in children and 2) to determine whether non-use or non-continuous use of inhaled corticosteroid drugs was an important factor in explaining increased hospitalization for asthma among children living in lower socioeconomic status households, independent of other risk factors for asthma hospitalization. We hypothesized that children with asthma living in lower income households were at increased risk for asthma hospitalization, and that this risk could be partially attributed to non-use or discontinuous use of inhaled corticosteroid prescriptions.

METHODS

Data for this study were obtained from four computerized databases maintained by the Manitoba Health Services Insurance Plan (MHSIP): 1) registration files, 2) records of physician reimbursement claims, 3) records of hospital discharge abstracts, and 4) records of prescriptions dispensed in retail pharmacies. The MSHIP registration file contains a record for every individual registered to receive insured health services and records birthdate, sex and geographic location. Records of physician reimbursement for medical care provided are submitted under a fee-for-service arrangement, and contain information on patient diagnosis at the 3-digit level of the ICD-9-CM classification system and physician specialty. Discharge abstracts for hospital services provided include information on 16 ICD-9-CM diagnostic codes, of which the first is the diagnosis which is most responsible for the hospital stay. Records of dispensed prescriptions, which are submitted by retail pharmacies for reimbursement by provincial drug insurance plans or for drug utilization review purposes, contain data on the date of prescription dispensing, drug name, strength, dosage form, and quantity, and a 9-digit drug identification number.

The registry of the provincial income assistance program operated by Manitoba Family Services was an additional data source utilized. Record linkages between databases were created by the use of anonymous personal health identifiers. Statistics Canada Census 1996 household income data, aggregated to the geographic unit of the enumeration area, were used to rank neighbourhood income quintiles from 20% of the population residing in the lowest income neighbourhood to 20% of the population residing in the highest

income neighbourhood. Data from a database characterizing Manitoba physicians were also accessed.

A total of 174,208 children, aged 5-15 years as of January 1, 1995 and registered with Manitoba Health until March 31, 1996, were identified from the MSHIP registry. This time period was chosen to capture data prior to a major policy change in the provincial drug insurance program. Approximately 48,000 (28%) of these children met the following case definition for asthma: 1) at least one diagnosis of asthma or bronchitis on a physician claim or hospital abstract record or 2) in the absence of these diagnoses, one prescription for an inhaled corticosteroid or antiallergic drug, or two prescription records for a bronchodilator, or one prescription for a bronchodilator and ketotifen over a 3+ year time period, January 1, 1995-March 31, 1998. The study cohort of 16,862 children was derived from this sample, representing children who had received at least one prescription for an asthma drug during a 15-month period, January 1, 1995 to March 31,1996. Asthma drug therapy was classified as follows: [26] 1) inhaled bronchodilators [eg. b2-adrenergic agonist, ipratropium bromide], 2) oral bronchodilators [eg. b2-adrenergic agonist, theophylline], 3) inhaled corticosteroids [eg. beclomethasone dipropionate, budesonide, fluticasone propionate], 4) antiallergic agents [eg. sodium cromoglycate, nedocromil sodium, ketotifen], and oral corticosteroids [eg. prednisone].

The cohort of 16,862 children was followed forward in time from January 1,1995 to March 31,1998 to observe the outcome of first hospital admission for asthma. Hospital admission for asthma was defined as hospital admission with a primary discharge

diagnosis of asthma, or a hospital admission for a secondary discharge diagnosis of asthma and a primary discharge diagnosis that was either an asthma-like condition (eg bronchitis, croup), a precipitating factor for asthma (eg. upper respiratory tract infections) or a complication of asthma (eg. pneumothorax). Hospital admissions with a primary discharge diagnosis of an asthma-like condition and no secondary diagnosis for asthma were also included.

The association between hospital admission for asthma and two social environment variables, household income status and single-parent status, was assessed. Household income status was characterized by three categories:

1) income assistance household if the child received prescription benefits from Manitoba Family Services or received prescriptions submitted for drug utilization review, which included prescriptions reimbursed 100% by Medical Services Branch (treaty status Indian) and other social services agencies,
2) low income Pharmacare household if the child received prescription benefits from Pharmacare and not Manitoba Family Services, and lived in the lowest income quintile neighbourhood, and
3) higher income Pharmacare household if the child received prescription benefits from Pharmacare and not Manitoba Family Services, and did not live in the lowest income quintile neighbourhood.

Single-parent household status was assigned if the adults with whom the child was living were listed by the Manitoba Family Services income assistance program or Manitoba Health registry as having single, widowed, divorced or separated marital status.

Continuity of inhaled corticosteroid utilization was evaluated from the date of first prescription for an inhaled corticosteroid to the date of first hospital admission for asthma or the study censor date, whichever came first. The time interval between the dispensing date of each prescription and the dispensing date of the following prescription was derived for each child's set of inhaled corticosteroid prescriptions.[27] The number of days supply for a prescription was also calculated by dividing the prescription quantity, expressed as the number of doses of inhaled corticosteroid, by two to represent twice daily administration.[26] The difference between the time interval and days supply was determined for each consecutive pair of prescriptions. The number of days of continuous receipt of an inhaled corticosteroid was defined as the sum of the time intervals for which this difference was 21 days or less, and the days supply of the prescription corresponding to the first interval for which the difference exceeded 21 days. The 21-day period corresponded to the maximum duration of time following discontinuation of inhaled corticosteroid therapy beyond which symptoms return.[28] The categorical form of this variable was created as follows:

1) discontinuous use, corresponding to 90 days or less of continuous use and representing 50% of children,
2) mostly continuous use, corresponding to 91-180 days of continuous use and representing 45% of children, and
3) continuous use, corresponding to greater than 180 days of continuous use and representing 5% of children.

Kaplan Meier curves for time to hospital admission by the categorical form of continuity of inhaled corticosteroid prescriptions were obtained for each level of asthma severity to

determine if the continuity of inhaled corticosteroid measure was associated with differing risks for hospital admission.

Additional explanatory variables evaluated were: 1) sociodemographic variables, such as age at study onset and gender, 2) asthma disease factors, such as asthma prognosis, asthma severity, prior hospitalization for asthma, time since first health care contact for asthma, and frequency of respiratory infection, and 3) asthma treatment factors, such as utilization of oral corticosteroids, continuity of physician care for asthma, and physician specialty. The occurrence of year-round wheezing, which has been found to differentiate persistent asthma from transient wheezing syndromes in children, was utilized as a measure of asthma prognosis.[29-31] Children were characterized as having persistent asthma, if there was evidence of year-round health care contacts and prescriptions for asthma, or as having transient wheezing, if winter only utilization was present. Asthma severity, a significant confounder in assessing risk for asthma hospitalization,[32-34] was derived from a drug treatment-based asthma severity measure. Severity categories of mild-moderate, moderate-severe, and severe asthma were assigned on the basis of the asthma drug prescription profile and markers of acute asthma episodes over two times periods: January 1995 - March 1996 and April 1996 - March 1998.[35-39] To account for change in asthma severity over the study period, asthma severity was determined for the time period in which the hospitalization occurred (eg. 1995/96 or 1996/98). If a child was not hospitalized, asthma severity for the time period April 1996-March 1998 was assigned.

The number of hospitalizations per year for a primary diagnosis code of asthma, from time of birth to the beginning of study period, was included as an additional severity measure.[7;34] Time from the first physician visit or hospitalization for asthma was also determined from birth to the beginning of the study period, to represent the time course of asthma [40] and parental familiarity with the disease.[41] The frequency of respiratory infection was included as a proxy measure for frequency of viral infection to describe exposure to an environmental factor which could precipitate asthma exacerbations.[42-45] A respiratory infection was enumerated as a physician visit or hospitalization for a respiratory infection or bronchitis, or a prescription for an antibiotic within 7 days of a physician visit or hospitalization for asthma. [46;47] The number of respiratory infections was divided by the time prior to outcome to obtain a rate. Children with a respiratory infection rate in the 90^{th} percentile or greater were defined as having high respiratory infection rates. This rate was equivalent to one infection per 6 month period.

Prior treatment with an oral corticosteroid, defined as a 10-day period following the dispensing date of the last prescription for an oral corticosteroid prior to hospitalization or censor date, was measured to adjust for the effects of oral corticosteroids in preventing asthma hospitalization. [48] Ever consultation with an asthma specialist was defined as at least one visit to an asthma specialist, according to a university listing of allergy, pediatric allergy or respirology specialty, or by the submission of reimbursement claims for allergy testing. Children seeing asthma specialists are more likely to receive a prescription for an inhaled corticosteroid and to be adherent to other treatment measures.[49;50] Continuous physician care for asthma was assigned to a child if 90% or greater of physicians visits

from study onset to hospital admission were made to one non-specialist and/or one specialist for a diagnosis of asthma or bronchitis.[51] A regular source of medical care has been associated with increased utilization of inhaled corticosteroid drugs, [22;52] and of reduced hospitalization for asthma.[19]

The relative risk (RR) of hospitalization for asthma was estimated from proportional hazards regression modelling, in which the outcome was expressed as a time to event variable.[53] To prevent bias associated with previous and short-term use of inhaled corticosteroids, the analysis was limited to new users of inhaled corticosteroid prescriptions, defined as a first prescription 180 days or more following study entry, who had received at least a 16 days supply of inhaled corticosteroid prior to hospitalization or censor.[11;12] The sample size required to detect a two-fold increase in asthma hospitalization among low income children in comparison to higher income children, assuming a hospitalization rate of 3% in higher income children with asthma, aged 5-15 years, and a sample size ratio of low to higher income children with asthma of 0.11, was 3597 (360 low income and 3237 higher income children). The power index for the sample size calculations was based on a confidence level of 98%, Bonferroni correction for multiple comparisons, one-sided test, and a power of 80%. Following the same assumptions, but assuming a sample size ratio of income assistance to higher income children with asthma of 0.24, the sample size required to detect a two-fold increase in asthma hospitalization among income assistance children in comparison to higher income children, was 2514 (503 income assistance and 2011 higher income children).

In the proportional-hazards model, person- time and events were censored at the date of last registration with Manitoba Health or end of study period. Explanatory variables evaluated in the model were: 1) household income status, 2) single-parenthood status, 3) age, 4) gender, 5) asthma prognosis, 6) asthma severity, 7) previous asthma hospitalization rate, 8) time since first contact for asthma, 9) continuity of inhaled corticosteroid prescriptions, expressed as a categorical, non-time dependent variable, 10) continuity of physician care for asthma, 11) ever consultation with an asthma specialist, and 12) frequency of respiratory infection. The reference group for continuity of inhaled corticosteroid use included children who did not receive an inhaled corticosteroid prescription. Explanatory variables were retained in the model by comparing the difference in deviance between nested models to the chi-square statistic for the difference in degrees of freedom between two models at a 95% level of confidence. Effect modification, namely modification by inhaled corticosteroid use of the association between household socioeconomic status and hospitalization for asthma, was assessed by the inclusion of interaction terms.

As the efficacy of inhaled corticosteroid drugs is limited to the time period of treatment, [28] proportional hazards modelling was repeated for a model containing continuity of inhaled corticosteroid prescription, expressed as a time-dependent variable.[54] In contrast to the previous model, in which risk of hospitalization was assessed among children categorized as continuous or discontinuous inhaled corticosteroid users, this model evaluated the risk of hospitalization during time periods of inhaled corticosteroid prescription use and non-use. The time period of inhaled corticosteroid use was defined

as the interval from the date of the first prescription to 21 days or less following the end of the days supply of the last prescription. Time outside of this period, which constituted the time prior to the date of the first prescription, or 22 days or more following the end of the days supply of the last prescription, was counted as non-use of an inhaled corticosteroid drug. An interaction term, defining continuous and discontinuous users on the basis of time periods of use and non-use, was created. This model was limited to children with previous contact for asthma to ensure that time periods of non-use preceding the first inhaled corticosteroid prescription, represented periods where children would be at risk for asthma hospitalization.

RESULTS

The base cohort was comprised of 16,857 children in treatment for asthma, following the exclusion of 5 children receiving Pharmacare benefits who could not be placed in neighbourhood income quintiles. On average, children were observed over 3.2, SD=0.4 years. During this time period, 55% of children had received at least one prescription for an inhaled corticosteroid; of these children, 6988 (75.9%) had received continuous prescriptions. Seventy-five percent of children were living in higher income Pharmacare households, 17% in income assistance households, and 8% in low income Pharmacare households. Income assistance and low income children with asthma were more likely than higher income children, to live in single-parent households, to have more severe asthma, to have frequent respiratory infections and be hospitalized for asthma.(Table 6.5.1) They were also less likely to have continuity of inhaled corticosteroid prescriptions

or to have regular sources of physician care for asthma. A gradient in the frequency distribution of risk factors across household income was observed, with income assistance children at one end of the continuum and higher income children at the other end.

The relative risk of hospitalization for asthma was evaluated among 12,534 non-users and "new users" of inhaled corticosteroid drugs, following the exclusion of 4,328 children with inhaled corticosteroid prescriptions within six months of study onset or with first-time use for less than 16 days. Adjusting for asthma severity, the intention-to-treat analysis showed that any utilization of inhaled corticosteroid drugs significantly reduced the risk for asthma hospitalization (relative risk=0.42, 95%CI: 0.33-0.52). Continuous utilization of inhaled corticosteroid prescription further decreased the risk for hospitalization for asthma. Kaplan Meier curves showed that the median time until hospitalization in 341 children with severe asthma was 250 days in children without inhaled corticosteroid prescriptions, 500 days in children with discontinuous use of inhaled corticosteroid prescriptions, and 900-950 days in children who received mostly continuous and continuous prescriptions (log-rank test, $p<0.0001$).(Figure 6.5.1) The risk of asthma hospitalization was also significantly reduced with continuous use of inhaled corticosteroid prescriptions among children with moderate to severe, and mild to moderate asthma (data not shown). Adjusting for asthma severity, the risk for asthma hospitalization among continuous users (mostly continuous and continuous combined) of inhaled corticosteroids, relative to non-users, was 0.37, 95%CI: 0.29-0.48, and the relative risk of discontinuous users was 0.59, 95%CI: 0.41-0.86.

The unadjusted risk for asthma hospitalization was increased one and one-half times in low income and income assistance children, relative to higher income children.(Table 6.5.2) Adjustment for continuity of inhaled corticosteroid use reduced, but did not eliminate the increased risk of hospitalization among low income and income assistance children. No interactions between continuity of inhaled corticosteroid use and household income status were documented. In a separate model, children with moderate-severe asthma and especially, children with severe asthma were at substantially greater risk for asthma hospitalization, than children with mild-moderate asthma. In this model, adjustment for asthma severity completely eliminated the increased risk of hospitalization among low income or income assistance children.

Independent of asthma severity, continuity of inhaled corticosteroid prescriptions and other risk factors for asthma hospitalization, an increased risk for asthma hospitalization was found among children with an increased likelihood of persistent asthma, with a greater number of previous asthma hospitalizations, with longer duration since time of first health care contact for asthma, and with frequent respiratory infections (RR=2.26, 95%CI:1.86-2.77).(Table 6.5.2) The relative risk for asthma hospitalization was lower among children with a regular source of physician care, and especially, among children who had received a prior course of oral corticosteroids (RR=0.08, 95%CI:0.05-0.12). Non consultation with an asthma specialist was excluded as a significant predictor of hospitalization following the introduction of oral corticosteroid measure into the model. Household single-parenthood status and gender were additional measures which were excluded from the model. No interactions were found between continuity of physician

care for asthma and continuity of inhaled corticosteroid prescription use. Adjustment for all the factors in the final model, did not eliminate the increased risk of asthma hospitalization among income assistance children (RR=1.30, 95%CI: 1.03-1.64).

Among the cohort of non-users and "new users" of inhaled corticosteroid drugs, 7,645 children had health care contacts for asthma prior to the study period. Among these children, an increased risk of asthma hospitalization was also observed in low income and income assistance children (Table 6.5.3). The final proportional hazards regression model contained similar predictors of increased or decreased asthma hospitalization, but shorter time from first contact for asthma and no regular source of physician care were no longer associated with increased risk of hospitalization. Children classified as continuous users of inhaled corticosteroid prescriptions during the treatment period were one quarter times as likely to be hospitalized for asthma (relative risk=0.22, 95%CI: 0.14-0.35), than children who were not yet users of inhaled corticosteroids. However, the risk of hospitalization was not reduced during the inhaled corticosteroid treatment period among discontinuous users. Moreover, children categorized as continuous and discontinuous users were less likely than non-users to be hospitalized for asthma while not receiving inhaled corticosteroid prescriptions. Household income assistance status was no longer a predictor of increased hospitalization for asthma following adjustment for these factors.

DISCUSSION

Children living in low income or income assistance households were significantly at greater risk for hospitalization for asthma than higher income children, without consideration of other risk factors. These findings are consistent with several cross-sectional and small area studies, which report a higher prevalence of lower income children among children hospitalized for asthma.[16-21] In the Canadian setting of universal health care insurance children living in low income neighbourhoods were almost twice as likely to be hospitalized for asthma than their higher income counterparts.[16] Our study further contributes to the literature by exploring risk factors which may explain this increased risk of asthma hospitalization in low income children living in a setting of universal health care insurance.

An important determinant of asthma hospitalization was continuity of inhaled corticosteroid prescription utilization. In comparison to children with no prescriptions for inhaled corticosteroid drugs, the risk of hospital admission for asthma was reduced to 0.42 (95%CI: 0.33-0.52) among children with prescriptions for these drugs, and to 0.37 (95%CI: 0.29-0.48) among continuous users. Decreased risk of asthma hospitalization among users and regular users of inhaled corticosteroid drug prescriptions has been reported by others.[7;11;12] Although prescription utilization may not represent actual use of the drug,[55] these findings are also consistent with more sensitive measures of inhaled corticosteroid utilization among children, which show that adherence to inhaled corticosteroid therapy is associated with decreased risk of asthma exacerbations.[56]

Independent of asthma severity and inhaled corticosteroid prescription use, several other factors predicted asthma hospitalization. Children with year-round health care utilization for asthma were at increased risk of hospitalization for their disease, than children with winter-only utilization, a marker of transient wheezing illness. The exclusion of children less than five years of age in our study eliminated children with transient wheezing of infancy, misdiagnosed as asthma. [34;57;58] Transient wheezing syndromes also occur in older children,[29-31] and we view our findings as evidence for the importance of controlling for the changing risk of asthma hospitalization in children who may no longer have "asthma" symptoms as they enter adolescence. Increased risk of asthma hospitalization was associated with an increased number of previous hospitalizations for asthma, as reported by others. [59] Previous hospitalization for asthma among younger children in the study cohort is a predictor for more severe asthma.[40;60] Increased risk of asthma hospitalization with longer duration since time of first contact for asthma may also represent increased severity among children with longer-standing airway inflammation.[40] Frequent respiratory tract infections more than doubled the risk for asthma hospitalization. Upper respiratory viral infections such as rhinovirus and influenza virus, have been linked to acute asthma exacerbations in children, [43-45] and are reported to be the strongest environmental trigger for asthma.[42] Inhaled corticosteroids may attenuate upper respiratory tract infection-exacerbations of asthma, [61;62], but do not prevent them from occurring.[63] Oral corticosteroid drugs also attenuate acute exacerbations of asthma, and the number of courses of oral corticosteroids has been utilized as marker of asthma severity.[7;34;47] Moreover, oral corticosteroid treatment of asthma exacerbations significantly reduces relapse of asthma symptoms at 7-10 days

post treatment.[48] In our study, the risk of asthma hospitalization was substantially reduced within a 10-day period of receipt of a prescription for an oral corticosteroid drug.

Children with a regular source of physician care for asthma were 20% less likely to be hospitalized than children without a regular source of care. These findings are consistent with previous reports that children with a regular source of medical care are more likely to be receive inhaled corticosteroid drugs,[22;52] and less likely to be hospitalized for asthma.[19] As noted, continuous inhaled corticosteroid prescription utilization decreased the risk of asthma hospitalization, but we also hypothesized that children with continuous use of inhaled corticosteroids and a regular source of medical care for asthma would least likely be hospitalized for their asthma. No interactions were found between continuity of inhaled corticosteroid prescription and a regular source of physician care, suggesting an independent effect of physician care. This independent effect may be related to adherence to physician recommendations for allergen avoidance, [64;65] or to ambulatory treatment of acute exacerbations of asthma.[66;67]

The association between household socioeconomic status and hospitalization for asthma was adjusted at several levels of risk factors. Sole adjustment for continuity of inhaled corticosteroid utilization did not entirely explain increased risk of asthma hospitalization among lower income children. In the absence of asthma severity measures, we would have expected this finding.[68] Children with more frequent wheezing are significantly more likely to use acute health care services,[69-71] but it is difficult to ascertain whether asthma morbidity represents poor control of asthma symptoms or more severe

disease. Prophylaxis with inhaled corticosteroid drugs improves control of asthma symptoms,[72-74] , and children adherent to inhaled corticosteroid regimens have fewer exacerbations than those who are not. [56] However, children with severe asthma remain at higher risk for asthma exacerbations than children with less severe asthma, despite optimal treatment with inhaled corticosteroids.[75] In our study, children with more severe asthma were substantially at increased risk for hospitalization. Adjustment for asthma severity alone, completely eliminated the increased risk of asthma hospitalization among low income and income assistance children. However, following the inclusion of all risk factors in the regression model, a higher risk of asthma hospitalization persisted in income assistance children, suggesting that income assistance children were exposed to risk factors for hospitalization which were not measured in this study. An increased risk of hospitalization has been reported among children with greater exposure to environmental triggers, such as tobacco smoke or dust/cockroach allergens.[6;76] Cockroach exposures are more common in lower income children in east coast US cities, but the prevalence of cockroach allergy has not been defined in Canadian prairie households.[23;77;78] Household smoking however, is more common in low, than higher income Manitoba households with asthmatic children. (data from Manitoba sample of 1994/95 National Longitudinal Survey on Children and Youth)

Parents of asthmatic children utilizing inhaled corticosteroid drugs are more likely to implement allergen avoidance measures.[41;69;79] In order to disentangle the effects of inhaled corticosteroid drugs, which are primarily restricted to the time period of administration, [74] and other asthma management practices, we ascertained the risk of

hospitalization during and outside the inhaled cortisoteroid treatment period in discontinuous and continuous users. In contrast to the earlier multivariate model, continuous, but not discontinuous users of inhaled corticosteroid prescriptions had a reduced risk of asthma hospitalization if the outcome occurred during the treatment period. These findings are also consistent with the literature.[11;12] However, independent of other risk factors, a lower risk for hospitalization was observed outside of the treatment period in continuous and discontinuous inhaled corticosteroid users, suggesting that parents of children receiving inhaled corticosteroid drugs may have implemented asthma management strategies such as allergen avoidance measures, reducing the risk of hospitalization.[80] It is noteworthy that the increased risk of asthma hospitalization among income assistance children was not statistically significant in this fully adjusted model.

The limitations of our research are related to the observational nature of the study design and the potential for bias in estimating the risk of asthma hospitalization.[81] To reduce selection bias, subsequent to the inclusion of children who did not have asthma, we excluded children less than 5 years of age. [82;83] We also adjusted the relative risk for asthma hospitalization with a marker of asthma persistence derived from health care utilization patterns.[29;30;84] Furthermore, "previous users" of inhaled corticosteroids were excluded because of the association between inhaled corticosteroid use, asthma severity and lower income status,[85] with the potential for creating a biased association between socioeconomic status and hospitalization at study entry. Excluding children with

previous prescriptions for inhaled corticosteroids also prevented left censoring of the continuity of prescription measure.[54]

Measurement bias in describing hospital admission for asthma was minimal because we utilized provincial hospitalization records, and also included diagnoses which would be associated with an exacerbation of asthma.[11;86] However, there existed the potential for measurement bias in describing continuity of inhaled corticosteroid, which may not represent actual utilization of the drug. [55] Confounding bias was adjusted for by the use of multivariate models which included factors related to socioeconomic status, inhaled corticosteroid utilization and asthma hospitalization.[87] Measures of potential confounders such as asthma severity, exposure to respiratory viral infections, and receipt of oral corticosteroids were derived from health care administrative records,[44;48;69] were themselves subject to bias associated with health care utilization data. Finally, although we included major determinants of asthma hospitalization, we were unable to include additional measures of environmental risk factors, such as exposure to tobacco smoke or allergens.[6;76]

In summary, our research findings indicate that lower income and income assistance children are at greater risk for asthma hospitalization than higher income children. Hospitalization for asthma contributes substantially to the costs of managing this disease[88-90] and affects the quality of life of asthmatic children.[70] What policy directives are needed to reduce hospitalization in this group of children? Severe asthma was a major predictor of hospitalization and explained entirely the increased risk of

hospitalization among low income children. While it may be prudent to recommend earlier treatment with inhaled corticosteroids to prevent irreversible lung changes which occurs subsequent to chronic inflammation, long-term studies in children are lacking [12;40;91] and what determines asthma severity is not completely understood.[92]

While not altering the baseline severity of asthma, treatment with inhaled corticosteroid drugs prevents a child with moderate symptomatic asthma from having moderate, "well-controlled" asthma, and according to our findings, prevents hospitalization for asthma. Low income children are less likely to be treated with inhaled corticosteriods.[22-25] Our study findings suggest that the increased risk for asthma hospitalization in low income children can in part, be reduced by improving continuity of their use. Physicians practising in low income neighbourhoods would benefit from education on the increased risk of hospitalization for asthma in their patients, and the need for prophylactic treatment.[93] However, prescription of an inhaled corticosteroid by a physician will not guarantee administration to the child if there are cost barriers to the purchase of these drugs. The high-potency inhaled corticosteroid drugs are expensive to purchase [94] and low income parents often report problems in paying for asthma drug prescriptions.[95-97] Future considerations of pharmaceutical reimbursement policy could include the provision of free prescription benefits to children, as is the practice in the province of Quebec, [98] or the requirement of nominal copayment or deductible payments for children's prescriptions.[96]

Adherence to inhaled corticosteroid regimens represents a major challenge to optimal asthma management; adherence in low income children is poor.[22;79;99;100] We documented that low income children were more likely to receive discontinuous treatment with inhaled corticosteroids. Low income parents have been reported to be less knowledgeable about their children's asthma management or to have a disbelief in the effectiveness of asthma drugs.[41;101] The observed use of inhaler devices has been reported to be dismal in low income children.[79] Strategies to improving adherence with inhaled corticosteroid treatment need to be multi-faceted, beginning with the education of physician, pharmacists and nurses on the proper use of inhaler devices [102;103] and on good communication techniques in talking about asthma to their patients.[99;104] Moreover, it is essential that asthma education sessions incorporate a greater understanding of how individuals experience asthma.[105] Disbelief in the effectiveness of preventing attacks among low income parents has been associated with non-adherence with asthma medications in their children.[71;106]

Education of professionals in public health clinics on asthma has resulted in increased utilization of inhaled corticosteroids by their patients.[107] In our research, we have identified factors which can inform the clinical management of childhood asthma by health professionals. Furthermore, we have developed measures of asthma severity, continuity of inhaled corticosteroid prescription utilization and exposure to respiratory viral infection, which are very useful in asthma pharmaco-epidemiologic research. Future applications of our methods to health care administrative databases can be used to profile children who are at high risk for asthma hospitalization.[108]

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Table 6.5.1. Characteristics of Children with Asthma by Socioeconomic Status

Household Type	Income Assistance (n=2,782)	Low Income Pharmacare (n=1,398)	High Income Pharmacare (n=12,677)
Age (mean, 95%CI)	9.3, (9.2-9.4)	9.2, (9.0-9.4)	9.8, (9.7-9.8)
Male gender (%)	53.1	56.2	56.6, NS
Single-parent household (%)	72.9	26.7	14.8, p<0.001
Visits for asthma since birth (%)	62.6	65.2	68.0, p<0.001
Time since 1st visit for asthma (mean, 95%CI)	3.0, (2.9-3.2)	3.1, (2.9-3.3)	3.4, (3.3-3.4)
Number of previous* asthma hospitalizations (mean, 95%CI)	0.060 (0.051-0.069)	0.037 (0.029-0.045)	0.031 (0.029-0.033)
Year-round health care contacts for asthma (%)	92.2	91.2	91.9, NS
Asthma severity (%)			
Severe	2.9	3.0	1.9
Moderate-severe	19.1	21.5	19.9
Mild-moderate	78.0	75.5	78.2, p<0.03
Frequent respiratory infections (%)	41.3	30.4	24.1, p<0.001
Regular use of medical care for asthma (%)	39.7	46.5	48.5, p<0.001
Ever use of specialist for asthma care (%)	14.3	17.2	17.9, p<0.007
Inhaled corticosteroid use (%)			
No prescriptions	50.4	49.1	43.9
Discontinuous use	8.8	12.5	14.2
Continuous use	40.8	38.3	41.9, p<0.001
Ever hospitalized for asthma (%)	5.1	4.7	3.2, p<0.001

Table 6.5.2. Relative Risk for Hospitalization for Asthma in Children with Asthma, Continuity of Inhaled Corticosteroid Prescription Use is Not Time-dependent (n=12,534)

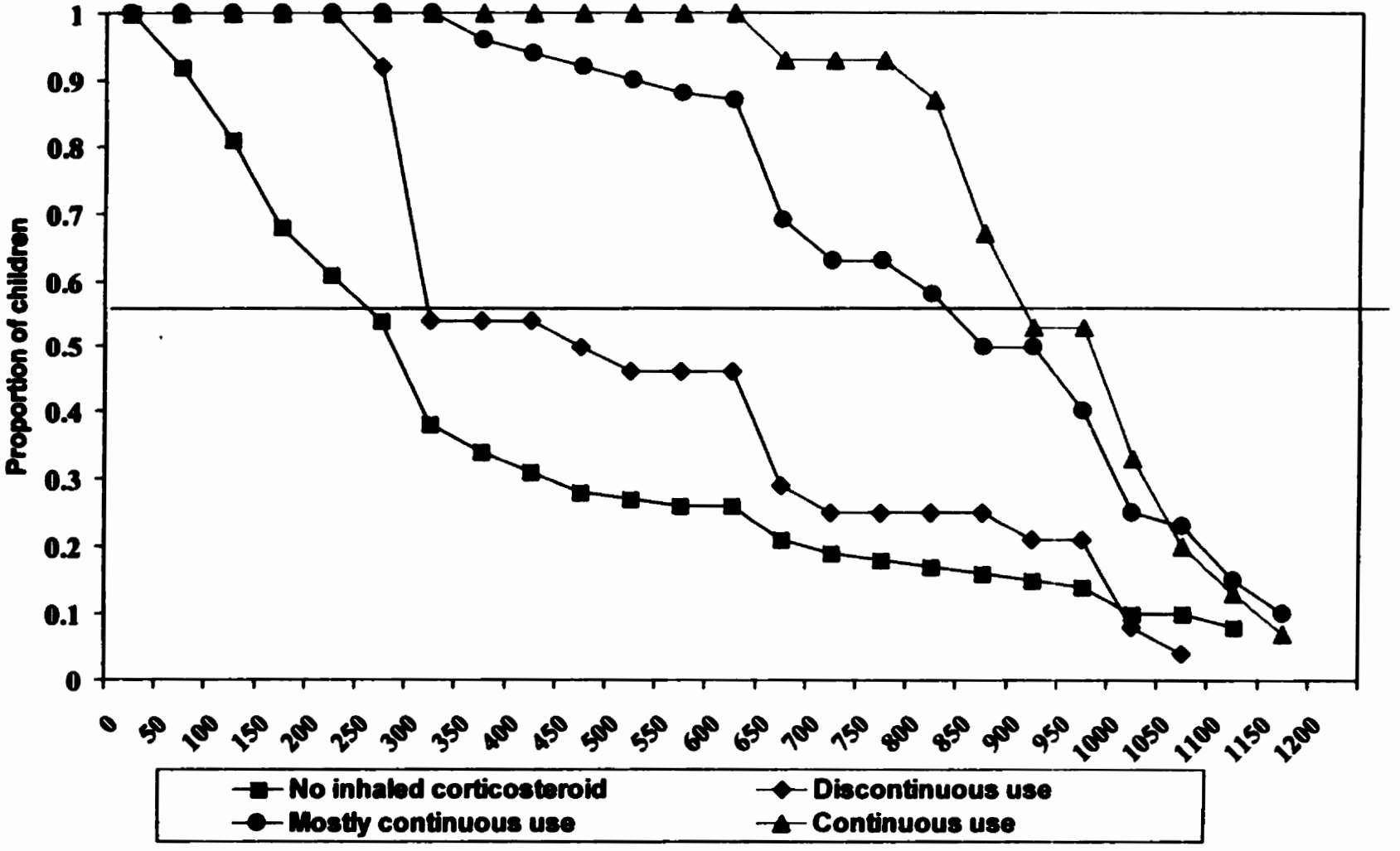
	Relative risk (95% Confidence Interval)	
Unadjusted relative risk		
Income assistance	1.52	(1.21-1.90)
Low income Pharmacare	1.44	(1.06-1.96)
(baseline: high income Pharmacare)		
Relative risk adjusted for continuity of inhaled corticosteroid prescriptions		
Income assistance	1.31	(1.01-1.70)
Low income Pharmacare	1.38	(1.01-1.87)
(baseline: high income Pharmacare)		
Discontinuous inhaled corticosteroid	0.60	(0.42-0.87)
Continuous inhaled corticosteroid	0.48	(0.37-0.61)
(baseline: no inhaled corticosteroid)		
Relative risk adjusted for asthma severity		
Income assistance	0.99	(0.76-1.29)
Low income Pharmacare	0.86	(0.62-1.17)
(baseline: high income Pharmacare)		
Severe asthma	470	(343-642)
Moderate-severe asthma	7.05	(4.89-10.16)
(baseline: mild-moderate asthma)		
Relative risk adjusted for severity, continuity of inhaled corticosteroid use and other risk factors		
Income assistance	1.30	(1.03-1.64)
Low income Pharmacare	0.90	(0.66-1.23)
(baseline: high income Pharmacare)		
Year-round utilization for asthma care	2.44	(1.15-5.18)
(baseline: winter only utilization)		
Severe asthma	577	(416-801)
Moderate-severe asthma	13.4	(9.2-19.3)
(baseline: mild-moderate asthma)		
Discontinuous inhaled corticosteroid	0.69	(0.47-1.00)
Continuous inhaled corticosteroid	0.37	(0.28-0.48)
(baseline: no inhaled corticosteroid)		
Number of prior asthma hospitalizations per year (increase)	1.76	(1.38-2.25)
Time since first visit for asthma (one year increase)	1.05	(1.01-1.08)
Age (one year increase)	0.97	(0.94-1.01)
Frequent respiratory infections	2.26	(1.85-2.75)
(baseline: few infections)		
Regular source of physician care for asthma	0.79	(0.63-0.98)
(baseline: no regular source)		
Oral corticosteroid 10 days prior to outcome	0.08	(0.05-0.12)
(baseline: no oral corticosteroid 10 days prior)		

Table 6.5.3. Relative Risk for Hospitalization for Asthma in Children with Previous Contacts for Asthma Care, Continuity of Inhaled Corticosteroid Prescription is Time-Dependent (n=7645)

	Relative Risk	(95% Confidence Interval)
Unadjusted relative risk		
Income assistance	1.53	(1.18-1.99)
Low income Pharmacare	1.52	(1.08-2.14)
(baseline: high income Pharmacare)		
Relative risk adjusted for severity, continuity of inhaled corticosteroid use and other risk factors		
Income assistance	1.21	(0.93-1.59)
Low income Pharmacare	0.87	(0.61-1.24)
(baseline: high income Pharmacare)		
Year-round utilization for asthma care	NS	
(baseline: winter only utilization)		
Severe asthma	806	(536-1214)
Moderate-severe asthma	12.9	(8.1-20.1)
(baseline: mild-moderate asthma)		
'Discontinuous user' during inhaled CCS treatment*	1.29	(0.77-2.17)
'Discontinuous user' outside of inhaled CCS treatment**	0.31	(0.16-0.60)
(baseline: no inhaled CCS or outside of CCS treatment)		
'Continuous user' during inhaled CCS treatment*	0.22	(0.14-0.35)
'Continuous user' outside of inhaled CCS treatment**	0.46	(0.33-0.63)
(baseline: no inhaled CCS or outside of CCS treatment)		
Number of prior asthma hospitalizations per year (increase)	1.92	(1.53-2.42)
Frequent respiratory infections	2.17	(1.74-2.71)
(baseline: few infections)		
Oral corticosteroid 10 days prior to outcome	0.08	(0.05-0.12)
(baseline: no oral corticosteroid 10 days prior)		

CCS= corticosteroid, *after 1st prescription and 21 days before end of days supply of last prescription
**before 1st prescription and 22 days or more after end of days supply of last prescription

Figure 6.5.1. Number of Days to First Hospitalization for Asthma by Continuity of Inhaled Corticosteroid Prescriptions in Children with Severe Asthma (n=341)



Chapter 7. Discussion of Research Findings

7.1 Summary of Research Findings

The introductory chapter described the organizational framework for the presentation of the findings of the dissertation research. A series of five essays was presented in the subsequent chapters which described research relating to the: 1) development of a case definition for childhood asthma, 2) development of a drug treatment-based asthma severity measure, 3) empiric evidence on the association between household socioeconomic status and inhaled corticosteroid prescription use in children with asthma, 4) empiric evidence on the impact of an income-based pharmaceutical policy on the utilization of inhaled corticosteroid prescriptions in children, and 5) empiric evidence on the association between socioeconomic status and hospitalization for asthma. The objective of this chapter is to highlight the findings of the research presented in the previous chapters, and discuss study limitations and policy implications.

7.1.1 Case Definition for Childhood Asthma Derived from Health Care Administrative Records

A case definition for childhood asthma, which supplements a diagnosis-based definition and can be applied to health care administrative records, was developed. Using population-based health care administrative data, a cohort of 48,146 children was assembled on the basis of the following case definition for asthma: 1) a physician contact

or hospitalization for asthma or bronchitis diagnoses during the period January 1, 1995 to March 31, 1998, or 2) in the absence of a health care contact for an asthma-like diagnosis, at least one prescription for a prophylaxis drug, at least one prescription for ketotifen concomittant with a bronchodilator, or at least two prescriptions for bronchodilator drugs during the same time period. The validity of the case definition in identifying children with "persistent asthma," defined as continuous health care utilization for asthma-like diagnoses and/or prescriptions for asthma drugs, was assessed.

Using a prescription for an asthma drug as the criterion, the asthma case definition identified 90% of children with a prescription for an asthma drug. A discriminant validity analysis was conducted for the drug and diagnosis domains of the case definition, as well as for other risk factors for asthma, to determine which domains were associated with persistent asthma versus transient wheezing. Children selected on the basis of an asthma drug prescription were 3-6 times more likely than children without an asthma drug prescription to have "persistent asthma." To a lesser extent, "persistent asthma" was more likely among children with an asthma diagnosis, than in those without an asthma diagnosis. The presence of an asthma prescription drug and year-round asthma health care utilization patterns substantially increased the likelihood of "persistent asthma" in children with and without asthma diagnoses. Convergent validity analyses documented that children with bronchitis diagnoses who were subsequently diagnosed with asthma, were more likely than children with bronchitis-only diagnoses to have markers of "persistent asthma."

In conclusion, an asthma case definition which incorporates data on asthma drug prescriptions and health care utilization patterns, as well as diagnosis information, improves the likelihood of identifying children with persistent asthma.

7.1.2 Development of a Drug Treatment-based Asthma Severity Measure

A drug treatment-based asthma severity measure was developed on the basis of stepwise utilization of asthma drug prescriptions with increasing asthma severity and indicators of asthma exacerbations. The measure was applied to a cohort of 16,862 children meeting a diagnosis and drug-based case definition for asthma, and having at least one prescription for an asthma drug during January 1995-March 1996. The reliability of the measure was assessed using test-retest reproducibility; predictive and construct validity of the measure were ascertained through comparisons with other markers of severe asthma, and responsiveness of the measure was determined by assessment of changes to asthma severity over time.

The drug treatment-based asthma severity measure classified 37% of children with mild asthma, 42% with moderate asthma, 19% with moderate-severe asthma and 2% with severe asthma. The weighted kappa score for agreement on asthma severity classification between two successive time periods was 0.82. Children classified with moderate-severe and severe asthma were significantly more likely to have previous asthma hospitalizations, to visit asthma specialists, to have 5 or more physician visits/15 month period and to require critical care upon hospitalization. These children were also twice as

likely to be re-classified in the same severity category, two years following the end of the study period.

In conclusion, a drug treatment-based asthma severity measure in children was developed for application to health care administrative data. The measure was found to be highly reliable and valid, and responsive to changes in asthma over time.

7.1.3 Socioeconomic Status and Inhaled Corticosteroid Use in Childhood Asthma

This research was conducted to determine whether the utilization of inhaled corticosteroid drugs in Manitoban children with asthma was related to their socioeconomic environment. Using population-based prescription and health care utilization data, a cohort of 16,862 children, aged 5-15 years, was identified on the basis of a diagnosis and drug-based case definition for asthma, and at least one prescription for an asthma drug during January 1995-March 1996. The proportion of children with an inhaled corticosteroid prescription by neighbourhood income, with adjustments for asthma severity and physician specialist use, was ascertained. A longitudinal assessment of the likelihood of a new prescription for an inhaled corticosteroid by household income, defined on the basis of drug insurance plan membership, was also conducted.

Forty-five percent of children had at least one prescription for an inhaled corticosteroid drug during January 1995-March 1996. The proportion of inhaled corticosteroid users increased with successive increases in neighbourhood income quintile. Adjustment for

asthma severity and asthma specialist use, eliminated the gradient in inhaled corticosteroid utilization among children with severe asthma, but among children with mild or moderate asthma, the income trend in utilization was present among children who had not seen a specialist. A new prescription for an inhaled corticosteroid was documented in 41% of 12,416 children without a prescription for an inhaled corticosteroid during the first six months of study. The relative risk for a new inhaled corticosteroid prescription, adjusted for asthma severity and specialist use, was 0.9 among low income or income assistance children, in comparison to higher income children. This risk was further reduced in income assistance children to 0.82 (95%CI:0.76-0.88) following adjustment for factors, such as frequency of upper respiratory tract infection.

In conclusion, low income children with asthma were significantly less likely to be prevalent or incident users of inhaled corticosteroid drugs.

7.1.4 Impact of an Income-based Pharmaceutical Policy on the Utilization of Inhaled Corticosteroid Drugs in Children

This research was conducted to determine if the introduction of an income-based reimbursement policy in Manitoba's Pharmacare drug insurance program resulted in change to inhaled corticosteroid drug utilization in children with asthma. Using population-based health care utilization data, a cohort of 10,918 children, aged 5-15 years, was identified according to a diagnosis and drug-based case definition for asthma, and the presence of one or more asthma drug prescriptions during a 15-month period

before and a 24-month period after the income-based policy. Children was categorized by drug insurance program: 1) non-Pharmacare, 2) low income Pharmacare, and 3) higher income Pharmacare. Low income Pharmacare children represented children living in the lowest neighbourhood income quintile. Non-Pharmacare children constituted the control group because no change to pharmaceutical reimbursement policy had occurred in this group. The impact of the income-based pharmaceutical reimbursement policy was evaluated by the monthly likelihood of a prescription for an inhaled corticosteroid, and by the mean number of inhaled corticosteroid doses among children receiving these drugs.

The income-based pharmaceutical reimbursement policy did not affect the utilization of inhaled corticosteroid prescription in children with stable, mild-moderate asthma, and in children with decreasingly or increasingly severe asthma. However, among children with stable, severe asthma, inhaled corticosteroid use did not change in control and low income Pharmacare groups, but was significantly less likely in higher income Pharmacare children (OR=0.82, 95% CI:0.77-0.88). Among higher income Pharmacare children utilizing inhaled corticosteroid prescriptions, the mean number of doses decreased significantly in the post policy period. The mean number of inhaled corticosteroid doses was lowest among low income Pharmacare children and remained unchanged post policy.

In conclusion, the introduction of an income-based drug reimbursement policy in Manitoba was associated with decreased utilization of inhaled corticosteroid prescriptions in higher income children with severe asthma, and did not improve utilization in low income children.

7.1.5 Increased Risk of Asthma Hospitalization in Lower Income Children: Can it be Explained by Suboptimal Utilization of Inhaled Corticosteroid Drugs?

This research was conducted to assess the impact of continuity of inhaled corticosteroid drug utilization on asthma hospitalization in children, and to determine whether continuity of inhaled corticosteroid drugs could explain higher rates of asthma hospitalization among children living in lower income households. Using population-based health care utilization data, a cohort of children, 5-15 years old, meeting a case definition for asthma, and receiving one or more prescriptions for asthma drugs during the time period January 1995-March 1996 was selected. Limiting the cohort to new users or non-users of inhaled corticosteroid drugs, a cohort of 12,534 children was followed over a 3-year period to observe first hospital admission for asthma. Household status of children was categorized as: 1) income assistance, 2) low income area and 3) higher income area. On the basis of congruence between the prescription refill-interval and days supply, children were classified as continuous or discontinuous users of inhaled corticosteroid prescriptions. The likelihood of asthma hospitalization in income assistance and low income children was determined from proportional hazards regression modelling, adjusting for continuity of inhaled prescription use, asthma severity and other risk factors for asthma hospitalization.

Continuous utilization of inhaled corticosteroids in children was associated with a lower risk of asthma hospitalization (RR=0.37, 95% CI:0.29-0.48, adjusted for asthma severity). Income assistance and low income children were less likely to receive continuous

prescriptions for inhaled corticosteroid drugs. The increased risk of asthma hospitalization in income assistance and low income children was reduced, but not eliminated following adjustment for continuity of inhaled corticosteroid use. Further adjustment for asthma severity and other risk factors for hospitalization, eliminated the increased risk of asthma hospitalization in these children.

In conclusion, an increased risk of asthma hospitalization in income assistance and low income children can be partially attributed to discontinuous use of inhaled corticosteroid drugs.

7.2. Internal validity of dissertation research

A study is reported to be internally valid if study findings are "true" for the study participants. In the hierarchy of study designs, randomized controlled trials have the greatest internal validity.[1,2] This is due to the strength of randomization in determining intervention or exposure status. Observational studies in which there is no manipulation of the intervention, are more susceptible to distorting influences or biases. Bias can be defined as a process which produces results that depart systematically from "true" values.[3]

The dissertation research is an observational study, which uses the cohort study design. Of the observational study designs, the cohort study has the least potential for study bias. However, an evaluation of the internal validity of the dissertation research was required,

in order to assess the degree to which the findings study were free from bias. There are three main domains of study bias: 1) selection bias, 2) information bias and 3) confounding bias. In this section, the dissertation research will be evaluated for the likelihood of each type of bias.

7.2.1 Selection Bias

Selection bias refers to a distortion in the estimate of the association between an outcome and an exposure, resulting from the manner in which subjects were selected for study. Selection bias arises from differential surveillance, diagnosis or referral of comparison groups so that the groups differ at the time of selection with respect to the likelihood of the outcome (cohort study design) or exposure (case-control study design).[1,2] In the dissertation research, the exposure of interest was household socioeconomic environment. Children residing in low or higher income households were evaluated for the occurrence of two outcomes: 1) inhaled corticosteroid utilization and 2) asthma hospitalization. The potential for selection bias in the dissertation is assessed on the basis of arguments that cohort children had an increased or decreased likelihood of an outcome, which was subsequent to how they were selected for study, rather than their "exposure" to low or higher income households.

Children were selected for study on the basis of a case definition for asthma, which was applied to health care utilization records. Creation of a childhood asthma cohort on the basis of health care utilization data can lead to the omission of children with asthma not

utilizing the health care system. Pertinent to selection bias, is whether exclusion of children with asthma is non-random or systematic across household income. As described in Chapter 2 (pages 34-36), the consequence of omission is dependent on which health care administrative databases are chosen for the sampling frame. For example, selection of children on the basis of physician visits for asthma may exclude children with mild asthma, who are more likely to live in higher income households.[4] The result would be over-representation of more severe asthma in higher income children, and an increased risk of inhaled corticosteroid prescription utilization and asthma hospitalization. When this group is compared to low income children, who are more likely to have more severe asthma, "true" differences in inhaled corticosteroid utilization and asthma hospitalization between the two groups could be diminished. In order to reduce this source of selection bias in the dissertation research, the case definition was applied to three data sources (physician visit, hospitalization and prescription records) over an extended 3-year evaluation period.

The potential for selection bias is also affected by the domains of an asthma case definition. In the dissertation research, children were selected on the basis of two domains of asthma: diagnosis and drug therapy. Asthma in childhood is complicated by the presence of other transient wheezing syndromes, which are indistinguishable clinically from asthma and compromise the validity of asthma diagnosis information contained in health care administrative databases.[5] Empiric research documents systematic variation in the acquisition of a physician diagnosis of asthma by socioeconomic factors (see Chapter 2, pages 22, 23); higher income children are more likely to diagnosed with

asthma. Children with a physician diagnosis of asthma are more likely to receive asthma drugs.[6] Assembly of a cohort on the basis of an asthma diagnosis could bias the association between household income and inhaled corticosteroid use by diminishing "true" differences in utilization because both low and higher income children would have a baseline increased likelihood of an inhaled corticosteroid prescription. To reduce the likelihood of excluding low income children with asthma, subsequent to systematic differences in asthma diagnosis, children were included on the basis of an asthma or asthma-like diagnosis (eg. bronchitis) in the dissertation research.

Conversely, an "inclusive" case definition, which identified asthma on the basis of "asthma-like diagnoses," had the potential to include children with respiratory conditions (eg. transient wheezing, chronic bronchitis) other than asthma. Children with transient wheezing also receive prescriptions for bronchodilators, but are less likely to receive prescriptions for inhaled corticosteroids.[7,8] Transient wheezing subsequent to diminished airway function, may be more likely in low birth weight children or children born to mothers who smoke; [5,9] low birth weight and maternal smoking are more common in lower income households.[10] While it is unclear whether transient wheezing is preferentially distributed in lower income children, a greater prevalence of transient wheezing in this group would differentially reduce the prevalence of inhaled corticosteroid utilization, and also of asthma hospitalization. The potential for this type of selection bias was addressed in the case definition by excluding children less than 5 years old, in whom transient wheezing syndromes are more common. However, transient wheezing syndromes also occur in older children. The dissertation research documented

that 40% of children with asthma health care utilization during the calendar year 1995 had no further utilization for asthma care in the following two years.

Children without any health care contacts for asthma-like diagnoses were included in the study cohort if they received prescriptions for asthma drugs. Systematic differences also exist in the utilization of asthma drugs subsequent to factors such as asthma severity and drug regimen adherence, which are related to household income status. (see Chapter 4, pages 120-125) Bronchodilators are the mainstay of asthma drug therapy, but the criterion of at least two prescriptions for bronchodilator drugs was implemented to exclude one time-only use of bronchodilators, which are prescribed for the symptomatic relief of wheezing during acute bronchitis or respiratory tract infections.[7,8] Lower income children are more likely to have respiratory tract infections, which would have increased the likelihood of bronchodilator utilization for non-asthma diagnoses in this group of children.[11] Furthermore, to prevent the exclusion of children with significantly reduced utilization of bronchodilators subsequent to prophylaxis drug therapy, children were also selected on the basis of an asthma prophylaxis drug (inhaled corticosteroid, cromoglycates). Higher income children are more complaint with prophylaxis drug therapy, and this criterion potentially prevented the omission of higher income children who had fewer than two bronchodilator prescriptions during the study period.

In the dissertation research, the cohort of children meeting the case definition of asthma was reduced to a sub-cohort of children with at least one prescription for an asthma drug.

The rationale for the drug therapy criterion was to: 1) identify children who had been treated with an asthma drug and could be candidates for inhaled corticosteroid drug therapy, and 2) to enable classification by the drug treatment-based asthma severity measure. Moreover, in doing so, the potential for including children with transient wheezing syndromes was decreased because a prescription for an asthma drug was shown to increase the likelihood of continued health care utilization for asthma in children with asthma and bronchitis diagnoses. Furthermore, a measure which classified asthma health care utilization as year-round or winter-only, was constructed in the dissertation research to help distinguish asthma from other wheezing syndromes. Children with transient wheezing and chronic bronchitis are more likely to have viral associated, winter-only, than year-round wheezing, which is characteristic of asthma.(see Chapter 2, page 19) It should be noted however, that this measure would only have been effective in adjusting the differential distribution of transient wheezing by socioeconomic status, if the case definition also selected higher income children with transient wheezing.

In summary, the case definition was carefully constructed to prevent the systematic exclusion of children with asthma. The end product was an "inclusive" case definition which identified children with asthma, according to the presence of an asthma-like diagnosis documented in physician and hospitalization records, or a prescription record for a prophylaxis drug or at least two bronchodilator drugs over a three-year study period.

7.2.2 Measurement Bias

Measurement bias refers to a distortion of the estimate of the association between an outcome and exposure, due to differences in which measures of exposure and outcome are obtained for comparison groups. [1,3] Measurement bias can result in differential and non-differential misclassification of subjects.[1,2] Random errors in the assignment of exposure status can lead to non-differential misclassification and dilute the strength of association between an exposure and outcome. Systematic error in exposure classification or differential misclassification, can underestimate or overestimate the true association. Measurement bias is an important issue for health administrative database research because of the finite amount of data contained in these files.[12] Prescription databases overcome problems of recall bias and are good measures of "ever" drug exposure, but may not describe actual drug use.[13-15] Measurement of health outcome data is subject to the variable reliability and validity of diagnosis information in health care administrative databases, as discussed in Chapter 2 (pages 32-34). All measures used in the dissertation research were created from administrative data and were subject to measurement bias. This discussion will be limited to outcome measures such as inhaled corticosteroid utilization, and determinants of outcome, such as neighbourhood and household income, and asthma severity. The potential for measurement bias in the asthma hospitalization measure will not be evaluated because health care administrative databases are considered reliable and valid sources for enumerating hospitalization events.(see Chapter 3, page 80-81) For information on the validity of asthma diagnoses recorded in hospitalization data, the reader is referred to the selection bias section.

Central to the dissertation research, was the measurement of household income. Two proxy measures of household income were created, one from neighbourhood income quintiles and the other from drug insurance plan status, both of which had the potential to misclassify the household income of children with asthma. Neighbourhood income, a group level measure of income, frequently used to approximate household income, could have attenuated the association between household income, and inhaled corticosteroid utilization or asthma hospitalization. However, Mustard et al's comparison of neighbourhood income deciles, created by aggregating household income from Canadian census data by neighbourhood, and individual household income data reported in the Canadian Census 1986, does not support this hypothesis. [16] They reported similar risks of health outcomes for neighbourhood level and household level measures of income. Furthermore, in the dissertation research children were placed into income quintiles on the basis of the residence postal code, which may not be updated as frequently in the Manitoba Health registry for lower income households, who are more likely to move than higher income households.[17] However, one can postulate that this would not result in misclassification error, on the assumption that lower income households are likely to move to other lower income neighbourhoods.

An alternate measure of household income was derived from the drug insurance plan status of the household, as recorded in the prescription database. Children were grouped as follows: 1) income assistance (provincial and municipal social assistance recipients, treaty status Indians, and other private drug plan beneficiaries), 2) low income area

Pharmacare, and 3) higher income area Pharmacare. This classification served two objectives: 1) to classify households according to their access to prescription drugs, and 2) to classify income at the household level for the purpose of grouping households of similar social and physical environment. Treaty status Indian, and provincial and municipal income assistance household children received free prescription drugs, while children in Pharmacare-eligible households received prescription drugs on a cost-sharing basis. Pharmacare beneficiaries were required to pay an income-based family deductible towards the receipt of prescription drugs, corresponding to 3% of annual household income.

The consequences of incorrectly categorizing Pharmacare children as living in low or higher income households, according to residence in a neighbourhood income quintile, were discussed previously. There also existed the potential for mis-classifying those children in the income assistance category who were receiving benefits from private drug insurance plans, because unlike Pharmacare and provincial assistance program prescriptions, prescriptions for treaty status Indian, municipal social assistance and private drug insurance programs are not identified separately in the prescription database. Misclassification of these children would occur at the level of household income, as well as access to prescriptions because private drug plans provide prescription benefits on a cost-sharing basis.[18]

Misclassification of household income was also possible for treaty status Indian children in the income assistance group, whose households received free prescription drugs, but

were not recipients of income assistance. Placement of treaty status Indian children in the income assistance category can be supported on the basis that treaty status Indians of child-bearing age have income profiles similar to single-parented, income assistance households, whose average annual income is below $15,000.[19] According to 1996 Canadian census data, 66% of Manitoba treaty status Indians, aged 15-44 years old, had received annual incomes below $15,000.[20] The median annual income for treaty status Indians, aged 15-24 years, was $3,134 and for those aged 25-44 years, it was $10,943. Approximately one-quarter of treaty status Indian households in Manitoba were single-parented and in Winnipeg, this proportion increased to 38.7%, suggesting that incomes reported for the treaty status Indian population are representative of many household incomes. Further rationale for grouping treaty status Indian and income assistance children was empiric evidence of an increased risk of asthma hospitalization in both groups, which suggested similar social and physical household environments. Asthma hospitalization has increased in aboriginal children in Canada and Australia over the past two decades to the point that asthma hospitalization rates are greater in aboriginal, than non-aboriginal children. [21,22]

An estimate of the extent of mis-classification of children in the income assistance category can be offered. There are few private drug insurance programs in Manitoba (eg. RCMP) and it was estimated that misclassification on the basis of the drug insurance program would affect 374 (13%) children in the income assistance group. This number represents children who were not treaty status Indian, who did not live in households receiving provincial assistance, and who did not live in the two lowest income quintile

neighbourhoods, a potential marker for households receiving income assistance from municipalities. It was estimated that mis-classification of treaty status Indian children on the basis of household income would affect 145 (5.2%) children in the income assistance group. This number represents children who were treaty status Indian, but did not live in the two lowest income quintile neighbourhoods. Despite the potential mis-classification of some children, dissertation research findings did show an increased likelihood of asthma hospitalization among children living in income assistance. However, it may well be that the reported relative risk was an underestimate of the true extent of increased asthma hospitalization in income assistance children.

Also central to the dissertation research was correctly classifying exposure to inhaled corticosteroid drug. The literature tells use that prescription databases are superior to patient self-reports in describing ever exposure to a drug, and in describing the actual drug name and dose.[14] The dissertation research reported that 45% of children had received a prescription for an inhaled corticosteroid, which is similar to the prevalence of use recorded in other population-based prescription databases, [23] but higher than the 15% prevalence reported in a population-based survey.[24] However, overall prevalence of inhaled corticosteroid use is represented in these numbers, and of relevance to misclassification bias is whether inhaled corticosteroid use is differentially distributed by household income, as an outcome of data collection methods and not true differences in drug use.

Previous research has shown that the completeness of Manitoba's prescription database is dependent on the type of drug insurance program, which was utilized as a measure of household income in the dissertation research.[25] Prescriptions submitted electronically to the prescription database for financial reimbursement (ie. Pharmacare drug program) are more likely to be found in the database, than those submitted for drug utilization review (ie. social assistance recipients, [1] treaty status Indian). It has been estimated that whereas over 90% of prescriptions submitted to the Pharmacare plan are found in the prescription database, this proportion is 80% for treaty status Indians. Thus, there existed the potential for differentially under-reporting inhaled corticosteroid use in the income assistance category, which contained treaty status Indian children. Furthermore, the dissertation research has shown that the average dose of inhaled corticosteroid drugs among children living in low income Pharmacare households was lower than that of children living in income assistance or higher income households. One can hypothesize that non-income assistance, lower income parents, who did not receive free prescription drugs, were more likely to obtain free samples of inhaled corticosteroid drugs from their physicians, which would not be recorded in the prescription database. The extent of distribution of inhaled corticosteroid samples by household income is unknown, but a province-wide increase in the distribution of corticosteroid inhaler samples occurred in the time period after the provincial drug insurance program had introduced an income-based deductible policy (data obtained from Glaxo Wellcome Inc and Astra Inc, manufacturers of high potency inhaled corticosteroids).

[1] Effective April 1996, provincial social assistance prescriptions were also submitted for reimbursement

Another measure of inhaled corticosteroid utilization in the dissertation, which was subject to misclassification bias, was the measure of continuity of inhaled corticosteroid prescriptions, a proxy measure for adherence to therapy. Prescription databases have been utilized to measure adherence to drug therapy, using methodology which enumerates discrepancies between the prescription refill interval and the prescription days supply.[26] Comparisons of prescription database records with home inventory of drugs suggest that approximately 70% of prescription database drugs are actually in use, according to the estimated days supply of the prescription.[13,27] Dissertation findings indicated that 75% of children had periods of continuous inhaled corticosteroid prescriptions. Adherence to inhaled corticosteroid therapy, assessed as the proportion of inhaler doses administered, has been reported to range from 44% to 77%.[28-30] Translating these values into the proportion of children adherent to therapy, an adherence rate of 58%, representing children who took 70% or more of doses, has been observed.[30] Defining adherence on the basis of the proportion of doses taken within pre-determined time windows for dosing, adherence rates as low as 32% are observed.[29]

Thus, it appears that prescription database methods overestimate adherence to inhaled corticosteroid therapy. Of relevance to differential misclassification bias is whether differences in the continuity of inhaled prescription use measure across household income represent true differences in drug use, or a function of creating the measure. In the dissertation analysis it was observed that higher income children were more sensitive to changes in the definition of continuity of inhaled corticosteroid prescription use, than low income or income assistance children. For example, setting the minimum difference

between the refill interval and prescription days supply to 14 days, resulted in a greater proportion of higher, than lower income children potentially being classified as being non-adherent. Subsequently, a difference of 21 days was selected as the minimum because at this value, low and higher income children were as likely to be classified as non-adherent.

Asthma severity is an important source of confounding bias in asthma pharmaco-epidemiologic research, and it was important to create a valid measure of asthma severity in the dissertation research. The asthma severity measure was modeled after the stepwise approach to asthma drug therapy, and children were categorized as having mild, moderate, moderate-severe or severe asthma, on the basis of prescription utilization and hospitalization data. As such, the severity measure was also subject to differential misclassification bias. Lower income children who were less likely than higher income children to receive prescriptions for secondary (prophylaxis) asthma drugs, were potentially at greater risk of not being classified with more severe asthma. In order to overcome this caveat in applying the severity measure, children not receiving prophylaxis asthma drugs had the opportunity of being classified as having more severe asthma if they were hospitalized or used high doses of inhaled corticosteroids. In addition, as inhaled corticosteroids are increasingly being used to treat mild to moderate asthma and higher income children with mild to moderate asthma are more likely to use inhaled corticosteroids, the boundary between severe and not severe asthma in the dissertation research was never the receipt of an inhaled corticosteroid. This prevented bias which

may have resulted in the misclassification of less severe asthma as severe asthma in higher income children.

In summary, the creation of measures, such as household income of residence, inhaled corticosteroid drug utilization and asthma severity from utilization-based data in the dissertation research, had the potential to create measures which were subject to misclassification error. Steps were taken in the creation of these measures to reduce misclassification error.

7.2.3 Confounding Bias

Confounding bias refers to distortion in the estimate of the association between an exposure and outcome by an extraneous variable, which is neither the exposure nor the outcome, but whose effect is tangled up with these variables.[1,3] A factor can only confound a relationship between an exposure, and outcome if it is independently associated with both the outcome and exposure, and is not involved in the causal pathway between them.[1,31] Asthma severity is a well known example of a confounding factor in epidemiologic research assessing the association between asthma drug therapy and asthma hospitalization, but other confounding factors include exposure to upper respiratory infections and indoor allergens.(Chapter 6, pages 203-205) In addition, observed associations between sociodemographic characteristics and asthma drug utilization can be confounded by the utilization of asthma specialists. (Chapter 4, pages 123-124)

Confounding bias is a major issue in epidemiologic research utilizing health care administrative records, subsequent to the limited number of measures contained in the databases. Despite this limitation, an effort was made to incorporate in the dissertation research, as many measures of confounding factors as possible. The evaluation of inhaled corticosteroid utilization in relation to household income was adjusted for asthma severity, exposure to respiratory tract infections, physician specialist use, continuity of physician care and previous health care contact for asthma care. These same measures, and others such as recent utilization of oral corticosteroid drugs, were also included in regression models evaluating the association between household income and asthma hospitalization.

However, exposure to upper respiratory tract infections was the sole measure of exposure to environmental factors in the dissertation analysis. Other environmental risk factors for asthma hospitalization, such as exposure to house dust mites, tobacco smoke and outdoor allergens were not evaluated. Lower income children are more likely to be exposed to these environmental risk factors. In an analysis of Manitoba data from the 1994/95 National Longitudinal Survey on Child and Youth, the prevalence of smoking in the lowest income quintile neighbourhood households with asthmatic children (59.6%) was twice the prevalence observed in higher income quintile neighbourhood households (28.2%). The effect of allergen avoidance on asthma hospitalization was also indirectly assessed in the dissertation analysis. The decreased risk of asthma hospitalization observed during periods of non-continuous use of inhaled corticosteroids in children with

prescriptions for inhaled corticosteroids, independent of asthma severity and exposure to respiratory tract infections, suggested that other unmeasured factors were contributing to the decreased risk. As parental adherence to asthma drug therapy regimens and allergen avoidance measures are often correlated, it was hypothesized that this unmeasured factor was related to decreased allergen exposure. Furthermore, one can argue that the most important environmental trigger of asthma exacerbations, exposure to respiratory tract infection, [32] was controlled for in the dissertation research.

Another issue related to confounding bias is the adequacy of measures of confounding factors, which falls in the domains of measurement bias. The possibility of differential misclassification of asthma severity using the drug treatment-based asthma severity measure was addressed in the measurement bias section. The adequacy of the asthma severity measure, independent of exposure status, or the likelihood of non-differential misclassification of asthma severity, will be discussed here. Moderate, moderate-severe and severe asthma were assigned if children had prescription records for maintenance asthma drugs, in addition to bronchodilator drugs; maintenance asthma drugs included inhaled corticosteroid drugs. This methodology had the potential to mis-classify children with mild asthma who were prescribed inhaled corticosteroids, as having more severe asthma. The outcome of this mis-classification could lead to findings of decreased asthma hospitalization among children utilizing inhaled corticosteroid drugs, when in fact, decreased hospitalization was the outcome of less severe asthma. To circumvent this problem, children classified with mild or moderate asthma were always grouped together in the dissertation research.

7.2.4 Overall assessment of internal validity

The dissertation research was an observation study of the association between household income, and inhaled corticosteroid drug utilization and asthma hospitalization in children with asthma. A cohort study design was employed to decrease the potential for study bias. As summarized in this section, the study cohort was selected and study measures were created with the goal of minimizing selection, measurement and confounding bias. Furthermore, validity assessments of measures such as the asthma case definition and severity measure, were conducted. On the basis of these considerations, it can be concluded that the dissertation research had good internal validity.

7.3 External validity of dissertation research

An assessment of the external validity of a study is an assessment of the degree to which study findings can be generalized to the population of interest, or other populations. Firstly, the dissertation research was a population-based study because data sources were records which had been collected for the administration of a universal health care and prescription drug insurance program. The cohort of children, aged 5 to 15 years old, was assembled on the basis of a shared Manitoba Health registration number with an adult to represent children living in households with parents or other designated care-givers. This enabled classification of households by family structure, ie. single-parent status, an additional measure of household income. The outcome of this definition was the exclusion of children, who did not share a Manitoba Health registration number with their

caregiver, because the Manitoba Health registry does not contain personal identifiers, such as a detailed address (only postal code is recorded), required to link caregivers and children. However, children sharing a household registration number with an adult represented virtually 100% of Manitoban children.

The next question of relevance to external validity, is whether dissertation findings can be generalized to Manitoban children with asthma who had received drug therapy. Many issues relating to selection bias are also important to the external validity of the dissertation research in describing children with asthma. The case definition of asthma employed in the research was "inclusive" to prevent the systematic exclusion of children not diagnosed with asthma or not treated with asthma drugs. However, at the second stage of cohort selection, for which drug therapy was the criterion, the potential existed to under-represent treaty status Indian children with asthma because of lower database submission rates of prescriptions for these individuals.[25] Historically, the prevalence of asthma in aboriginal children have been reported to be much lower than non-aboriginal children, but the Manitoba First Nations Regional Health Survey reports an asthma prevalence of 10%, similar to the prevalence for all Canadian children.[33] If we estimate that 20% of treaty status Indian prescriptions were not submitted to the database,[25] and that the prevalence of asthma in aboriginal children is 10%, this corresponded to the exclusion of about 2% of aboriginal children treated with asthma drugs.

In summary, a multi-domain case definition for asthma was applied to a population-based data source to identify a cohort of children with asthma in the dissertation research, so

that the likelihood of excluding populations of children with asthma was minimal. It can be concluded that the dissertation research also had good external validity and findings can be applied to the Manitoba population of children with asthma being treated with asthma drugs.

7.4 Policy Implications of Dissertation Research

7.4.1 Contribution to pharmacoepidemiologic research

A number of measures were developed in the dissertation research, which are of value to asthma epidemiologic research. They included: 1) case definition for childhood asthma, 2) asthma severity in children, and 3) continuity of inhaled corticosteroid prescriptions.

a) Case definition for childhood asthma

The identification of asthma in childhood is complicated by the presence of other transient wheezing syndromes, which are indistinguishable clinically from asthma and compromise the validity of asthma diagnosis information contained in health care administrative databases.[5] A case definition was developed to select children who had physician visits and hospitalizations for asthma-like diagnoses, or prescriptions for asthma drugs, as defined in the definition. The likelihood of identifying children with persistent asthma was greater in children with asthma drug prescriptions, than in children with an asthma diagnosis. Subsequently, in the second stage of the cohort selection, the

criterion of at least one prescription for an asthma drug among children meeting the case definition, was implemented.

In addition, a proxy measure for the persistence of asthma in children was developed, in which children were classified on the basis of health care use for asthma-like diagnoses and receipt of asthma prescription drugs, as having year-round or winter-only patterns of asthma health care utilization. Year-round health care utilization for asthma-like diagnoses or asthma drug prescriptions was associated with "persistent asthma" to a substantial degree. This finding is compatible with clinical observations of wheezing in children; children with asthma have year-round symptoms, whereas those with transient wheezing have winter-only symptoms.[34] Moreover, it has been recently documented that children with viral-associated wheeze in the winter season are differentiated from children with continuous symptoms by the presence of bronchial inflammatory cells, indicative of asthma.[35] The concept of year-round asthma symptom occurrence was translated into the measure of year-round asthma health care utilization patterns, with the anticipation that it would predict asthma persistence. Due to the strong association between year-round health care utilization patterns and persistence of asthma, we believe that this measure is a valuable addition to the case definition of asthma in childhood.

In summary, a drug and diagnosis-based case definition for childhood was developed and validated, using a construct of persistent asthma in childhood. This case definition can be applied to health care administrative databases and utilized in longitudinal studies of the natural history of asthma. In addition, methods for validating the case definition, which

are more commonly applied to psychometric, than clinical measures, are of interest to researchers validating clinical case definitions.

b) Asthma severity measure

Measurement of asthma severity is critical in asthma pharmacoepidemiologic research to diminish potential confounding of associations between drug therapy and asthma outcomes. Without an adequate measure of asthma severity it is impossible to determine whether an outcome such as asthma hospitalization, is related to a drug exposure or to more severe asthma. Previous hospitalization for asthma has traditionally been employed as a severity measure, but hospitalization for asthma can be influenced by hospital admission policy.[36] Functional asthma severity measures such as symptom frequency, and physiologic measures such as pulmonary function tests, are constrained by the paucity of data in the medical record,[27-39] and are limited in their ability to discriminate between disease severity and disease control.[40-42]

For the dissertation research, a drug treatment-based asthma severity measure, modelled after the stepwise drug treatment of asthma, was developed for application to health care administrative records. The reliability of the asthma severity measure, assessed by test-retest, was found to be excellent, and the measure was responsive to changes in asthma severity over time. The latter attribute is important because asthma severity in children can change as they age. [5] The asthma severity instrument also had construct validity, and predicted asthma severity outcomes of increased need for hospital critical care, of increased ambulatory physician care and of increased consultation with asthma or

pediatric specialists. Drug treatment scales of asthma severity have been criticized on the basis that they are influenced by physician prescribing practices. However, the predictive validity of the asthma severity scale was found to be independent of physician specialty.

In conclusion, a drug treatment-based asthma severity measure for childhood asthma was developed in the dissertation, which can be applied to prescription and hospitalization records. Further, methods utilized to assess reliability and validity of the asthma severity measure are of interest to researchers.

c) Continuity of inhaled corticosteroid utilization measure

Adherence to drug therapy is an important source of confounding bias in assessing the association between drug exposure and an outcome. Commonly, drug adherence to inhaled drugs has been assessed through canister weights and electronic inhalers, measures which are difficult to collect on a population basis. [43] Drug adherence has been measured using data from prescription databases by assessing the discrepancy between the time interval between the dispensing of prescriptions and the days supply of a prescription.[26] In the dissertation research, similar methodology was utilized to determine the continuity of inhaled corticosteroid therapy. Several verifications were undertaken to ensure the validity of the measure. Firstly, there was concern over the accuracy of the days supply variable for inhaled corticosteroid drugs because this measure was calculated at the time of prescription dispensing by pharmacists and its accuracy was a function of the ease in determining the days supply for a prescription. It was hypothesized that while the days supply for an antibiotic tablet could be readily

determined from the quantity and the frequency of administration as written on the prescription, the determination of the days supply for an inhaler was subject to more error because the number of doses in an inhaler is not usually specified on the prescription. The number of days supply for a prescription, recorded in the prescription database was not utilized, but was calculated by dividing the prescription quantity, expressed as the number of doses of inhaled corticosteroid, by two to represent twice daily administration.[44]

Secondly, subsequent to a concern over the validity of the continuity of the inhaled corticosteroid measure several forms were used. Initially, a categorical form of the continuity of inhaled corticosteroid prescription measure was created, according to a minimum number of days of continuous use from the beginning of the first inhaled corticosteroid prescription, as follows: 1) discontinuous use, corresponding to 90 days or less of continuous use, 2) mostly continuous use corresponding to 91-180 days of continuous use and 3) continuous use, corresponding to greater than 180 days of continuous use. Similar to the methodology used by others, [45] this categorization was intended to represent adherence over the number of courses of inhaled corticosteroid drug. High-potency corticosteroid inhalers normally deliver a three month supply. Continuous use over 90 days or less described a delay in refill after the first prescription, and continuous use over 91-180 days described a delay in refill after the second prescription. Recognizing that continuity of use over a short time period may not reflect long-term adherence, the face validity of the categorical form of the measure was ascertained by evaluating the time to hospital admission for each level of continuous use.

As reported in the literature, continuous users were less likely to be hospitalized, than discontinuous users.

However, a reduced risk of asthma hospitalization was also observed in children defined as discontinuous users, which was not entirely compatible with the knowledge that inhaled corticosteroid effectiveness is limited to the time period of administration. Therefore, continuity of inhaled corticosteroid use was also expressed as a time-dependent variable, in which the risk for asthma hospitalization was assessed over periods of continuous use in children, rather than by defined categories of continuous users. The outcome of this methodology was that risk of asthma hospitalization, when evaluated over the time period of receipt of inhaled corticosteroid prescriptions, was no longer reduced in children classified as discontinuous users. The lower risk of asthma hospitalization remained over the time period of inhaled corticosteroid use among children defined as continuous users. The difference in study findings, resulting from the method of defining continuity of inhaled corticosteroid prescription, illustrates the importance of assessing asthma outcome over actual periods of inhaled corticosteroid use.

In summary, a measure of inhaled corticosteroid adherence, based on similar methodology in the literature, was developed for application to prescription databases. Several steps were undertaken to assess the validity of the measure, which can benefit researchers using this methodology.

7.4.2 Contribution to the health of children with asthma

The dissertation research has concurred with two findings in the literature: 1) continuous utilization of inhaled corticosteroid drugs reduces the risk of asthma hospitalization in children asthma, and 2) lower income children with asthma are more likely to be hospitalized for asthma. Moreover, the research has yielded two additional findings, which have not been well documented and are of importance to the health of children with asthma. Firstly, household income has an impact on the utilization of inhaled corticosteroid drugs in children with asthma, and reduced utilization in low income children may contribute to greater hospitalization. Secondly, the utilization of inhaled corticosteroid drugs in children with asthma is influenced by pharmaceutical policy. These new findings will be discussed in greater detail in the following sections, and recommendations offered regarding their translation into public policy.

a) Lower utilization of inhaled corticosteroid drugs in lower income, asthmatic children

Almost 50% of Manitoban children, aged 5-15 years old, with health care contacts for asthma had received a prescription for an inhaled corticosteroid in 1995/96. On average, children in Manitoba appeared to have the same likelihood of receiving an inhaled corticosteroid prescription, as children living in the United Kingdom, a country which has a similar system of universal health care and cost-sharing prescription insurance. [24] However, the likelihood of receiving a prescription for an inhaled corticosteroid was not equally distributed among children. Prevalent and incident use of inhaled corticosteroid drugs was significantly decreased in lower, than higher income children. Lower income

children were also less likely to receive continuous prescriptions for inhaled corticosteroids. We know from the dissertation research, and other similar studies, that continuous use of inhaled corticosteroid decreases the risk for asthma hospitalization.[45-48] Furthermore, discontinuous utilization of inhaled corticosteroid prescriptions was one of the factors which explained the increased risk of asthma hospitalization in low income children.

An immediate reaction to these findings would be a recommendation to implement policies which improve the utilization of prophylaxis drugs in lower income children. However, two additional findings are noteworthy: 1) prevalent utilization of inhaled corticosteroid drugs declined progressively with decreasing neighbourhood income, independent of asthma severity and physician specialty, and 2) incident use of inhaled corticosteroid prescriptions was lower in children living in lower income and income assistance households, independent of asthma severity, physician specialty, previous health care contact for asthma, frequency of respiratory infections, and continuity of medical care. How should we interpret these findings when making policy recommendations to improve utilization of prophylaxis drugs in lower income children with asthma, who are already utilizing the health care system for asthma care?

Firstly, policy initiatives to improve the utilization of inhaled corticosteroid drugs need to take into consideration findings that neighbourhood income differences in utilization were relative to each other, placing higher income children also at risk for under-utilization.[49] Thus, it appears that policies need to be directed at all children. Moreover,

the gradient was apparent in children not seeing specialists, suggesting that general practitioners should be the benefactors of these policies. However, these findings do not provide direction with respect to type of policy required. Is decreased receipt of prescriptions for inhaled corticosteroids in low income households subsequent to the cost of the prescription or asthma management practices?[50-52] The neighbourhood income measure does not allow one to distinguish what type of barrier is operative in low income households. The literature tells us that low income families report payment problems in acquiring asthma drug prescriptions, [53,54] but independent of cost barriers, low income persons with asthma are less likely to be adherent to their drug regimen.[55]

A measure of "cost barrier" was implemented in the dissertation research by categorizing households according to the extent of cost-sharing required for drug insurance program benefits. Children living in social assistance and treaty status households, which received free prescription benefits, were grouped together, as were children residing in Pharmacare households, which paid an income-based deductible towards prescription drugs. Pharmacare children were divided into low or higher income households according to the neighbourhood income of their residence. When defining household income on the basis of drug insurance plan membership, we found a lower likelihood of inhaled corticosteroid utilization in lower income, Pharmacare children, indicating that cost was a potential factor affecting utilization. The impact of income-based prescription benefit cost-sharing on inhaled corticosteroid utilization will be discussed more fully in the next section.

We also found a decreased likelihood of inhaled corticosteroid utilization in income assistance children, suggesting that asthma management practices were also issues in utilization of these drugs. Adherence to inhaled corticosteroid regimens represents a major challenge to optimal asthma management; adherence in low income children is poor.[29,30,55,56] Low income parents have been reported to be less knowledgeable about their children's asthma management or to have a disbelief in the effectiveness of asthma drugs.[57,58] The observed use of inhaler devices has been reported to be dismal in low income children.[29] Parental disbelief in the effectiveness of asthma medication in preventing symptoms has been reported to be associated with recurrent emergency department utilization by low income children.[59,60]

How can health professionals help low income parents manage their child's asthma? Asthma education programs aimed at parents have had an impact, although a modest one, on improving asthma outcomes, such as hospitalization and emergency room use.[61-67] However, asthma education programs are not a substitute for good medical care. Physicians practising in low income neighbourhoods need to be reminded that their patients are at increased risk for asthma hospitalization, and that this can be prevented by the prescription of prophylactic treatment.[68] Asthma education of professionals working in low income area, public health clinics has resulted in increased utilization of inhaled corticosteroids by their patients.[69] Strategies to improving adherence with inhaled corticosteroid treatment need to be multi-faceted, beginning with the education of physician, pharmacists and nurses on the proper use of inhaler devices [70,71] and on good communication techniques in talking about asthma to their patients.[55,72]

Moreover, it is essential that the provision of any asthma education incorporate a greater understanding of how individuals experience asthma.[73] Encouraging the use of symptom diaries may demonstrate to parent the benefits of inhaled corticosteroid drugs in preventing asthma exacerbations in their children.

Recommendation #1

Implement academic detailing[2] of physicians on the benefits of asthma prophylactic agents, including the presentation of data on the income distribution of asthma hospitalization rates in children. Accessing data from Manitoba's prescription database, provide practitioners with feedback on their prescription of inhaled corticosteroid drugs in comparison to the proportionate utilization for all Manitoba. Target academic detailing and prescribing feedback at family physicians practicing in low income areas.[74]

Recommendation #2

Enhance effectiveness of communication of asthma therapy information to parents with asthmatic children through education of health professionals on the correct utilization of inhalers and on differences in perception of the benefits of asthma drug therapy, which may exist among parents. Target education programs at health professionals working in low income areas.

[2] physician is visited by a health professional, eg. pharmacist, who leaves asthma education material

Recommendation #3

Encourage parents with asthmatic children to keep symptom diaries to demonstrate the benefits of daily treatment with inhaled corticosteroid drugs in preventing asthma exacerbations.

b) Income-based pharmaceutical policy did not improve utilization of inhaled corticosteroids in working poor families

In April 1996, the provincial drug insurance program, Pharmacare, introduced an income-based deductible towards the receipt of prescriptions drugs. Under the income-based policy, households with annual income greater than $15,000 were required to pay a deductible of 3%, and those below this income paid a deductible of 2%.[75] High potency inhaled corticosteroids drugs are expensive to obtain and it was hypothesized that the utilization of these drugs would be sensitive to pharmaceutical policy. The utilization of inhaled corticosteroid drugs in low and higher income, Pharmacare children was compared in the post-policy period to income assistance children, whose households did not experience a change to pharmaceutical policy. Regardless of drug insurance plan membership, children whose asthma severity had decreased in the post-policy period were less likely to utilize inhaled corticosteroid drugs, and children whose asthma severity had increased were more likely to have prescriptions for these drugs. However, higher income Pharmacare children with severe asthma, were less likely than income assistance children to receive prescriptions for inhaled corticosteriods post income-based policy. Among higher income Pharmacare children with severe asthma, continuing to receive inhaled corticosteroid prescriptions, utilization decreased from a mean of

approximately one dose of inhaled corticosteroid per day to about 300 doses per year. These findings are not dissimilar to other reports of a decline in utilization of essential prescription drugs following changes to pharmaceutical policies which impose increased costs on its recipients.[76-79]

Prior to the income-based policy, the mean number of doses of inhaled corticosteroid per child with severe asthma was significantly lower among low income, Pharmacare children than income assistance children, and this difference widened post policy. These findings allude to a further outcome of the new Pharmacare policy: the income-based policy did not improve drug utilization among low income Pharmacare children, despite diminishing cost barriers to acquiring these drugs. Low income adults report problems in being able to pay for their children's asthma prescriptions,[54] and are less likely to fill prescriptions for asthma drugs. [50] A very high deductible level relative to inhaled corticosteroid prescription may explain why higher income families would decrease their use of these drugs. Moreover, it also potentially explains why low income families failed to increase utilization of these drugs. The annual deductible of approximately $300.00 for families earning less than $15,000.00 was not much different from the pre-policy deductible amount, and would require out-of-pocket payments for an annual supply of corticosteroid inhalers.

Cost barriers to the use of prescription drugs in the management of chronic disease impose increased morbidity among those affected. [80-82] Lower utilization of inhaled corticosteroids has been associated with increased hospitalization for asthma. [45-48]

Hospitalization for asthma contributes substantially to the costs of managing this disease [83,84] and reduces the quality of life of asthmatic children. [85] Despite an increase in use of inhaled corticosteroid over the last ten years, [86-88] inhaled corticosteroids remain underutilized.[6,23,89,90] It is therefore, imperative that pharmaceutical reimbursement policy not be a deterrent to the utilization of these drugs, especially in children, among whom prescription payment problems are more common.[53,91] In our era of cost containment, income-based pharmaceutical benefit policies appear to be good choices for equitably distributing the burden of prescription costs.[92] However, the impact of these policies on prescription utilization requires evaluation and if necessary, as done in other jurisdictions, readjustments need to be made to levels of patient cost sharing.[53]

Recommendation #4

Implement a pharmaceutical reimbursement policy which provides free prescription benefits to children, as is the practice in the province of Quebec, [94] or introduce the requirement of nominal copayment or deductible payments for children's prescriptions.[53]

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