AN EVALUATION OF THE DETERMINANTS OF ASTHMA MANAGEMENT AND ASTHMA CONTROL: A STUDY OF BRITISH COLUMBIA ASTHMATICS

by

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ABSTRACT

Objectives: The primary objective of this study was to assess the relationship between socioeconomic status and the magnitude of short-acting β-agonist use and asthma control. The primary hypothesis of this study was that lower socioeconomic status asthmatics are more likely to use greater amounts of short-acting β-agonist medications and experience poorer asthma control than asthmatics in higher social classes, independent of asthma severity.

Methods: Retrospective administrative data was used to evaluate the association between inappropriate asthma management and health care resource utilization, and to assess trends in asthma medication use between 1996 and 1998 in British Columbia. Using camouflaged sampling and volunteer recruitment, 202 asthmatics between 19 and 50 years of age were recruited for direct assessment to evaluate the relationship between socioeconomic status and asthma control, adjusting for asthma severity. Recruiting rates of camouflaged sampling were evaluated, and characteristics of sampled participants and volunteers were compared. Asthma control was measured using the magnitude of short-acting β-agonist use, and the Asthma Control Questionnaire. Five methods of adjusting for asthma severity were used. Socioeconomic status was measured at the individual level based on self-reported income, education, and receipt of social assistance, and at the population level according to neighbourhood median household income, proportion of neighbourhood with at least a bachelor's degree, and neighbourhood unemployment rate.

Results: Initial analyses of administrative data revealed that inappropriately managed asthmatics utilize more health care resources relative to appropriately managed asthmatics. Longitudinal analysis of Pharmacare prescription data did not reveal any
reduction in short-acting β-agonist use or increase in inhaled corticosteroid use. Asthmatics receiving social assistance were more likely to increase their use of SA β-agonists versus those who were not. Independent of the method of measuring socioeconomic status or adjusting for asthma severity, less education, lower income, and receipt of social assistance were consistently associated with the use greater amounts of SA β-agonists independent of asthma severity, and to have more poorly controlled asthma based on the Asthma Control Questionnaire. Population measures of socioeconomic status revealed similar and consistent relationships.

**Conclusions:** Inappropriately treated asthmatics in BC utilize more health care resources, and the excessive use of SA β-agonist medications persists. Camouflaged sampling resulted in a more heterogenous sample of SA β-agonist users compared to voluntary recruitment. Socioeconomic status is strongly and consistently negatively associated with the magnitude of SA β-agonist use, independent of asthma severity, and is positively associated with asthma control. Improvements in asthma control in lower social class asthmatics may result in a narrowing of the social gradient in asthma-related outcomes.
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CHAPTER 1
INTRODUCTION

1.1 ASTHMA: EPIDEMIOLOGY AND RELATED OUTCOMES

Asthma is one of the most prevalent chronic conditions affecting Canadians, and is a significant chronic health problem worldwide. It is a chronic, controllable disease of the lungs that involves inflammation of the airways, and is characterized by paroxysmal and persistent symptoms of dyspnea, chest tightness, wheezing, sputum production and cough. These symptoms are associated with various degrees of airflow limitation and airway hyper-responsiveness to endogenous and exogenous stimuli. In 1995, the World Health Organization and the National Heart Lung and Blood Institute estimated that more than 100 million people worldwide suffer from asthma. It has been suggested that asthma is the leading chronic disease in children and is the second most common childhood disease, second only to the common cold.

Clinical and objective measurements and criteria have been developed for the diagnosis of asthma, but because they are inconsistently and often inappropriately applied, and because the definition of asthma and the diagnostic criteria have varied over time, the determination of the true prevalence of asthma is difficult. Furthermore, most studies that have attempted to estimate the prevalence of asthma have relied upon questionnaires that merely ask the general population if they have been diagnosed with asthma by a physician. Thus, the true prevalence is likely to differ from the published estimates.

Numerous studies performed in different countries and varying populations over the last 30 years have provided relatively consistent estimates of asthma prevalence and
good evidence suggesting that it is continuing to increase worldwide. Asthma surveillance in the United States has shown a consistent increase in the prevalence of asthma over the past three decades.\(^4\) The overall prevalence of self-reported asthma in all ages in the twelve months prior to a survey in 1980 was 3.1%, which increased to 5.5% in 1999 when the prevalence was highest in children (5 – 14 years; 7%) and young adults (15 – 34 years; 6.7%), which was more than 2-fold higher in young adults than it was in 1980. Although there was no gender difference in prevalence in 1980, in 1999 relatively more women reported having experienced asthma symptoms in the previous twelve months (6.6% versus 4.3%). Analysis of the prevalence of having experienced an episode of asthma or an asthma attack in the previous twelve months resulted in similar findings.

In Canada in 1979, the prevalence of asthma was estimated to be 2.3% in people over the age of 15 years. This increased to 4.9% in 1988 and 6.1% in 1992.\(^5\) Analysis of data from the National Population Health Survey showed that the prevalence of asthma diagnosed by a physician and requiring treatment with an asthma medication, or of having experienced symptoms of asthma in the previous twelve months remained essentially unchanged (6.2%) in 1996.\(^6\)\(^7\)

The prevalence of asthma varies with age, ranging from 3% to 6% in adults to 10% to 11% in children and adolescents.\(^6\)\(^7\) The most current estimates of asthma prevalence in Canada derived from the 1998/99 National Population Health Survey showed an overall population prevalence of 7.9%, with 10.7% of the population under the age of 20 and 7.5% of those 20 years of age and over reporting having been diagnosed with asthma by a physician.\(^8\) This accounts for approximately 845,000 Canadians under the age of 20 years, and 1.6 million adults. Thus, it appears that over the last 20 years the
prevalence of asthma in Canada has more than tripled, with a recent increase of almost 2% over only two years.

Hessel et al. performed a survey of elementary school children in Fort Saskatchewan, Alberta in an attempt to determine the prevalence and impact of asthma in this age group.\textsuperscript{9} They found that in children in grades one to six, 12.9% (16.0% of boys and 9.7% of girls) had a history of physician diagnosed asthma, and at the time of the survey the point prevalence of asthma was 9.9%. From the Student Lung Health Survey, a school based survey conducted in 1995 and 1996 of students between five and nineteen years of age in nine health units across Canada, the prevalence of asthma in this age group was estimated to be 13%.\textsuperscript{10}

In Australia, a cross-sectional study of the prevalence of respiratory symptoms and atopy in children between eight and eleven years of age in one community found that between 1992 and 1997 the prevalence of self-reported wheeze in the previous twelve months increased from 36.9% to 42.3%.\textsuperscript{11} The prevalence of physician diagnosed asthma also increased significantly by 8.1% (95% CI 3.8% to 12.4%) from 30.5% to 38.6%. These rates are considerably higher than those that were expected, and higher than the world norm.

Although the potential etiologies of this apparently increasing prevalence of asthma remain essentially hypothetical and relatively poorly understood, data from numerous countries using different methods and data sources are consistent, suggesting that this apparent increase is real, and is occurring in both children and adults. The significant proportion of the population with asthma results in the potential for a significant burden of illness, particularly in conjunction with inadequate control. In the early 1990’s, approximately 10.1 million missed school days in the US were attributed to
asthma which may be at least partially attributable to inadequate control. The increasing prevalence would suggest that this is likely currently even greater. However, the burden of a chronic illness on children extends far beyond the tangible outcome of school absenteeism to many psychosocial and developmental consequences which can have considerable detrimental long-term effects. Specifically, children with asthma have been shown to be at greater risk of learning disability and failure at school, and to have lower self-esteem than their otherwise healthy peers.

Asthma also results in a considerable burden on adults both directly and indirectly through a family member with the disease. This burden on an individual may be economic as a result of missed work, decreased productivity, or the cost of managing a chronic disease, or it may cause psychological adverse effects and have a significant detrimental effect on an individual’s quality of life. With the advances in medicine and the associated improvements in health, one of the primary limitations on quality of life in the developed world is the psychosocial burden of illness. Asthma-related morbidity also poses a significant societal burden in terms of not only decreased productivity at the individual level, but also economically as a result of demands put on the health care system by the physician and emergency room visits and hospital admissions related to asthma.

Over a 12 month period in 1996-1997, 44.2% of Canadian children with asthma visited a physician up to three times for the management of their asthma, with an additional 15.4% going four or more times. 75% of these children visited their family physician, 40% visited a pediatrician, and 27% were assessed in an emergency department. In a study of adults with asthma, more than 18% that reported having ‘active
asthma had visited an emergency department in the previous year because of their asthma, and 5.3% required hospitalization.\textsuperscript{18}

In 1994, there were more than 54,000 hospital admissions due to asthma in Canada (Laboratory Centres for Disease Control unpublished data). Using data from the 1994/1995 National Population Health Survey, the population attributable risk of hospitalization due to asthma was estimated to be 3.7% for men and 2.4% for women.\textsuperscript{19}

In Canada between 1970 and 1987, there was a steady increase in the age-adjusted rates of hospital separations attributable to asthma from approximately 135 per 100,000 to more than 250 per 100,000.\textsuperscript{20} The highest hospital separation rates occurred in children less than five years of age, peaking in 1986 at over 4,500 per 100,000. These rates drop dramatically with age, being almost four-fold lower in children between five and fourteen years of age, and less than 500 per 100,000 in 15 and 34 year olds. The most recent data extracted from the Hospital Morbidity File of the Canadian Institute for Health Information by the Centre for Chronic Disease Control and Prevention show that the hospitalization rates in children under 5 years of age continue to be more than four times the rate in the rest of the population.\textsuperscript{8} Despite this decline, asthma continues to be a major cause of hospitalization in Canada, accounting for 12% of all hospital admissions in children under 5 years of age, and 10% of admissions in those 5 – 14 years of age.\textsuperscript{8}

In adults, men less than 35 years of age appear to experience the highest rates of hospitalization secondary to asthma.\textsuperscript{8} Conversely, men 35 years of age and older experience the lowest rates of hospitalization. Although secular trends indicate that men have always experienced greater asthma-related morbidity based on this measure, the differential between men and women has increased over the last three decades. Since
1987, the hospitalization rate has consistently declined to near 1971 rates for all subgroups except men over the age of 34 years.

The high prevalence of asthma and its burden on the health care system and individual productivity results in a significant economic impact. The total (direct and indirect) cost of asthma in Canada in 1990 was estimated to be between $504 million and $604 million (1990 Canadian dollars), of which the largest component was drug costs ($124 million) followed by illness-related disability costs ($76 million). A more recent study evaluated the per patient costs of asthma in south-central Ontario in 1995-1996 and found that the average annual cost of asthma (in Canadian dollars) from a societal prospective was $2,549.60, comprised equally of direct and indirect costs. Adjusted for disease severity, the costs were $1,617, $2,218, and $3,905 per person for mild, moderate, and severe asthmatics, respectively. A US study estimated the total economic burden of asthma in that country in 1990 at $US6.2 billion. Two subsequent studies projected the costs of asthma in the US to be $US10.7 billion and $US12.6 billion in 1994 and 1998, respectively, of which approximately 58% were direct costs.

There was a worldwide surge in asthma-related mortality in the 1980's. Currently, it is estimated that 50 children and 500 adults die from asthma in Canada each year, however, it has been suggested that 80% of asthma deaths could be prevented with proper asthma education, which could be extrapolated to mean appropriate asthma management. The Canadian age-adjusted rate of asthma-related mortality increased from approximately 1.6 per 100,000 in 1971 to 2.5 per 100,000 in 1982, following which it has progressively declined to a low of 1.25 per 100,000 in 1997. This is the most current data available.
This overview is meant to provide a summary of the current state of knowledge of asthma, particularly in Canada, in terms of its burden on society. The prevalence of asthma appears to be continuing to increase, which will further exacerbate the already significant morbidity, mortality, and costs associated with this disease if asthma management and asthma control are not improved. Although appropriate management has no effect on the prevalence of the disease, it will result in the reduction of asthma-related morbidity and mortality to the lowest possible level, and thus, minimize the societal burden of the disease. Any amount of inadequate asthma management, given the availability of effective therapy, will result in a corresponding excess of unnecessary adverse asthma-related outcomes.

To this end, recent advances in the understanding of the mechanisms of airway obstruction and inflammation, exacerbating factors, and asthma pharmacotherapy have lead to the development of asthma management guidelines which if adhered to, should theoretically result in essentially complete asthma control in all but those with the most severe, treatment recalcitrant disease.1,27,28

1.2 RESEARCH NEEDS AND STUDY JUSTIFICATION

The appropriate and most efficient use of health care resources has resulted in the need to identify specific populations or types of patients at risk for adverse health-related outcomes from any disease. It is well established that the poor experience greater disease-related morbidity and mortality. This knowledge results in the need to study the relationship between socioeconomic status and different facets of health and health care in an attempt to elucidate the specific factors that might be contributing to the social gradient in health outcomes.
Currently, we have both the knowledge and the therapeutic modalities that, if used appropriately, should permit anyone suffering from asthma to live an essentially normal, symptom-free life. Despite the development and dissemination of these guidelines, there is evidence suggesting persistent non-adherence to these guidelines, and thus, sub-optimal asthma management and consequently a higher incidence of adverse asthma-related outcomes than is theoretically obtainable.\textsuperscript{29-31} This continued non-compliance with management guidelines suggests that a reduction in asthma-related morbidity through improved management is achievable. Further optimization of asthma management should therefore be a primary goal of achieving ultimate control and better asthma-related outcomes.

Among the next logical steps in the endeavour of optimizing asthma management, improving asthma care, and minimizing asthma-related morbidity is the identification of the factors related to, and the characterization of, specific populations at risk for poor asthma control. Although there is growing evidence of specific populations who appear to be at greater risk of adverse asthma-related outcomes and inappropriate management, much of this evidence is based on US populations where access to medical care and prescription drugs differs significantly from Canada,\textsuperscript{32-34} and / or on studies which failed to separate the dimensions of asthma severity and control.\textsuperscript{35,36}

Although there are many hypotheses about what factors might contribute to inadequate control, the primary focus of this study was the evaluation of a potential social gradient in asthma control. Socioeconomic and demographic factors figure prominently in overall health, and in asthma control specifically. Numerous studies have already demonstrated that lower socioeconomic status asthmatics experience more frequent hospital admissions,\textsuperscript{34,37-40} emergency room visits, and visits to their family physician.\textsuperscript{41-}
Furthermore, in addition to increased morbidity, retrospective data analysis in which socioeconomic status was based on occupation also showed that asthma-related mortality is also higher in lower social classes.\textsuperscript{45,46} The magnitude of the excess of these rates in the lower social classes suggests an attributable risk to factors that remain to be identified.

One study performed in the UK concluded that adults in the lower two quintiles of socioeconomic status were more likely to have disabling asthma than those in the upper two quintiles.\textsuperscript{47} In a Canadian study, Erzen et al. found that low income adults with asthma experienced more frequent physician visits, higher hospitalization rates, and less frequent referral to a specialist relative to asthmatics with higher household incomes.\textsuperscript{44} Both of these studies concluded that the social gradients in asthma-related outcomes were related to more severe asthma in poorer asthmatics. However, both studies were limited to survey data and were therefore unable to differentiate between asthma severity and asthma control. In both studies, the outcomes assessed could have been equally related to poor asthma control as to greater asthma severity.

Only one previous study in adults has shown poorer asthma control in poorer asthmatics, based on a greater reversibility of airway disease in men in lower social classes.\textsuperscript{48} The only studies to evaluate the social gradient in the pharmacologic management of asthma were done in the US, and only in children and adolescents.\textsuperscript{49,50} Different factors likely impact asthma control in children and adults, and lower socioeconomic status asthmatics in the US are more likely to be uninsured and experience barriers to the access to health care and prescription drugs than a comparable population in Canada.

This study was conceived based on the need to assess the relationship between socioeconomic status and asthma control, independent of asthma severity, in a population
where there are theoretically no barriers to the receipt of health care. Because survey and database studies do not permit the differentiation between asthma severity and asthma control, adequately assessing the social gradient in asthma control while adjusting for asthma severity necessitated that a sample of asthmatics be recruited and directly evaluated. A detailed discussion of the current data pertaining to socioeconomic status and asthma, and of the complex relationship between asthma severity and control is provided in chapter 2.

1.3 STUDY HYPOTHESIS, OBJECTIVES, AND THESIS ORGANIZATION

The aim of this study was to evaluate the association between socioeconomic status and asthma control, independent of asthma severity. The primary hypothesis of this study was that lower socioeconomic status asthmatics residing in the Greater Vancouver Regional District (GVRD) were more likely to use greater amounts of SA β-agonist, independent of asthma severity, and to have more poorly controlled asthma relative to asthmatics of higher socioeconomic status. Prior to the testing of this hypothesis, it was necessary to evaluate the population in which this hypothesis would be tested to ensure that asthma management in British Columbia is consistent with that demonstrated in other populations.

The first objective of this study was therefore to determine if, in British Columbia, inappropriate asthma management is associated with greater asthma-related morbidity.

The second objective was to evaluate time trends in asthma treatment in British Columbia to determine if pharmacotherapeutic management is improving in accordance with the asthma management guidelines, and to assess the prevalence of inappropriate
asthma management, and specifically, of the over-utilization of SA β-agonists for the management of asthma. It was imperative that this be evaluated prior to embarking on a study of the characteristics of inappropriate over-use of SA β-agonists to determine if this was a significant enough problem in this population to warrant investigation. Preliminary analysis of factors related to increasing SA β-agonist use was also performed.

The third objective was the accrual of a sample of asthmatics, heterogeneous for different levels of SA β-agonist use. In order to achieve this objective, a novel recruiting methodology was used which facilitated the sampling of individuals identified from the same administrative database that was used to fulfill the first two objectives. A random sample of potentially eligible study participants was selected, and stratified by the number of canisters of salbutamol (or the equivalent) multi-dose inhalers that they received in the year prior to recruitment. Based on an a priori belief that the majority of asthmatics in the general population would use relatively small amounts of SA β agonist, we hypothesized that the utilization of this sampling strategy would result in a more heterogeneous sample of SA β-agonist users than would sampling from the general population.

Finally, the fourth and primary objective was to assess the association between both individual (proximate) and population (contextual) measures of socioeconomic status and asthma control. This objective was achieved by evaluating the relationship between socioeconomic status and the magnitude of SA β-agonist used, which can be used as a measure of asthma control and has been shown to be positively associated with adverse asthma-related outcomes, and with overall asthma control quantified using a validated asthma control score.51
This thesis is comprised of eight chapters, organized chronologically, addressing each of the objectives in order. This first chapter provides a brief introduction to the epidemiology of asthma and outcomes related to inappropriate management, and provides some insight into the motivation and justification of this study.

Chapter 2 delves more specifically into the development of the hypothesis from the literature as it relates to social class and asthma management and related-outcomes, and to the complex relationship between asthma severity and asthma control. Chapters 3 and 4 present the results of the background administrative data analysis required to establish the association between inappropriate asthma management and adverse outcomes, to determine the magnitude of over-utilization of SA β-agonists in British Columbia, and to provide the first evidence of an association between lower socioeconomic status and increasing use of SA β-agonists. Chapter 5 provides a detailed description of the method of camouflaged sampling as it was applied specifically in this study, and some empirical evidence of its overall utility. Chapters 6 and 7 present the final results of the evaluation of the social gradient in asthma control. Chapters 3 through 7 are each stand alone manuscripts which have either been published, are in press, or are under review by a major, peer-reviewed, scholarly journal. The work presented in this thesis was conceived, conducted, and disseminated by the doctoral candidate as has been declared by the co-supervisors of the candidate (Appendix I).

The final chapter provides a summary of the research findings and outlines the strengths, limitations and the unique contributions and potential impact of the findings of this study.
1.4 SUMMARY

The prevalence of asthma is high, with the most recent estimates indicating that approximately one in twelve Canadians, or approximately 2.4 million people, have been diagnosed with asthma. Despite decreasing hospital admissions and mortality, inappropriate management appears to be persisting. This creates an opportunity for further improvements in asthma management and consequently asthma-related outcomes which will require that persons or subgroups of the population at risk for poor asthma control be identified.

This study focused on the specific association between socioeconomic status and asthma control. The evaluation of this association in this population required an analysis of treatment-related outcomes and asthma medication utilization patterns in BC, and the recruitment of a sample of asthmatics for direct assessment to facilitate the delineation of asthma severity from asthma control.

1.5 REFERENCES


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CHAPTER 2
BACKGROUND

2.1 SOCIOECONOMIC GRADIENTS IN ASTHMA-RELATED OUTCOMES

The presence of a social gradient in health and health-related outcomes has been well established. In general, the poor appear to be less healthy and utilize more health care resources than the more wealthy or affluent. A social gradient in health-related outcomes has been identified in approximately 80% of the 80 most common diseases.\(^1\) The only diseases in which there is clearly no social gradient are breast cancer and skin cancer.\(^1\)

Much of the heterogeneity between populations can be attributed to differences in the rates of risky or harmful behaviours such as smoking, obesity, and drunk driving, which may not be individual choices, but rather, conditioned social responses or actions.\(^2\) It has also been suggested that the prevalence of psychosocial risk factors is also highest in the least well off, and that it is more likely relative social class as opposed to absolute poverty that predicts the overall health of a population.\(^1\) This has been exemplified by evidence from the Black report that showed a gradient in health within a group of white collar employees.\(^3\) Marmot also showed similar gradients associated with hierarchy within groups, and not specifically with deprivation.\(^4,5\) This demonstrates that not only is there a gradient across social classes, but also the power of the effect of social discrepancy or discordance within social classes.

This effect is most likely tied closely to the impact of lifestyle, which encompasses the socially, culturally, economically and environmentally conditioned actions characteristic of an individual or group as a pattern of habituated behaviours that
can be health related, but not necessarily seen as health directed. Although the social class gradient cannot be attributed solely to differences in health care, these lifestyle effects may play a role in social class differences in health care utilization and the adoption of beneficial health care practices. Thus, although modern medical care is not the primary etiologic factor related to the gradient in health outcomes, this gradient may be at least partially attributable to social class differences in disease management as opposed to just health care utilization.

Asthma is one of the 80 most common diseases in which there is a social gradient. Apter et al. evaluated the influence of demographic and socioeconomic factors on health-related quality of life, and specifically on asthma-related quality of life. They found that in addition to factors related to asthma severity, race and socioeconomic status were also associated with asthma-related quality of life. Socioeconomic status was quantified specifically by education, unemployment, family income under $US 20,000, receipt of social assistance, and whether or not an individual had health insurance. These variables combined explained 67% of the variance of the total asthma-related quality of life score; however, because they are highly correlated, asthma severity and socioeconomic status uniquely explained only 12% and 9% of the variance, respectively. Regardless, in this population, lower socioeconomic status was strongly associated with poorer asthma-related quality of life. A study of asthma-related work disability in adults showed that although asthma severity was the strongest predictor, working conditions including job related exposures were associated with a greater risk of disability, even after taking into account disease severity. Considering that individuals of lower socioeconomic status are more likely to be working in labor-related blue-collar occupations, it is conceivable that
occupational exposures in this population may be a contributing factor to the higher rates of adverse asthma-related outcomes.

Studies evaluating the effect of social class on morbidity have used the frequency of hospital admissions, emergency room visits, and physician visits as a measure of asthma-related morbidity. Although emergency room and physician visits may occur as a result of merely seeking care and may be unrelated to morbidity, a hospital admission is likely due to an asthma exacerbation suggestive of inadequate control, and thus provides a valid surrogate measure of asthma-related morbidity. A retrospective database analysis of hospitalizations of five to 35 years olds in Chicago found a significant association between higher hospitalization rates and both lower median neighborhood income and a greater proportion of the community receiving Medicaid, Medicare, or having no health insurance. Asthma hospitalization rates for 18 to 34 year old men on Medicaid (the lowest socioeconomic status) were 17 to 34 times higher than among men with other forms of health insurance. Lin et al. report similar findings using similar methods in New York state between 1987 and 1993.

A study of a large administrative claims database in Connecticut also found that the type of health care insurance a person had was the strongest predictor of treatment site. Adults with commercial health insurance or Medicare were the most likely to be treated as outpatients, while those with public insurance were 2.4 times more likely to be treated in hospital and those without health insurance were five times more likely to be treated in an emergency department relative to those with commercial insurance. The authors concluded that socioeconomic status may be “the most important determinant of higher morbidity”. This is supported by a study of children less than 18 years of age living in the northeastern United States which found that, over a ten year period,
hospitalization rates due to asthma increased the most in blacks and Hispanics and in children living in areas with the lowest median neighborhood incomes or in metropolitan areas, relative to those living in more affluent neighborhoods.\textsuperscript{12}

Three British studies used the Townsend Index of Deprivation to evaluate associations between social deprivation and hospital admission rates at the population level.\textsuperscript{13-15} The Townsend Index of Deprivation, used widely by demographers, is a composite score of social status derived from census data and is based upon neighborhood unemployment rate and the proportion of private households that are not owner occupied, do not possess a car, and have more than one person per room.\textsuperscript{13} Consistently, hospital admission rates due to asthma were strongly and positively correlated with deprivation (Spearman's $\rho = 0.65 - 0.87$). Significantly more hospital admissions occurred via emergency departments than through practitioner referrals in areas of higher deprivation suggesting a greater reliance on emergency rooms for routine care.\textsuperscript{14} This may have significant implications in terms of continuity of care and the ability to obtain consistent and appropriate asthma management.

In Canada, the most recent study using data from the 1995/1996 cycle of the National Population Health Survey found that age and social class were significant risk factors for hospitalization due to any cause, and that asthmatics had higher hospitalization rates than did non-asthmatics.\textsuperscript{16} Within asthmatics, the incidence of hospital admissions related to asthma was the highest in those with the least education and lowest incomes, independent of gender. However, compared to non-asthmatics, asthma appeared to have the biggest impact on hospitalization rates in males less than 25 years of age relative to older men, in less educated asthmatics relative to the well educated, and in middle income men and low to middle income women relative to those from higher income.
families. This study therefore suggests that income (i.e. socioeconomic status) may modify the risk of hospitalization due to asthma, particularly in men.

Lower social status asthmatics also appear to be treated in emergency rooms and assessed in physician’s offices more often.\textsuperscript{11,17-20} Kolbe et al. examined the characteristics of asthmatics requiring asthma treatment in an emergency department in New Zealand and found that less education, lower socioeconomic status (although not clearly defined), and having become unemployed in the previous twelve months were all associated with greater asthma-related morbidity.\textsuperscript{17} Having not filled a prescription due to its cost was also related to visiting an emergency department. In one study of emergency department management of asthma in children in which 16% of patients accounted for more than one-third of the emergency room visits, the highest frequency of emergency room visits occurred in children less than five years of age, African Americans, and those with Medicaid health insurance.\textsuperscript{18}

A similar study conducted in Quebec also found that 75% of emergency department visits were made by 25% of the patients studied,\textsuperscript{21} and as a follow up to this study, these investigators sought to identify the characteristics of this sub-population of asthmatics who frequently require emergent asthma management.\textsuperscript{19} In addition to factors relating to knowledge of asthma management and control, although they were not statistically significant, they also found that those seen in emergency were of slightly lower socioeconomic status than the control group.\textsuperscript{19} Specifically, patients requiring emergency room management had lower incomes, less education, were more likely to be unemployed, and had more psychosocial problems. The lack of a statistical association may have been a reflection of a lack of power of the study to detect a difference given the limited sample size of only 30 patients.
Another Canadian study examined income and its relationship with the prevalence of physician diagnosed asthma and total respiratory morbidity and care patterns in Manitoba.\textsuperscript{20} Socioeconomic status was classified based on the median neighborhood income of their place of residence. In this study, a larger proportion of low income asthmatics visited their physician on multiple occasions relative to higher income asthmatics, which was particularly significant for children and adults over 35 years of age. They also found that higher income patients were more likely to be referred to a specialist (p<0.0005), and that children and adults over 35 years living in high income neighborhoods were less likely to be hospitalized. Although there was no income gradient in hospitalizations in adults between 15 and 35 years, asthma accounted for essentially all hospitalizations for respiratory disorders in this age group.

This study was based on administrative data, and as such, in their assessment of referrals it was only possible to determine who actually visited an asthma specialist, but not if there were social class differences in who might have received a referral but were not subsequently assessed by a specialist. The authors deduced that, because in Canada there are no income-related barriers to health care and they did not find any evidence of more fragmented care in the lower income asthmatics, the gradients in outcomes that they identified were at least partially related to greater severity of asthma in the lower income quintiles of the population. There was no direct evidence of this.

A social gradient in asthma-related mortality has also been identified. Analysis of data collected from 19,698 individuals for the Copenhagen heart study in 1976 identified education as a significant predictor of death due to asthma.\textsuperscript{22} Relative to participants with less than seven years of education, the relative risk of death for those with seven to ten, and more than ten years of education was 0.9 (95\% CI 0.7 – 1.0) and 0.8 (95\% CI 0.6 –
respectively. A population-based study done in the UK also found that overall mortality due to asthma was higher in people employed in manual labor occupations relative to those in non-manual occupations.\(^{23}\) Subgroup analysis revealed that this entire effect occurred in men between 35 and 64 years of age.\(^{23}\) In the US, although asthma-related mortality rates for most ages appear to have stabilized since 1988, the rates in African Americans continue to be higher than in Caucasians.\(^{24}\)

Health-related quality of life can also be used as a measure of disease-related morbidity. If one accepts this premise as true, Apter et al. showed that lower socioeconomic status asthmatics had poorer asthma-related quality of life, quantified using the Asthma Quality of Life Questionnaire (AQLQ).\(^{7,25}\) Asthmatics with incomes less the $20,000 had lower overall AQLQ scores (representative of poorer asthma-related quality of life) than did those with incomes greater than $20,000 (3.2 vs. 4.9; \(p<0.001\)), as did those with less than twelve years of formal education relative to those with twelve or more years (2.8 vs. 4.7; \(p<0.001\)). Similar associations were also found on the Mental Component Score and the Physical Component Score of the SF-36.

In addition to asthma severity and socioeconomic status, numerous other factors are also associated with a greater risk of asthma-related mortality, including the underestimation of severity by either the physician or the patient, psychosocial dysfunction, inadequate management, over-use of short-acting bronchodilators, and the use of psychotropic medications, to name only a few.\(^{24,26-28}\) The relationship between mortality and psychosocial stressors has been demonstrated on many occasions, and as such, the presence of a social class gradient in mortality is not unexpected.\(^{26,29,30}\) Situations of life, a weaker social support system, lower self-esteem, motivation, and self-efficacy, as well as economic limitations all contribute to greater psychosocial stress in the less affluent.
Although there is a theory that differences in health occur as a result of differences in an individual's willingness to adopt a healthy lifestyle, in cardiovascular disease, it appears that only approximately 30% to 40% of disease can be accounted for by the major risk factors suggesting an effect of other unknown etiologies which may include lifestyle and social factors.

Current evidence also supports the presence of a social gradient in asthma-related outcomes. More frequent hospital admissions and emergency room visits, higher mortality, and poorer quality of life are all related to lower socioeconomic status. This evidence is strengthened by the diversity of the populations in which the studies have been performed, the analysis of both populations and individuals, and the measurement of social class at both proximate and contextual levels. As with the social gradients identified in other diseases, many of the etiologic factors of poorer asthma-related outcomes in poorer asthmatics remain to be determined.

2.2 HYPOTHETICAL ETIOLOGIC FACTORS OF THE SOCIAL GRADIENT IN ASTHMA-RELATED OUTCOMES

Based on available evidence from different populations using different study methods in different countries, it is evident that poorer asthmatics experience poorer outcomes. The question remains, why do poorer asthmatics do more poorly? It has been hypothesized that this gradient may be the result of a higher prevalence of asthma in the lower social classes, or because lower socioeconomic status asthmatics suffer from more severe disease.

The question of a social gradient in the prevalence of asthma has been addressed numerous times. In the UK, a health survey conducted between 1995 and 1997 revealed
little class difference in the prevalence of physician-diagnosed asthma and self-reported wheeze in children between two and fifteen years of age.\textsuperscript{31} In adults, although there was no difference in physician-diagnosed asthma, there was a clear trend towards a higher prevalence of wheeze in lower social classes, with one-third more people in classes IV and V reporting wheeze than reported wheeze in classes I and II. Similarly, a study of five to 17 years olds in the UK did not identify any social gradient in the prevalence of wheeze in this age group, but did find a trend towards ‘greater severity’ which was defined by more severe, more frequent, and more sleep-disturbing exacerbations of asthma-related symptoms in the lower socioeconomic status groups.\textsuperscript{32}

Mielke et al. provided a summary of 31 studies of socioeconomic status and asthma published between 1969 and 1994.\textsuperscript{33} These studies measured either the prevalence of asthma, wheeze, asthma or wheeze combined, or a specific level of asthma severity derived either via questionnaire, from the medical record, or through direct physician examination. Sixteen studies did not identify any social gradient in the prevalence of asthma, whereas only five found a positive association and nine found a negative association. More recently, Persky et al. studied children in the inner city of Chicago where asthma mortality is among the highest in the US, to determine how much of this differential could be attributed to a greater prevalence of asthma.\textsuperscript{34} They found that the prevalence of asthma was the highest in schools with greater than 98% African American children, and in schools in census tracts where poverty levels were 40% or higher. A strong association between enrollment in a school in a more impoverish neighborhood and indices of asthma severity was also found. Another US study also found that adults with an annual income less than $US50,000, with less than a high school education, or living in a high poverty neighborhood were also at greater risk of having asthma.\textsuperscript{35}
African Americans and Hispanics were also more likely to have asthma than were Caucasians.

To date, the evidence of a higher prevalence of asthma in lower social classes is equivocal, and may in fact just differ between populations. In direct contradiction to this hypothesis, it has been posited that asthma prevalence may be increasing in the western world, and that a positive social gradient exists within western societies secondary to improvements in hygiene and medical interventions such as antibiotics and vaccinations which have lead to an increase in atopic disease. Furthermore, it has been suggested that family size and household crowding may be negatively associated with the prevalence of asthma. Wickens et al. found that in New Zealand, there was a strong association between family size and asthma, with the prevalence of asthma in children from one child families being 2.5 times greater than in children from families with two or more children. Similar findings were reported from an Italian study which found that skin test positivity was greater in children with fathers with the most education relative to those with the least education (prevalence ratio 1.58; 95% CI 1.21, 2.06).

The higher frequency of adverse asthma-related outcomes in lower social class asthmatics does not appear to be attributable specifically to a higher prevalence of asthma in the population. Furthermore, the ability to achieve essentially complete control of asthma with appropriate therapy means that a higher prevalence should theoretically not necessarily extrapolate to a higher frequency of adverse outcomes. Thus, it has also been postulated that this social gradient in asthma related outcomes may not be related to merely a higher prevalence of asthma, but rather to a higher prevalence of more severe asthma in the poor.
Mielk et al. reported a higher prevalence of ‘severe asthma’ in the low socioeconomic groups relative to those in higher social classes. Asthma severity was based solely on the frequency of asthma attacks in the previous year. Strachan et al. reported that although there was no greater prevalence of asthma in lower socioeconomic status children, there was a trend towards more severe asthma in children from lower social classes. The metrics of asthma severity used in this study were the frequency of asthma exacerbations and the presence of nocturnal symptoms. In their study of the relationships between socioeconomic status and asthma prevalence in US children, Persky et al. found a greater prevalence of symptoms related to asthma severity in lower socioeconomic status children attending schools with more than 98% African American students, or living in a neighborhood with more than 40% of the population below the poverty level. Once again, their measures of asthma severity included nocturnal awakenings, difficulty with speech, absence from school, and the need for either treatment of their asthma in an emergency department or admission to a hospital.

Littlejohns and MacDonald specifically studied the relationship between asthma severity and social class in the UK using data from a national study of disabled adults. This study was limited to data collected in a survey previously conducted by the Office of the Population Censuses and Surveys which was not designed to test this hypothesis, and only included adults who met the criteria for being considered disabled, i.e., had a “restriction or lack of ability to perform normal activities which [has] resulted from the impairment of a structure or function of the body or mind.” Individuals who met the criteria were recruited and subsequently interviewed during which they were asked about doctor diagnosed conditions, including asthma. 338 of 10,000 people interviewed reported that asthma was a contributing cause of their disability. Of the 291 for whom
social class could be determined, 14% were in social classes I and II, 44% were in social class III, and 42% in social classes IV and V, with social class I being the most well off. Thus, the investigators concluded that adults in social classes IV and V were more than twice as likely to have disabling asthma compared to adults in social classes I and II.

From their study of the relationship between income and asthma care patterns in Manitoba, Erzen et al. also concluded, albeit in the absence of any objective measurements of asthma severity, that the social gradient in hospitalization was attributable to "more serious" disease. They drew this conclusion based at least partially on the existence of previously published studies in both children and adults, and the fact that they did not find any evidence of more fragmented care in the lower income groups. Because there was no evidence of differential care between classes they concluded that the gradient in outcomes they identified must have been associated with greater asthma severity. This is merely a hypothesis developed through deduction without foundation, and therefore provides no support for this hypothesis.

Although these studies may suggest an association between social class and asthma severity, each has specific limitations that necessarily preclude the conclusion of definitive support of the social gradient – severity hypothesis. The primary limitation of each of the studies is their inability to separate the different effects of asthma severity and asthma control. Three studies defined asthma severity based solely on symptoms, or symptoms in conjunction with absenteeism and health care utilization.

This simplistic approach to defining asthma severity neglects the possibility that each of these symptoms and outcomes is equally as likely to be related to asthma control. In fact, most are included in either the definitions of asthma control that are incorporated into the asthma management guidelines, or are included in the asthma control score
developed by Juniper et al. Utilizing survey data, administrative data, or previous studies not designed specifically to measure asthma severity limits the ability to separate the effects of asthma severity from asthma control. Thus, it can be argued that these studies that claim to provide evidence of a relationship between social class and asthma severity have not employed a methodology that ensures the identified gradients are indeed severity related, and may in fact be providing evidence of a social gradient in asthma control.

2.3 ASTHMA SEVERITY VERSUS ASTHMA CONTROL

The disease management paradigm around which the asthma management guidelines were developed is that asthma management is a multi-faceted, stepped-care approach based upon the frequency of symptoms and disease severity, encompassing not only the optimization of therapeutic management, but also environmental control and education. Environmental control, including limiting exposure to exacerbating factors such as pets, cigarette smoke, dust, etc. should be initiated at the outset of asthma management. The failure of environmental modification and preventative strategies to control symptoms or exacerbations necessitates the implementation of pharmacologic management.

Initial pharmacologic management in patients with the mildest disease and only intermittent or exercise-induced symptoms involves the use of only SA β-agonists on an as needed basis to control symptoms when they occur. As the frequency of symptoms increases, indicative of worsening disease or deteriorating control, low dose inhaled corticosteroids are introduced, with the dose increased as necessary until symptoms are controlled and SA β-agonist use is minimized. Persistent symptoms with moderate doses
of inhaled corticosteroids necessitates the implementation of additional add-on therapies such as a leukotriene antagonist (montelukast or zafirlukast), nedocromil, theophylline, sodium cromoglycate, or a long-acting β-agonist such as salmeterol or formoterol. Failure to control symptoms with a combination of first line and add-on medications necessitates the addition of oral corticosteroids to the regime. This strategy should be the last line of therapy given the significant adverse effects related to oral corticosteroid therapy, and is indicative of severe, treatment refractory asthma.

The fundamental component of this asthma management model is the achievement of asthma control, and thus, includes specific criteria for its evaluation. Optimal asthma control has been defined by eight specific criteria which include the minimization of the frequency and severity of symptoms and exacerbations, the limiting of SA β-agonist use, the normalization of physical activity and pulmonary function, and the prevention of absence from work or school. Each of these criteria has been defined with an objective quantification of an acceptable frequency. With regards to SA β-agonist use specifically, asthma control has been defined as the optimization of asthma controller medication use (if required) such as inhaled corticosteroids, nedocromil, long-acting β-agonists, leukotriene antagonists and oral corticosteroids such that fewer than four doses (2 puffs/dose) per week of a SA β-agonist (salbutamol, fenoterol or terbutaline) are required.

Asthma control can also be measured and quantified on an interval scale using the Asthma Control Questionnaire (ACQ). Juniper et al. developed the ACQ which is comprised of seven items, five questions relating to asthma symptoms, and one item each relating to the magnitude of SA β-agonist use and forced expiratory volume in one
second (FEV₁). It has been shown to be both a valid and reliable quantification of asthma control, and possesses both strong evaluative and discriminative properties. Symptoms included in the score were derived from those selected by one hundred asthma physicians from 18 countries from a list of symptoms generated by the investigators. Each item is scored on a seven point Likert scale ranging from zero to six, representing the best and worst possible asthma control, respectively. The mean score of the seven items provides a quantitative measure of overall asthma control. The most recent evaluation of the ACQ revealed that the SA β-agonist use and pulmonary function components can be omitted without affecting the validity of the score. This lends further evidence to the argument that previous studies claiming to have identified greater asthma severity in lower social status asthmatics based only on symptom-related measures of asthma severity have failed to consider the potential effect of poorer control.

The misunderstanding of this complex severity-control relationship often results in asthma control (or lack thereof) being used to define asthma severity. The failure to separate these two dimensions of the disease results in the perpetuation of the antiquated concept that asthma is primarily a bronchospastic disease, and that symptoms, physiologic abnormalities and SA β-agonist use are to be expected rather than prevented. This exemplifies the need to delineate between asthma severity and asthma control. Although not easily done practically, the concept is very simple.

With appropriate management, asthma is a controllable disease such that a patient with very severe asthma may be essentially symptom free. Many asthmatics with severe disease meet all the symptomatic and physiologic criteria for 'mild' disease, except for their anti-inflammatory medication requirements. Conversely, a patient with relatively mild, easily reversible airway disease may have significant symptoms of frequent
nocturnal wakenings, frequent daytime symptoms, and may even require emergent management of their symptoms in an emergency department or admission to a hospital. In simple terms, the symptomatic patient may have only mild disease that could be easily controlled with only low doses of anti-inflammatory medications. Conversely, the asymptomatic patient may have very severe disease, but requires very high doses of inhaled corticosteroids and other add-on medications to control their symptoms.

This leads to the concept proposed by Cockcroft and Swystun that asthma severity can only be measured in asthmatics who are well-controlled and therefore symptom-free, using the magnitude of asthma medications required to maintain their control to classify their severity. This illustrates the premise that asthma-related symptoms are more closely related to asthma control than asthma severity, such that the presence of symptoms or the occurrence of an exacerbation is indicative more of inadequate control than a specific level of severity. It also suggests that drug therapy is used not only to achieve adequate control, but also paradoxically to determine asthma severity.

Although this is a theoretically sound approach to asthma severity classification that may be applicable in clinical practice or clinical trials, it is not practical in epidemiologic studies where it is not possible, or necessarily desirable, to optimize drug therapy in all patients prior to classifying each subject by severity. It does provide the basis around which asthma severity should be measured. This theoretical framework shows that any valid quantification or classification of asthma severity must include not only symptoms, but also measures of pulmonary function and asthma medication requirements. As outlined previously, none of the studies that claim to have provided evidence of greater disease severity in lower social classes were able to do this.
2.4 THE ASSOCIATION BETWEEN ADVERSE ASTHMA-RELATED OUTCOMES AND INAPPROPRIATE ASTHMA MANAGEMENT

Intuitively, it seems logical that asthmatics with more severe disease should experience greater asthma-related morbidity. However, asthma is essentially a controllable disease and therefore this should not necessarily be the case. Worse outcomes may also be related to poor asthma control, such that even individuals with very mild disease may suffer unnecessary exacerbations and decreased quality of life. In support of this control theory, numerous studies have identified an association between inadequate asthma management and greater asthma-related morbidity. The measures of morbidity used in these studies are similar to those used in the studies that demonstrated a social gradient in outcomes.

In a three-month pediatric study, the adherence rate to prescribed asthma management in children who suffered an exacerbation of their asthma was only 13.7% compared to 68.2% adherence in children who did not.\textsuperscript{51} A study of children requiring emergency room management of their asthma found that 28% of patients used a SA β-agonist daily and 63% used one intermittently, and that only 16% were using an inhaled corticosteroid prior to admission.\textsuperscript{18} This was merely a characterization study without a control or comparator group, so it cannot be inferred that there was a causal relationship between what appears to be sub-optimal drug use and the need for emergency assessment. What it does show is the unacceptably high under-utilization of controller medication from which it can be hypothesized that a higher prevalence of inhaled corticosteroid use may have resulted in the prevention of some exacerbations and the ensuing emergency room visit. In similar studies, the highest rates of inhaled corticosteroid use by patients requiring emergency treatment were only 40%.\textsuperscript{52,53} In a
Canadian study of emergency room visits related to asthma, only 46% of patients who reported having at least one-quarter of their nights sleep disturbed by asthma were using an inhaled corticosteroid prior to presenting to the emergency department.\textsuperscript{54}

The benefits of inhaled corticosteroid use in the management of asthma appear to be conferred at relatively low doses. The relative risk of hospitalization due to asthma with any use of an inhaled corticosteroid was estimated to be 0.5 (95% CI 0.7 – 0.9) relative to not using any inhaled corticosteroid.\textsuperscript{55} A higher ratio of inhaled corticosteroid to SA $\beta$-agonist medication also appears to decrease the risk of hospital admission,\textsuperscript{56} and each additional canister of inhaled corticosteroid used results in approximately a 20% reduction in the risk of asthma-related mortality.\textsuperscript{57}

The benefits of adding an inhaled corticosteroid to SA $\beta$-agonist therapy are well established, with the most marked benefits occurring in those patients using the highest doses of SA $\beta$-agonist.\textsuperscript{55-60} Although it is now well established that the over-use of any SA $\beta$-agonist is a risk factor for adverse outcomes, this has not always been the case. The surfeit of evidence of greater asthma-related morbidity and mortality in patients using excessive amounts of these medications for asthma control, and the evidence of improved outcomes associated with the use of inhaled corticosteroid, has resulted in the development of the current asthma management guidelines.

The concern over the risk of short-acting beta-agonists started as early as 1960 when an increase in asthma deaths was identified in association with the introduction of a new high-dose SA $\beta$-agonist, isoprenaline-forte.\textsuperscript{61-63} Ecological evidence of a dramatic increase in asthma-related deaths in a number of countries following its introduction ensued, with the largest increase in morality reported in New Zealand.\textsuperscript{64}
Following the second epidemic of asthma-related mortality in New Zealand in the late 1970's and early 1980s, an analysis of sales patterns of asthma medications revealed that fenoterol had been released onto the market in 1976 and had achieved a 30% market share within three years compared to only 5% in other countries. This circumstantial evidence incriminating fenoterol as the causative factor in the epidemic was followed by a series of case-control studies of asthma-related mortality in New Zealand.

In the first study, asthma deaths were compared to a group of hospital control subjects with a hospital discharge diagnosis of asthma. The only treatment found to be consistently associated with a greater risk of mortality was the use of fenoterol (OR 1.55). Defining subgroups based on markers of asthma severity (hospitalization in the previous twelve months, use of an oral corticosteroid, or receipt of three or more classes of asthma medications), they found that the risk of death in patients using fenoterol increased (OR 2.2 to 13.3), and was the highest in those with the most severe asthma. A major criticism of this study was that the data for cases and controls were derived from different sources, and thus an information bias may have affected the results. In an attempt to address this limitation, the same investigators followed up this study with two subsequent studies of New Zealanders which resulted in similar findings. In both subsequent studies, the odds ratio for death in patients treated with fenoterol relative to those treated with salbutamol was approximately 2.0, adjusted for markers of asthma severity.

To test this hypothesis further in a population outside New Zealand, Spitzer et al. used administrative data from the Saskatchewan Asthma Epidemiology Project for another case control study comparing 44 asthma deaths to 233 controls between 1980 and 1987. Using a similar analysis to that used in the New Zealand studies, they found that
the relative risk of mortality in patients receiving fenoterol was 5.3 times that of patients using salbutamol. Overall, the relative risk of mortality for both drugs was 4.4, suggesting the presence of an overall class effect, but a greater risk of mortality attributable specifically to fenoterol. Because fenoterol was available in a 200 μg per puff formulation compared to salbutamol that was only available as 100 μg per puff, further analysis adjusting for this difference resulted in no difference in the risk of either a fatal or near fatal asthma exacerbation between fenoterol and salbutamol. Overall, the odds ratio for either outcome was 6.1 (95% CI 3.1 – 12.2) for any use of fenoterol and 4.1 (95% CI 2.1 – 8.0) for salbutamol. They also determined that the risk of either a fatal or near fatal event increased approximately 2-fold with each additional canister of SA β-agonist, independent of which SA β-agonist was used.

This was the first evidence to suggest that the greater risk of adverse outcomes related to fenoterol identified in previous studies may have been due to a difference in the dose of fenoterol administered relative to the dose of salbutamol. Consistent with Bradford Hill’s criteria of causation, the presence of this dose-related association supports the theory of an association between short-acting β-agonists as a class, and adverse outcomes.

This dose effect may have occurred because although the usual dose of salbutamol is two puffs of 100 μg per puff, the recommended dose of fenoterol was only one puff due to its 200 μg per puff formulation; however, patients routinely used two puffs of fenoterol. Thus, it was hypothesized that this difference in dose may have resulted in confounding by severity, with more severe asthmatics being prescribed fenoterol because the patient ultimately received double the dose of bronchodilator and
experienced better symptom relief relative to treatment with salbutamol. If this was the case, patients receiving fenoterol would be at greater risk of asthma-related morbidity and mortality by virtue of their more severe disease. The inability to adequately adjust for disease severity in any study would result in the erroneous incrimination of fenoterol due to the channeling of fenoterol into use in patients already at risk for adverse outcomes.

Although the New Zealand investigators did not find any evidence of channeling, it has been demonstrated empirically. A Dutch study found that patients receiving fenoterol were 2 – 2.5 times more likely to have received concomitant corticosteroid therapy, and were more likely to have used other add-on medications. Blais et al. studied a cohort of incident SA β-agonist users to evaluate the effect of channeling and found that although there was no preferential prescribing of fenoterol initially, fenoterol was preferentially prescribed to asthmatics that showed signs of increasing severity or worsening asthma control while receiving salbutamol. They therefore concluded that the channeling of fenoterol into use by more severe asthmatics was occurring and thus, there was confounding by indication in the association of only fenoterol with adverse asthma-related outcomes.

The next study to evaluate the association between SA β-agonist use and excess mortality was a cohort analysis of the Saskatchewan data which showed that that asthma-related mortality was primarily associated with the use of more than two canisters of SA β-agonists each month. Although the association was not significant, there was a trend towards a greater risk of mortality associated with fenoterol relative to salbutamol. It was again postulated that this may be due to channeling, but this could not be evaluated in this study. Suissa et al. subsequently performed another study evaluating the risk of adverse
outcomes associated with using 'increasing' doses of SA β-agonists and concluded that adverse outcomes were not related to the absolute amount of SA β-agonist used, but rather that increasing use was the major predictive factor of adverse outcomes. They found that the relative risk of an adverse event in a person using 21 canisters of SA β-agonist over a twelve month period, but using only one canister in the first month and three in the last month was 24.4. Conversely, the relative risk of an adverse event for a person consistently using three canisters a month (36 canisters over twelve months) was only 2.6. This may suggest that increasing SA β-agonist use over a relatively short time period is a marker of worsening asthma or deteriorating control.

These studies were all based on administrative data, with adjustments for asthma severity and other potential confounders being less than ideal. At least five randomized control trials have been undertaken to specifically address the question of whether the chronic use of SA β-agonists is associated with adverse outcomes relative to their use on an as needed basis only. Although the most recent study of chronic SA β-agonist administration did not find an increase in the rate, timing, or duration of asthma exacerbations in patients treated with regular SA β-agonists, four other prospective, randomized studies showed that the regular use of salbutamol and/or fenoterol had detrimental effects on lung function, symptoms, exacerbations, and/or airway responsiveness when compared to their use on an as needed or rescue basis only.

Because the association between using high doses of SA β-agonists and adverse outcomes could be related to greater asthma severity, initial studies attempted to control for asthma severity within the limitations of using administrative data for this purpose. No study found that the association could be explained by confounding by severity. To
overcome the limitations of attempting to control severity using administrative data only, Ernst et al. subsequently addressed this question specifically in a case-control study using the data from the Saskatchewan asthma cohort.81 Both cases and controls were initially identified using the administrative data; however, because more specific clinical data (i.e. symptoms and pulmonary function) are required to more accurately classify asthma severity, specific data for each patient were extracted by chart review. In this study, there was no significant difference in the odds ratios for fenoterol and salbutamol in either the crude or adjusted models, and adjusting for asthma severity using the clinical measures had little effect on the odds ratios for both fenoterol and salbutamol exposure on the occurrence of fatal or near-fatal asthma. This study provided further evidence that this association is a class effect, and also that it was not confounded by asthma severity.

Despite the paucity of evidence and the general acceptance that this is a class effect, the debate continues as to whether the association between SA β-agonist use and adverse outcomes is a class effect, or is related specifically to fenoterol. This debate has been ongoing, but is essentially isolated to the two research groups from separate hemispheres who remain on their respective sides of the argument. Fenoterol continues to be available in Canada in a 100 µg per puff formulation (equivalent to salbutamol) and none of the current asthma management guidelines make any distinction between fenoterol, salbutamol, or terbutaline in terms of the recommended magnitude of use.46,47 This leads to the next consideration of whether this association is causal, or if increasing use is merely a marker for worsening severity or deteriorating control.

There are numerous hypotheses and mounting evidence supporting the biological plausibility of a direct causal association. Chronic SA β-agonist administration can lead
to down-regulation of the expression of β2-receptors on airway smooth muscle and other cells, and induce changes in β2-adrenergic signal transduction pathways.\textsuperscript{82-84} It has been shown that the use of a SA β-agonist regularly for one week results in a functional down-regulation of β2-receptors, demonstrated by a reduction in the protective effect of an acute dose of salbutamol on the bronchoconstrictive effects of methacholine, adenosine, and antigen.\textsuperscript{85} Further studies have also shown non-specific airway hyper-responsiveness after the chronic administration of a SA β-agonist,\textsuperscript{86-89} as well as a decrease in the anti-inflammatory effects of corticosteroids.\textsuperscript{90}

At the cellular level it has been shown that the chronic administration of SA β-agonists can increase IgE production of human peripheral blood mononuclear cells by increasing the secretion of interleukin-4.\textsuperscript{91} If this were to occur in vivo when an asthmatic is exposed to an aeroallergen, it could enhance the sensitization and increase the severity of the hypersensitivity-induced inflammation. β-receptor stimulation also has the potential to inhibit the release of mast cell mediators, and as a result may prevent the action of mast cell derived anti-inflammatory autocoids.\textsuperscript{92,93} Finally, regular SA β-agonist use promotes airway secretions which may contribute to increased airway obstruction, and produces an acute bronchial vascular dilatory effect in experimental animals which could aggravate vascular congestion and edema in the airway wall.\textsuperscript{94}

In addition to these direct effects, there are also some potential indirect adverse effects. Over reliance on bronchodilator therapy may lead to a delay in seeking appropriate care which in turn increases the risk of a more severe or even fatal asthma attack.\textsuperscript{94} This continued reliance on bronchodilator therapy may also result in sustained
bronchodilation permitting a greater aeroallergen or irritant exposure, also resulting in more severe exacerbations.94

The available clinical and experimental data showing a relationship between chronic over-utilization of SA β-agonists, worsening asthma control and greater asthma-related morbidity and mortality, along with the potential biologic plausibility of the association, has resulted in a move away from these agents as the mainstay of asthma therapy. Although much of the evidence supports a direct causal association, the association may also merely be that excessive SA β-agonist use, or increasing use as suggested by Suissa et al.,75 is a marker for increasing severity or worsening control. In fact, it is likely that short-acting β-agonists are both causally associated with, and a marker for, adverse outcomes. Regardless of the true etiology, it is well accepted that the over-reliance and excessive use of SA β-agonists is either a direct or indirect risk factor for adverse asthma related outcomes, and is therefore undesirable.

Inadequate utilization of inhaled corticosteroids, or asthma management discordant with management guidelines, is associated with an increased risk of adverse asthma-related outcomes. This is also demonstrated by greater asthma-related morbidity and mortality in asthmatics that rely upon, or utilize, excessive amounts of SA β-agonists. Thus, within the framework of the asthma control guidelines, controller medication should be optimized such that SA β-agonist requirements are minimal, and as such, the magnitude of SA β-agonist use can be used as a measure of asthma control.
2.5 SOCIOECONOMIC STATUS, SHORT-ACTING BETA-AGONIST USE, AND ASTHMA SEVERITY: WEAVING THE WEB

Evidence has been presented which shows that a social gradient in asthma-related outcomes exists. It has been posited that this gradient is related to greater asthma severity in asthmatics of lower socioeconomic status. Asthma-related morbidity and mortality have been shown to be independently related to socioeconomic status, inappropriate asthma management, and the chronic or excessive use of SA β-agonists. The association between SA β-agonist use and adverse asthma-related outcomes may be the result of either a direct effect of the drug, or indirectly as a result of poorer asthma control. The hypothesis of this study is that this association could also be related to poorer asthma control in lower socioeconomic status asthmatics (Figure 2.1).

FIGURE 2.1: CONCEPTUAL MODEL OF THE RELATIONSHIP BETWEEN SOCIOECONOMIC STATUS, β-AGONIST USE, ASTHMA SEVERITY, AND ASTHMA-RELATED MORBIDITY AND MORTALITY
There are many reasons why a person may utilize excessive amounts of SA β-agonists in their asthma management. The primary and most obvious reason is that severe, treatment refractory disease necessitates the continuous use of high doses of SA β-agonists to control the symptoms, despite the maximization of other controller medications and oral corticosteroids. Conversely, there are also many non-severity related factors which may contribute to inappropriate management.

Ineffective medical care may result in an inadequate therapeutic regime, or poor patient compliance with an appropriately prescribed asthma management plan may also manifest as sub-optimal therapy. Individual differences in the perception of airway limitation, a lack of knowledge and understanding of appropriate management, acceptance of symptoms as a consequence of the disease, and economic barriers may also play a role. There is also evidence indicating that there may be a genetic component to the magnitude of SA β-agonist that one requires to achieve adequate bronchodilation. Each of these factors individually may result in sub-optimal asthma control, but one can logically surmise that a combination of these factors further increases the likelihood of poor asthma management, and consequently poor asthma control.

One can postulate that for all aforementioned risk factors of excessive SA β-agonist use except the genetic association, that there may be a social gradient. Furthermore, more frequent exposure to exacerbating factors or asthma triggers such as cockroach feces, cigarette smoke, or occupational allergens in the poor may further worsen asthma control. A ‘determinants of health’ model proposed by Evans and Barer includes factors such as one’s social and physical environment, well being, personal self worth, self esteem, motivation, and self efficacy, each of which may have an
effect on one’s ability or desire to treat one’s illness.\textsuperscript{105} Health habits of individuals may not be choices, but rather are more likely conditioned social responses as a result of the influences of each individual’s physical and social environments, and their lifestyle.\textsuperscript{6} It is therefore reasonable to not only expect a social gradient in asthma-related outcomes, but that this gradient may be the result of inadequate control consequent of factors unrelated to the provision of, or access to, health care.

This hypothesis is partially supported by the studies that claim to have demonstrated a social gradient in asthma severity, considering that the measures of asthma severity used in these studies could equally have been considered measures of asthma control.\textsuperscript{33,34,41} Contrary to the theoretically framework of measuring asthma severity proposed by Cockcroft, these studies used only symptoms to quantify severity.\textsuperscript{50} The two studies that have attributed the social gradient in asthma-related outcomes specifically to greater asthma severity in the poor were both based on administrative data and thus, could not adequately separate the effects of asthma severity and asthma control.\textsuperscript{20,41} As with most other studies, the study by Littlejohns and MacDonald\textsuperscript{41} also used a definition of asthma severity that could equally as been used to define asthma control, and Erzen et al. attributed the differences in outcomes in their study to asthma severity purely by deduction without any measurements of asthma severity.\textsuperscript{20}

To date, there is limited data on the relationship between socioeconomic status and asthma control. A study comparing 17 children using excessive amounts of SA β-agonists to 38 children who did not found that excessive users were more likely to be male, minority, and of lower socioeconomic status.\textsuperscript{106} Togias et al. also found that, in 151 adolescents between 13 and 18 years of age, only 6% of those from families in the lowest quartile of family income were prescribed an inhaled corticosteroid versus 28% in the
highest quartile on income (Fisher Exact $p<0.03$), and that only 42% were prescribed a SA β-agonist compared to 89% in the highest quartile ($p<0.00001$). Although this study showed that asthma management was not in accordance with treatment guidelines, they did not measure asthma control. Although patients may not have been ‘symptomatically’ uncontrolled, they may have still been at risk for adverse outcomes due to their excessive use of SA β-agonists. This significant discrepancy in management, particularly in SA β-agonist use considering its generally ubiquitous use by asthmatics, may suggest an economic barrier to management in this population.

A similar study of children in New Zealand found that the prevalence of utilization of both a SA β-agonist and an inhaled corticosteroid was higher in children from families in the highest social classes that reported having wheeze or bronchial hyper-responsiveness in the previous twelve months. The high prevalence of bronchial hyper-responsiveness in these children also demonstrates a lack of asthma control in conjunction with inappropriate management. Connolly et al. showed that poor control of potentially reversible airway obstruction was significantly associated with lower social class, suggesting under-utilization of controller medications in this population; drug use was not evaluated. We are not aware of any studies in adults evaluating the relationship between social class and the appropriateness of drug use.

The studies demonstrating a social gradient in asthma medication utilization were limited to only children and adolescents. Factors contributing to inappropriate management and a lack of asthma control are likely to be much different in adults than children, and thus, the presence of a gradient in children cannot necessarily be extrapolated to the adult population. Furthermore, all three studies were done in the US
which has considerably more liberalist policies of health care provision, thereby potentially imparting more barriers to health care than in Canada which has a much more egalitarian approach to the provision of health care.

2.6 SUMMARY

There is evidence of numerous independent associations with adverse asthma related outcomes, including inappropriate asthma management (i.e. the over-utilization of SA β-agonists), socioeconomic status, and asthma severity. However, the evidence implicating greater asthma severity as the etiology of poorer outcomes in lower socioeconomic status asthmatics is less than compelling. Furthermore, studies that have demonstrated an association between poorer asthma control and lower social class have been performed primarily in children, and in the US where social class differences in access to health care may be a more significant factor than in Canada.

Asthma severity can be considered unmodifiable. Attributing the social gradient to asthma severity has significant implications on the necessity and ability to attempt to narrow the gap. The complacent attribution of the social gradient in outcomes to asthma severity precludes the need for corrective action. Erroneously attributing this gradient strictly to asthma severity, without considering poorer control as a contributing etiology will result in an unnecessary persistence of the gradient. Current evidence provides a clear mandate to evaluate the potential association between socioeconomic status and excessive use of SA β-agonists and asthma control in a population where there are no barriers to health care.

It is evident from existing studies that the delineation of the effects of severity and control cannot be achieved using administrative data. The objective of investigating the
social class-control relationship while adjusting for asthma severity necessitates the simultaneous measurement and collection of clinical symptoms, pulmonary function, and asthma medication use. Thus, the successful achievement of this mandate will require the recruitment of a sample of asthmatics, representative of all levels of asthma severity, control, and socioeconomic status.

2.7 REFERENCES


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CHAPTER 3

THE RELATIONSHIP BETWEEN INAPPROPRIATE ASTHMA MEDICATION USE AND HEALTH CARE RESOURCE UTILIZATION

3.1 FORWARD

This chapter has been previously published as "Double trouble: inappropriate asthma medication use linked to increased use of health care resources", in *CMAJ* 2001;164 (5): 625 – 31. Co-authors of the study included Xiao-hua Wang, a statistician involved in the database linkage and the analysis, Drs. Greg King, Tony Bai, and Mark FitzGerald, respiratory clinicians who participated in the development of the conceptual framework and methodology of the study, and Drs. Anis, Spinelli, and Paré, members of the supervisory committee.

The candidate is second author on this manuscript, and was involved in the statistical analysis and dosage standardization, the development of the subsequent hypotheses from the findings, and wrote the final manuscript.

3.2 INTRODUCTION

The concern over the regular use of inhaled short-acting (SA) β-agonists for the chronic management of asthma began in the 1960’s when an increase in asthma deaths occurred following the introduction of a potent non-selective β-agonist, isoprenaline-forte.\(^1\) Although numerous studies subsequent to this have resulted in significant controversy and ongoing debate on this topic,\(^1-8\) it has become widely accepted that these
agents should be used on an “as needed” or “rescue” basis only. As a result, current asthma management guidelines define appropriate asthma management as optimization of inhaled corticosteroid (ICS) doses with or without add-on therapy such that SA β-agonists are required <4 times weekly, on an as-needed basis only.9,10

Although asthmatics may be using greater than recommended doses of SA β-agonists due to the presence of severe asthma which is refractory to treatment, it was our impression that the excessive use of inhaled SA β-agonists without adequate doses of inhaled corticosteroids persisted in British Columbia despite the wide dissemination of the guidelines. We postulated that it was also likely that those patients who used excessive doses of SA β-agonist as their mainstay of therapy (i.e. without sufficient concomitant ICS) would require greater amounts of health care services, suggesting poor asthma control, greater health care expenditures, and potentially poorer quality of life.

We hypothesized that asthmatics between 5 and 50 years of age whose asthma was ‘inappropriately’ managed would require more frequent hospitalization and physician visits for respiratory conditions, relative to ‘appropriately’ managed patients. ‘Inappropriately’ managed patients were those prescribed ≥9 canisters of salbutamol (100µg/dose, 200 doses) or equivalent in 1995 concurrently with <100µg/day of beclomethasone (or equivalent) by inhalation, and ‘appropriately’ managed patients were those who received ≤4 canisters of salbutamol (100µg/dose, 200 doses) concurrently with ≥400µg/day of beclomethasone by inhalation. By taking this approach, we limited our analysis to only those patients who could be considered ‘controlled’ based on their SA β-agonist use, and those considered ‘uncontrolled’ and may therefore benefit from higher doses of ICS. This resulted in the exclusion of patients using excessive amounts of β-
agonists with high doses of ICS and who may therefore have severe intractable asthma and be at greater risk of adverse outcomes, independent of the magnitude of their β-agonist use.

3.3 METHODS

We conducted a one year cross-sectional study of 1995 data on hospital admissions, physician visits, and medications prescribed and dispensed in 1995 for individual patients by linking three British Columbia Ministry of Health administrative databases: Hospital Programs, Medical Services Plan (MSP) of BC, and Pharmacare. All patients between 5 to 50 years of age who filled at least one prescription for SA β-agonist in 1995, and were in the Pharmacare database were included in the study. Patients >50 years were excluded to decrease the probability that patients were receiving β-agonists for other chronic respiratory illnesses such as chronic obstructive pulmonary disease (COPD) or emphysema.

Pharmacare is the BC government’s pharmaceutical reimbursement program which provides comprehensive coverage for all seniors (Plan A, ≥ 65yrs), all persons on social assistance (Plan C) and the general population reaching a $600 annual family deductible (Plan E). Once the $600 threshold has been reached, the individual becomes eligible for reimbursement of drug expenditures from Pharmacare, and their entire drug profile (including drugs prescribed prior to their achievement of the threshold) is added to the database. Because Plan A includes only patients ≥ 65 years, only patients in Plans C and E were included in this study.

The MSP database contains the billing records of all physicians in the province and was used to ascertain total number of physician visits by each subject in the study.
The provincial hospital programs database captures data on all hospitalizations in the province including the urgency, primary diagnosis and length of hospital stay associated with each event.

Each individual ICS and SA β-agonist formulation was uniquely identifiable in the Pharmacare database using the drug identification number, facilitating the standardization of doses prescribed. To control for differences in potency, strength, and formulation, the amount of each inhaled corticosteroid and SA β-agonist prescribed was determined from the total quantity prescribed over the year, and these amounts were standardized to the equivalent dose of beclomethasone dipropionate (μg/day) or the number of 200-puff canisters of salbutamol 100μg, respectively. Multi-dose inhaler and dry powder formulations of each medication were assumed to be equivalent. All SA β-agonists (salbutamol, fenoterol, and terbutaline) were considered to be equipotent, whereas budesonide 40 μg and beclomethasone dipropionate 50 μg were considered equivalent.

1995 asthma guidelines define asthma control as the utilization of ≤3 doses (6 puffs) of SA β-agonist per week, which equates to less than one 200 puff canister per year. Patients were stratified into ‘low’ and ‘high’ drug use groups according to the standardized number of canisters of SA β-agonist received and their average standardized daily dose of ICS. ‘Low’ use of SA β-agonists was defined as receipt of the equivalent of ≤4 canisters to allow for utilization due to exercise-induced asthma and use of more than one canister at a time, and ‘high’ use as receipt of the equivalent of ≥9 canisters. Additionally, an average daily ICS dose ≤100 μg beclomethasone was defined as ‘low’ corticosteroid use, and an average daily dose of ≥400 μg was classified as ‘high’ use.
Next, each patient was classified into sub-groups of “appropriate” and “inappropriate” use, based on the combination of their β-agonist and ICS use group. ‘Appropriate’ users were those patients who received ≤4 canisters of β-agonist and ≥400 μg/day of ICS (low β-agonist/high corticosteroid users), and ‘inappropriate’ users were patients prescribed ≥9 canisters of SA β-agonist but their prescribed daily ICS dosage was ≤100 μg (high β-agonist/low corticosteroid users). For the purposes of this study, all patients not falling into these two sub-groups were excluded from the analysis.

The number of visits to each “prescribing” physician by each patient was determined from the Pharmacare database utilizing a unique physician identifier recorded for each prescription of any asthma medication. Additionally, the total number of physicians (i.e. “all physicians”) seen by each patient during the year, regardless of whether they received a prescription for an asthma medication from that physician (i.e. “all physicians”) was determined from the MSP claims database. The occurrence and frequency of respiratory-related hospital admissions were determined from the Hospital Programs database based on ICD-9 code 08 (diseases of the respiratory system, Clinical modification of International Classification of Diseases, 9th Revision). Only admissions with the primary reason for the admission designated as being respiratory-related were included for this analysis. The proportion of patients hospitalized, the frequency of hospitalization among hospitalized patients, and the percentage of hospitalized patients requiring urgent admissions (admitted following emergency room assessment) were calculated.
3.3.1. Statistical analysis

The primary comparison of interest was between ‘appropriate’ and ‘inappropriate’ users. Student t-tests and chi-square tests were initially applied to evaluate baseline differences between the two study groups. Multivariate analyses were then conducted to assess whether appropriate use was an independent predictor of health resource utilization adjusting for the effect of age (in years), gender and social status (health plan type). Unadjusted and adjusted relative risks due to inappropriate use for the various outcome variables along with 95% confidence intervals were computed using the appropriate model.

Logistic regression was used to estimate the relative risks of the occurrence of hospitalization and urgent admission. Poisson regression was applied to model the frequencies of hospitalization and urgent admission. The Poisson regression model was also utilized to evaluate physician visitation pattern (the number of unique ‘all physicians’ and unique ‘prescribing’ physicians). Gamma regression models (generalized linear models with gamma distributed outcomes and logarithmic link functions) were developed to estimate the relative risks for the mean number of visits per physician and the mean number of prescriptions per ‘prescribing’ physician.

For each model, the estimated relative risk (RR) was computed as \( \exp \beta \) where \( \beta \) is the coefficient in the regression model. For Poisson and gamma regression models, the RR is the ratio of the mean outcome for inappropriate users to that for appropriate users. For the logistic regression models (modeling the probability of hospitalization or emergency admission), the RR is the odds ratio (OR) for inappropriate users compared to appropriate users.
3.4 RESULTS

23,986 patients between 5 and 50 years of age received at least one prescription for a SA β-agonist in 1995: 16,881 on Plan C, and 6,959 on Plan E. The overall prevalence of β-agonist prescribing among all patients on Plans C and E was 8.1%. Table 3.1 illustrates the SA β-agonist and ICS use patterns of all patients in the study group. Although the majority of patients were in the low β-agonist / low ICS use group (53.1%), 3,069 (12.7%) patients received ≥ 9 canisters of SA β-agonist, or an average of 500μg (5 puffs) of salbutamol/day. Of these, 1,292 (42.1%) patients receiving ≥ 9 canisters of salbutamol concurrently received the equivalent of ≤ 400μg/day of ICS, whereas only 1,159 (38.0%) received the equivalent of ≥ 800μg/day. 4,671 patients met the criteria of ‘low’ SA β-agonist and ‘high’ ICS use, and therefore comprised the ‘appropriate’ users. Conversely, 763/3069 (24.9%) of patients receiving ≥ 9 canisters of SA β-agonist concomitantly received the equivalent of ≤ 100μg/day of ICS, and were deemed ‘inappropriate’ users; 96.4% of inappropriate users did not receive any ICS.

Table 3.2 shows the demographics of the patients, based on appropriate and inappropriate drug use. There was a higher proportion of females in the appropriate use group (p=0.004), appropriate users were younger (p=0.0001), and were more likely to be on Plan C (p=0.001).

Table 3.3 illustrates the comparison between appropriate and inappropriate users in terms of hospital admissions, emergency room visits, physician visits, and prescriptions. A greater proportion of inappropriate users were hospitalized and visited emergency at any time during the year, and were hospitalized or visited emergency more frequently. The number of unique ‘prescribing’ physicians per patient was significantly
higher in the inappropriate use group, and appropriate users received significantly fewer prescriptions per ‘prescribing’ physician, and fewer prescriptions overall. Although there was no difference in the number of ‘all physicians’ visited between the groups (p=0.16), appropriate users had significantly fewer visits to ‘all physicians’ and significantly fewer total visits. Appropriate users also visited their ‘prescribing’ physician less frequently than inappropriate users (2.9 versus 7.2 visits, p = 0.0001).

Table 3.4 lists the estimated relative RRs and corresponding 95% confidence intervals of hospitalization and physician visits, obtained from the logistic, Poisson, or gamma regression analysis. In particular, inappropriate users were more likely to be hospitalized (RR= 1.68, 95%CI = 1.25 – 2.26), and be admitted urgently via the emergency department due to respiratory diseases (RR= 1.93, 95%CI = 1.35 – 2.77). Inappropriate users were also hospitalized 1.7 times more frequently (RR= 1.81, 95%CI= 1.43 – 2.32) and had two times more urgent admissions due to respiratory diseases (RR= 2.07, 95% CI= 1.52 – 2.83) relative to appropriate users. Furthermore, this analysis also showed that the inappropriate users had more ‘prescribing’ physicians (RR= 1.33, 95%CI= 1.26 - 1.42), more prescriptions per patient (RR= 2.35, 95%CI= 2.26 - 2.41), and received more prescriptions from each ‘prescribing’ physician (RR= 1.99, 95%CI= 1.91 - 2.07).

The pattern of ‘all physician’ visits was similar between the two study groups, except that the inappropriate users visited slightly fewer physicians (RR=0.94, 95%CI=0.91-0.98). The inappropriate users were more likely to visit more ‘all physicians’ (RR= 1.14, 95%CI= 1.07 - 1.22) and had more visits per ‘all physician’ (RR= 1.06, 95%CI= 1.01 - 1.12). There is little difference in the adjusted and unadjusted RR
estimates which indicates that age, gender and social status does not confound the effect of appropriateness of treatment on the various measures of health resource utilization.

3.5 DISCUSSION

This comparison of inappropriate and appropriate asthma drug users reveals that inappropriately treated asthmatics are more likely to receive more prescriptions, visit more prescribing physicians, are more likely to be hospitalized, and are hospitalized more often. These results suggest that inappropriately treated asthmatics appear to have poorer outcomes, independent of disease severity or control.

If one were to attempt to evaluate all patients prescribed a SA β-agonist, “appropriate” and “inappropriate” users could only be truly identified by combining drug use data with clinical and physiologic markers of disease severity and control. In the absence of a clinical assessment, we felt that it was reasonable to limit our analysis to those patients whose appropriateness of management could be determined from their drug utilization data alone. It can be argued that any patient using ≥9 canisters of SA β-agonist per year and <100μg/day of ICS is being inappropriately managed, independent of disease severity, given that this usage level of SA β-agonist significantly exceeds the asthma management guidelines (~1 canisters/yr.)⁹,¹¹. Conversely, patients using ≤4 canisters of SA β-agonist and ≥400μg/day of ICS are being appropriately managed. Similarly, this cutoff of 4 canisters for appropriate users is conservative, and allows for individuals to have multiple canisters for convenience, or use greater than the recommended doses of SA β-agonist for exercise-induced asthma.
The drug usage pattern of British Columbian asthmatics that we have identified reveals that asthma mismanagement persists, despite guidelines advocating the optimization of ICS use to limit SA β-agonist utilization to “rescue” use only.\textsuperscript{9,11} This analysis illustrates the presence of a subset of patients prescribed excessive amounts of SA β-agonist in conjunction with inappropriately low amounts of ICS, and who are likely to benefit from an increase in ICS dose, which may result in lower β-agonist use, fewer physician visits, and fewer hospitalizations.

It is not possible from this analysis to determine if this increase in health care utilization in inappropriate users is related specifically to excessive β-agonist use. An alternative may be that excessive β-agonist use is a marker of poor asthma management, and it may be that the under utilization of ICS is responsible for the poorer outcomes. One can conclude, however, that these patients experienced greater asthma-related morbidity and generated higher health care costs, and because urgent admission is defined as “a need for immediate assessment due to life-threatening conditions”, mortality may also be higher among inappropriate users.

This study design does not facilitate the determination of which patient and/or physician factors are responsible for the excessive use of β-agonists and the inadequate use of inhaled corticosteroids. Individual patients may use excessive amounts of β-agonist due to poor compliance with inhaled corticosteroid medication (which most clinicians would agree is common among asthmatics), “addiction” to other side effects of the β-agonists, genotypic predisposition to β-receptor down-regulation\textsuperscript{12}, steroid unresponsive asthma, or simply asthma which is refractory to treatment. Physician factors favoring excessive β-agonist use may include a lack of awareness of recent asthma
therapy guidelines, or a practice with a high percentage of severe asthmatics and/or transient patients.

Despite our inability to say why some patients are prescribed excessive amounts of β-agonists, the results of the study do show that patients who receive excessive doses of SA β-agonist with sub-optimal doses of ICS utilize more health services. Although it was not unexpected that inappropriate users would receive more prescriptions per prescribing physician, the finding that patients in this group received prescriptions from more unique physicians was not expected. This may indicate deliberate solicitation of prescriptions from multiple physicians, or may be reflective of a lack of continuity of care, which may partially explain the poorer outcomes.

Both the number of unique physicians seen, and physician visits by this group of young individuals is high. This may be a reflection of bias in this study population of Plan C and Plan E Pharmacare recipients. Plan C covers patients on social assistance who therefore comprise the lower socioeconomic strata and the unemployed in whom greater health care utilization has been demonstrated.\textsuperscript{13-18} Individuals in Plan E are those who individually, or as a family, exceeded the $600 deductible for the year and may therefore over-represent individuals using more drugs, having co-morbid conditions, or sick family members.

We estimate that this sample represents approximately 20% of asthmatics in BC, and although this limits the generalizability of our results, our study still illustrates the prevalence of inappropriate management and related outcomes in this population. Given that 77% of our study population were of lower socioeconomic status indicates that further research is needed to investigate the possibility of a causal relationship between income and asthma management.
We utilized hospitalization for any respiratory illness in our analysis. Therefore, some of these admissions may have been for indications such as pneumonia, chronic obstructive pulmonary disease (COPD), chronic bronchitis, or emphysema, since all of these patient groups may use SA β-agonists. However, we believe that contamination of the data by these non-asthmatics is likely minor given the relatively low prevalence of these disorders relative to asthma in this age group.

The implications of the drug use patterns exemplified in this study are significant. Despite increasing evidence of excessive SA β-agonist use as either a marker for, or cause of adverse outcomes, the use of greater than recommended doses continues to be prevalent. Inappropriately managed patients use more health services, suggestive of greater asthma-related morbidity and greater health care costs. We propose that the strategy employed in this study may be useful for identifying excessive β-agonist users who may benefit most from an asthma education program, with the ultimate goal of improved asthma management and lower health care utilization.
TABLE 3.1: SA β-AGONIST AND INHALED CORTICOSTEROID USE PATTERN

(All patients 5 < age < 50 yrs.)

<table>
<thead>
<tr>
<th>β-agonist (Canisters/Yr)</th>
<th>Inhaled Corticosteroid (µg/day)</th>
<th>&lt;100</th>
<th>101-200</th>
<th>201-400</th>
<th>401-800</th>
<th>&gt;800</th>
<th>Total</th>
</tr>
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<td>1430</td>
<td>671</td>
<td>3033</td>
<td>1638</td>
<td>18691</td>
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<tr>
<td></td>
<td></td>
<td>(49.7%)</td>
<td>(6.0%)</td>
<td>(2.8%)</td>
<td>(12.6%)</td>
<td>(6.8%)</td>
<td>(77.9%)</td>
</tr>
<tr>
<td>5 - 8</td>
<td></td>
<td>808</td>
<td>205</td>
<td>176</td>
<td>406</td>
<td>631</td>
<td>2226</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3.4%)</td>
<td>(0.9%)</td>
<td>(0.7%)</td>
<td>(1.7%)</td>
<td>(2.6%)</td>
<td>(9.3)</td>
</tr>
<tr>
<td>9 - 12</td>
<td></td>
<td>345</td>
<td>90</td>
<td>88</td>
<td>206</td>
<td>442</td>
<td>1171</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.4%)</td>
<td>(0.4%)</td>
<td>(0.4%)</td>
<td>(0.9%)</td>
<td>(1.8%)</td>
<td>(4.9%)</td>
</tr>
<tr>
<td>13 - 20</td>
<td></td>
<td>248</td>
<td>89</td>
<td>89</td>
<td>207</td>
<td>380</td>
<td>1013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.0%)</td>
<td>(0.4%)</td>
<td>(0.4%)</td>
<td>(0.9%)</td>
<td>(1.6%)</td>
<td>(4.2%)</td>
</tr>
<tr>
<td>&gt;20</td>
<td></td>
<td>170</td>
<td>82</td>
<td>91</td>
<td>205</td>
<td>337</td>
<td>885</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.7%)</td>
<td>(0.3%)</td>
<td>(0.4%)</td>
<td>(0.9%)</td>
<td>(1.4%)</td>
<td>(3.7%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>13490</td>
<td>1896</td>
<td>1115</td>
<td>4057</td>
<td>3248</td>
<td>23986</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(56.2%)</td>
<td>(7.9%)</td>
<td>(4.6%)</td>
<td>(16.9%)</td>
<td>(14.3%)</td>
<td>(100.0%)</td>
</tr>
<tr>
<td></td>
<td>appropriate Users</td>
<td>Inappropriate Users</td>
<td>p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------------</td>
<td>---------------------</td>
<td>---------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=4,671) Mean (SD)</td>
<td>(n=763) Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender: Female</td>
<td>60.4%</td>
<td>54.9%</td>
<td>0.004</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Years)</td>
<td>25.3 (13.7)</td>
<td>32.8 (11.2)</td>
<td>0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plan C (social</td>
<td>72.6%</td>
<td>61.4%</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>assistance)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SA β-agonist</td>
<td>1.9 (1.0)</td>
<td>16.9 (10.2)</td>
<td>0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Canisters prescribed)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled Corticosteroid (μg/day)</td>
<td>716.6 (479.8)</td>
<td>2.7 (12.1)</td>
<td>0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 3.3: Comparison of Health Care Utilization Between Appropriate and Inappropriate Users

<table>
<thead>
<tr>
<th></th>
<th>Appropriate Users</th>
<th>Inappropriate Users</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admission§</td>
<td>5.5%</td>
<td>8.4%</td>
<td>0.002</td>
</tr>
<tr>
<td>Frequency of Hospitalization†</td>
<td>0.07 (0.34)</td>
<td>0.11 (0.42)</td>
<td>0.006</td>
</tr>
<tr>
<td>Emergency visit§</td>
<td>3.3%</td>
<td>5.8%</td>
<td>0.001</td>
</tr>
<tr>
<td>Frequency of emergency visit†</td>
<td>0.04 (0.26)</td>
<td>0.08 (0.33)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

**Prescribing Physicians†**
- Number of physicians: 1.4 (0.7) vs. 1.8 (1.4), p-value = 0.0001
- Number of prescriptions per physician: 2.5 (1.5) vs. 5.2 (4.2), p-value = 0.0001
- Number of prescriptions per patient: 3.3 (1.9) vs. 7.5 (4.9), p-value = 0.0001

**All Physicians†**
- Number of physicians visited: 5.1 (4.2) vs. 4.8 (4.3), p-value = 0.16
- Number of visits per physician: 3.2 (3.0) vs. 3.9 (3.8), p-value = 0.0001
- Number of visits per patient: 14.9 (15.9) vs. 16.7 (19.3), p-value = 0.015

§ Proportion  
† Mean (Standard deviation)
### TABLE 3.4: RELATIVE RISK (95% CI) OF HOSPITALIZATION, EMERGENCY ADMISSION, AND PHYSICIAN USE – INAPPROPRIATE VS APPROPRIATE USERS

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted RR (95% CI)</th>
<th>Adjusted† RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospitalization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>1.56 (1.17, 2.07)</td>
<td>1.68 (1.25, 2.26)</td>
</tr>
<tr>
<td>Hospitalization frequency§</td>
<td>1.70 (1.34, 2.16)</td>
<td>1.81 (1.41, 2.32)</td>
</tr>
<tr>
<td>Emergency admission</td>
<td>1.81 (1.28, 2.55)</td>
<td>1.93 (1.35, 2.77)</td>
</tr>
<tr>
<td>Emergency admission frequency§</td>
<td>1.95 (1.45, 2.63)</td>
<td>2.07 (1.52, 2.83)</td>
</tr>
</tbody>
</table>

| **Physician Usage**     |                        |                       |
| **Prescribing Physician** |                        |                       |
| Number of physicians § | 1.29 (1.21, 1.36)      | 1.33 (1.26, 1.41)     |
| Number prescriptions/patient § | 2.28 (2.21, 2.35) | 2.35 (2.26, 2.41)     |
| Number of prescriptions/physician ** | 2.06 (1.98, 2.15) | 1.99 (1.91, 2.07)     |

| **All Physicians**      |                        |                       |
| Number of physicians visited § | 0.96 (0.92, 0.99) | 0.94 (0.91, 0.98)     |
| Number of visits per patient § | 1.14 (1.05, 1.20) | 1.12 (1.07, 1.22)     |
| Number of visits per physician ** | 1.20 (1.14, 1.26) | 1.06 (1.01, 1.12)     |

† Adjusted for age, gender, and Pharmacare Plan
* Logistic regression
** Gamma regression
§ Poisson regression (e.g. The frequency of hospitalization is 1.7 times greater in inappropriate users relative to appropriate users, and the frequency of hospital admission is 2 times greater in inappropriate users relative to appropriate users.)
3.6 REFERENCES


CHAPTER 4

PATTERNS OF INHALED ASTHMA MEDICATION USE:
A 3 YEAR LONGITUDINAL ANALYSIS OF PRESCRIPTION CLAIMS
DATA FROM BRITISH COLUMBIA, CANADA

4.1 FORWARD

This chapter has been accepted for publication, under the same title, in the journal Chest. The candidate is first author of this manuscript which is co-authored by Daphne Guh, a statistician who provided statistical consultation and SAS programming expertise in the analysis of the data, and by Drs. Aslam Anis and Peter Paré, the candidates co-supervisors. The candidate’s role in this manuscript was the development of the primary hypothesis and methods, all prescription data manipulation and statistical analysis, and writing of the final manuscript.

4.2 INTRODUCTION

Historically, short-acting (SA) inhaled β-agonists were the mainstay of asthma management; however, their excessive use has been identified as a potential risk factor for, or marker of, increased asthma-related morbidity and mortality.1-6 Although the most recent study of chronic SA β-agonist administration did not find an increase in the asthma exacerbation rate in the population studied,7 in at least four previous prospective studies the regular use of salbutamol and/or fenoterol had detrimental effects in terms of lung function, symptoms, exacerbations, and/or airway responsiveness when compared to their use on an as needed or rescue basis only.8-11

The increased recognition that airway inflammation plays an integral role in asthma has resulted in a shift from SA β-agonists to inhaled corticosteroids (ICS) as the
mainstay of therapy in all but the most mildly affected patients. Current asthma management guidelines define appropriate asthma management as the optimization of ICS doses with or without add-on therapy (e.g. leukotriene antagonists, long acting β-agonists, or chromoglycans) such that no more than three doses/week (two puffs per dose) of a SA β-agonist are required.\textsuperscript{12-14} Appropriate asthma therapy can therefore be defined as the utilization of <1 canister of SA β-agonist per year.

Given the evidence of the risks of excessive SA β-agonist utilization, either causally or as a marker for deteriorating control or worsening disease, and the recent dissemination of asthma management guidelines, it was our hypothesis that the acceptance and adoption of these guidelines should be reflected in a trend towards more appropriate asthma management in the population. Although the guidelines had been published prior to 1995, it was expected that the effect of this would have deteriorated resulting in a demonstrable improvement in management in the three years immediately following their re-publication. We postulated that this trend should be illustrated by a decrease in SA β-agonist prescribing and an increase in the utilization of ICS particularly by those most likely to benefit from their use, i.e. asthmatics receiving greater than four canisters of SA β-agonists per year. Using British Columbia (BC) Ministry of Health Pharmacare prescription claims data, we evaluated asthma prescribing practices over three years following the release and dissemination of the 1995 asthma management guidelines.\textsuperscript{12} A secondary objective of the analysis was to investigate factors potentially associated with increasing utilization of SA β-agonists.
4.3 METHODS

4.3.1 Subjects and Sources of Data

Prescription records for all asthma medications were obtained for all patients covered by Pharmacare in BC who filled at least one prescription for an inhaled SA β-agonist medication (i.e. salbutamol, fenoterol, or terbutaline) in 1996, 1997, or 1998. Pharmacare, the BC government’s pharmaceutical reimbursement program, provides comprehensive first-dollar coverage for all BC residents on social assistance (Plan C; ~220,000 people in 1990) and the general population (Plan E) whose annual family pharmaceutical expenditure exceeds their deductible limit ($600 prior to April 1, 1998 and $800 thereafter). Once a family reaches this threshold, each family member becomes eligible for reimbursement of drug expenditures for those drugs covered by Pharmacare, and their entire drug profile (including drugs prescribed prior to their achievement of the threshold) is added to the database.

4.3.2 Drug Utilization Determination

The annual quantity of inhaled SA β-agonist received was determined for all patients between 13 and 50 years of age on Plans C and E identified in the Pharmacare database. To control for differences in potency, strength, and formulation, the amount of each specific SA β-agonist prescribed was standardized to the number of canisters of salbutamol metered dose inhaler (MDI) (100μg/puff, 200 puffs/canister). Comparative dosages were derived from dosage comparison data and recommended dosages. Salbutamol by dry powder inhaler (DPI) was considered to be half as potent as by MDI, and fenoterol and salbutamol were considered equipotent by MDI and
Each dosage form of ICS was also standardized to the equivalent dose of beclomethasone dipropionate (BDP) by MDI. BDP was considered equipotent to budesonide by MDI\textsuperscript{19,20}, and half as potent by dry powder inhaler.\textsuperscript{21,22} Triamcinolone\textsuperscript{14} and fluticasone\textsuperscript{23-27} were considered half and twice as potent as BDP by MDI, respectively.

All patients were classified ordinally based on the amount of SA β-agonist they received each calendar year into low (≤4 canisters), intermediate (5-12 canisters), high (13-20 canisters), or excessive (>20 canisters) users, and on their average daily ICS dose for each year (none, 1 – 400 μg/day, 401 – 800 μg/day, and >800 μg/day). This ordinal classification scheme was developed to reflect increasingly poor asthma control and to provide a gradient of asthma severity, and has been applied in a previous study.\textsuperscript{28}

### 4.3.3 Study Design

Overall drug utilization patterns were assessed in a cross-sectional analysis of all patients. Longitudinal analyses of only patients who received at least one SA β-agonist prescription in each of the three years were undertaken to assess transitions between drug use classes. We hypothesized that improved asthma management would be demonstrated by a trend of decreasing SA β-agonist and increasing ICS use over the three years. Trends in ICS use were evaluated using two methods: 1) a trend analysis of the annual prevalence of not receiving a prescription for an ICS; and 2) an analysis of transitions between receiving and not receiving an ICS prescription. In the second analysis, the proportion of subjects who received an ICS prescription in 1996 but not in 1998 was
compared with the proportion that did not receive an ICS prescription in 1996 but did in 1998. Each of these analyses was stratified by baseline (1996) SA \( \beta \)-agonist use group.

Factors associated with increasing SA \( \beta \)-agonist use were assessed in two discrete samples of this population: 1) users of low doses of SA \( \beta \)-agonist (\( \leq 4 \) canisters) in 1996 who could be considered "controlled", and 2) users of more than four canisters in 1996 whose utilization could increase, decrease, or remain static and could be deemed "uncontrolled". "Controlled" subjects who consistently received \( \leq 4 \) canisters of SA \( \beta \)-agonist each year were compared with those who were controlled in 1996 but received more than four canisters in 1997 and 1998, and at least four more canisters in 1998 relative to 1996. Because the usage patterns of "uncontrolled" subjects could change in either direction (as well as remain static), those whose use increased were compared to those whose use decreased. For this analysis, increasing use was defined as the receipt of more SA \( \beta \)-agonist in both 1997 and 1998 relative to 1996 with an overall increase of at least 50% over the three years. Similarly, decreasing use was defined as a consistent decrease of at least 50% in the amount of SA \( \beta \)-agonist received over the three years. These cutpoints were selected based on what was deemed to be indicative of a significant change; one-way sensitivity analysis around these cutpoints was performed.

4.4.4 Statistics

Between group differences in mean values were compared using Student’s t-test. To account for correlation within individuals, trends in SA \( \beta \)-agonist and ICS use over time were evaluated using repeated measures Mantel-Haenszel tests for dichotomous and ordinal responses.\textsuperscript{29-31} Within-patient transitions between groups were analyzed using McNemar’s test.
The relationships between increasing SA β-agonist utilization and age, gender, Pharmacare plan, and change in mean annualized daily ICS dose were evaluated using multiple logistic regression; mean daily ICS dose at baseline was also evaluated and included in the adjusted models if significant. The dependent variable for analysis of both subgroups was increasing use, resulting in the determination of odds ratios for increasing use relative to remaining in the low use group over the 3 years in “controlled” users, and for increasing use relative to decreasing use in “uncontrolled” users. All variables significant in univariate analyses at a level of alpha=0.10 were included in the multiple regression models. Model fit was assessed using -2 Log likelihood. Crude and adjusted odds ratios and 95% confidence intervals (CI) are reported for each variable.

4.5 RESULTS

4.5.1 Demographics

78,758 individual patients in Pharmacare plans C and E filled at least one prescription for a SA β-agonist in any of the three years: 43,277 in 1996, 41,790 in 1997, and 33,781 in 1998 (Table 4.1). 618,519 prescriptions for asthma medications (SA β-agonists, ICS, ipratropium bromide, theophylline, long-acting β-agonists, chromoglycans and nedocromil) were filled or refilled over this time period. The majority of the population was female (62%) and were receiving social assistance (Pharmacare Plan C) (56%). The number of patients included in the entire sample accounts for approximately 17% of all patients covered by both Pharmacare plan C and plan E in 1996. The average age was 32.3 ± 11.4 years. Patients on Plan E were significantly older than patients on Plan C (33.3 vs. 31.6 years; p<0.0001) and women were significantly older than men.
(32.9 vs. 31.5 years; p<0.0001). 1,408/10,686 (17%) of patients who received at least one SA β-agonist prescription each year were between 13 and 17 years, and 3,463 (32.4%) were between 18 and 35 years of age.

4.5.2 Cross-sectional analysis

Although the majority of patients received ≤4 canisters of SA β-agonist each year, more than 2,000 patients (>6%) received 13 or more canisters, more than 40% of which received more than 20 canisters (Table 4.1). 1,147 patients received an average of more than 20 canisters/year of which 152 (13.2%) averaged more than 40 canisters/year. We had hypothesized that over time, fewer patients would receive inappropriately high doses of SA β-agonists; however, the proportion of patients in each SA β-agonist use group varied <1% between years.

4.5.3 Longitudinal analysis

10,686 patients received at least one prescription for a SA β-agonist each year, 50% of which consistently received ≤4 canisters/year. 1,141 (10.7%) patients consistently received between five and twelve canisters, and 1,066 (10%) received more than 12 canisters in both years, of which approximately 40% received in excess of 20 canisters/year. 1,589 (14.9%) patients transitioned upward between usage groups between 1996 and 1998, versus 1,804 (16.8%) who transitioned downward. Trend analysis did not provide any meaningful indication of either increasing or decreasing SA β-agonist use over the three years.

Each year, approximately 40 percent of patients in this population did not fill a prescription for an ICS. Even though the majority of these patients received ≤4
canisters/year of SA β-agonist and thus for whom an ICS would not necessarily be indicated, more than one-third of ICS non-users consistently received in excess of twelve canisters/year of SA β-agonist. Trend analysis did not reveal any evidence of increasing ICS use over the three years. To the contrary, Figure 4.1 illustrates a trend towards an increasing prevalence of not receiving any ICS (p<0.0001) among subjects who received at least one SA β-agonist prescription each year. Because this finding could be related to decreasing asthma severity, we repeated the analysis in the 966 patients who received at least thirteen canisters of SA β-agonist in all three years and found that their probability of not receiving an ICS increased from 0.16 to 0.20 (p=0.002) between 1996 and 1998.

Figure 4.2 illustrates the comparison of the proportion of patients who filled at least one prescription for an ICS in 1996 but not in 1998 to the proportion that did not fill an ICS prescription in 1996 but did so in 1998. Although there was no difference in proportions in the low use group, significantly more patients appear to have discontinued ICS therapy than were initiated on it over the three years. The most salient discrepancy occurred in the excessive SA β-agonist users, 16.4% of whom received a prescription for an ICS in 1996 but did not in 1998 compared to only 4.7% who initiated ICS therapy (p<0.0001).

4.5.4 Factors associated with increasing SA β-agonist use

The analysis of factors associated with increasing SA β-agonist use in previously 'controlled' patients is presented in Table 4.2. 6,449 patients received ≤4 canisters of SA β-agonist in 1996; 4,932 remained in this use group in all three years versus 631 who consistently increased their use over the three years, and received at least 4 more canisters in 1998 relative to 1996 (median increase 6.0; IQ range 4.6 – 9.0).
Logistic regression analysis revealed a positive association between increasing β-agonist use and all factors tested. In the adjusted model, individuals between 18 and 34 years of age were 1.5 times more likely than those under 18 to increase their use, and being male or receiving social assistance increased the risk of increasing SA β-agonist use by 1.7 and 2.3 times, respectively. A positive association between increasing SA β-agonist use and both average daily ICS dose in 1996, and the change in ICS dose between 1996 and 1998 was also found.

Of 4,237 patients who received >4 canisters of SA β-agonist in 1996, 584 and 1,332 met the criteria of increasing and decreasing use, respectively (Table 4.3). Patients whose use decreased received significantly more canisters of SA β-agonist (13.0 vs. 9.3; p<0.0001) and had a higher mean daily ICS dose (475 μg/day vs. 326 μg/day; p<0.0001) at baseline than those whose use increased. More Plan C than Plan E patients also increased their use over the three years (32.0% vs. 25.9%; p=0.004). Although their was no relationship between age and increasing use in “uncontrolled” patients, and the association between gender and increasing use was attenuated in the adjusted model, receipt of social assistance remained significant. Patients on Pharmacare plan C were 1.3 times more likely to increase than decrease their SA β-agonist use by at least 50%, relative to patients on plan E. Sensitivity analysis, varying increasing use from 2 to 6 canisters in controlled users, and varying increasing and decreasing use from 30% - 70% in uncontrolled users, resulted in consistent findings.
4.6 DISCUSSION

Current asthma management guidelines stipulate that a primary goal of asthma management should be the minimization of SA β-agonist use to no more than three doses (six puffs) per week by increasing the use of ICS and other add-on agents. Realizing that the goal of asthma management should not be to merely decrease the amount of SA β-agonist use but rather to improve overall asthma control, given the absence of other measures of control we have used SA β-agonist use as a surrogate measure of asthma control.

Each year approximately 5% of this population received >12 canisters of SA β-agonist per year, more than half of whom were prescribed in excess of 20 canisters, far exceeding the desired management goal. Although the total number of clients decreased from 1997 to 1998, there was no change in the distribution of the users. This decrease may have been at least partially attributable to the increase in the deductible effective April 1, 1998. The prevalence of SA β-agonist use in this sample was greater than the prevalence of asthma in the general population (17% vs 5% – 10%). This was not unexpected given the potential higher prevalence of asthma in lower social classes.32,33

In a previous Canadian study, Habbick et al. demonstrated an increase in the annual prevalence of ICS use between 1989 and 1992, with a subsequent decrease in 1993.34 This reversal may have occurred due to the weakening of the effect of the 1990 publication of the guidelines. Although we expected to identify some effect following their republication, we were unable to identify any trends toward improved asthma management in terms of either decreasing SA β-agonist or increasing ICS use. In this population it appears that inappropriate management persists, and may be paradoxically
deteriorating. Even though this is only a sample of the population of asthmatics in BC and provides a conservative estimate of the overall magnitude of inappropriate over-utilization of SA β-agonists, it provides ample evidence of persistent inappropriate over-reliance on short-acting bronchodilators.

The benefits of adding ICS to SA β-agonist therapy are well established, with the most marked benefits occurring in those patients using the highest doses of SA β-agonist. Although our finding that patients whose SA β-agonist use decreased were receiving greater amounts at baseline can be attributed at least partially to regression to the mean, the finding of higher average annual daily doses of ICS at baseline in uncontrolled patients whose SA β-agonist use decreased cannot. This is not an unexpected finding, and may further illustrate the beneficial effects of ICS therapy. Despite this, each year approximately 500 patients who received >12 canisters of SA β-agonist did not receive any concomitant ICS. Furthermore, we identified a paradoxical trend of decreasing ICS use, illustrated by an increasing prevalence of not receiving an ICS, and a greater likelihood of not receiving an ICS after having received one previously than starting on one. Most disconcertingly, these trends were most pronounced in patients most likely to benefit from concomitant ICS therapy, i.e. the excessive SA β-agonist users.

Sub-group analysis of factors associated with increasing use identified increasing ICS dose as the strongest risk factor for increasing SA β-agonist use which is likely indicative of increasing asthma severity. These analyses therefore demonstrate different associations between age, gender, and receipt of social assistance with increasing SA β-agonist use in controlled and uncontrolled patients, independent of disease severity.
One of the most noteworthy associations identified was the greater risk of increasing SA β-agonist use by subjects on social assistance. However, because this sample is comprised of only patients who exceeded their family deductible or who received social assistance benefits, a sample selection bias is potentially manifest. Patients receiving benefits under Pharmacare Plan E may represent the general population with the most severe or poorly controlled asthma. If so, this analysis will provide a conservatively biased estimate of the true risk of increasing SA β-agonist use by Plan C patients relative to the general population. Although previous studies have attributed class differences in asthma-related outcomes to disease severity, this study indicates that poorer asthma control may also be contributory.\textsuperscript{38,39}

Previous studies have shown increases in the annual prevalence of ICS use, but utilized annual cross-sectional analysis only and may therefore be confounded by asthma prevalence.\textsuperscript{40,41} By utilizing a repeated measures analysis and including only subjects in the dataset each year, we controlled for this potential confounding and were able to more accurately assess drug utilization patterns, independent of asthma prevalence. In spite of this, a limitation of this analysis is that this is not an incident cohort, and in fact is likely comprised of mostly prevalent SA β-agonist users. Patients on long term therapy may be less likely to alter their therapy or have it changed, whereas newly treated asthmatics may be more apt to be treated in accordance with the guidelines. It was not possible to test this hypothesis using these data.

The majority of patients in this sample received ≤ 4 canisters of SA β-agonist and may therefore not be asthmatic. To determine the frequency of prescribing of SA β-agonist medications for indications other than asthma in this population, we utilized
IMSHealth Canada data (an independent pharmaceutical research firm) and estimated that approximately 85% of prescriptions for SA β-agonists in this age group are prescribed for asthma. Most non-asthmatics likely received a SA β-agonist for an acute indication and will therefore be classified as ‘low’ users, resulting in a conservatively biased estimate of the proportion of asthmatics using inappropriately high amounts of SA β-agonist. This bias is less likely to affect the longitudinal analysis given the inclusion of only patients who received a SA β-agonist prescription each year.

At least two previous studies have also identified potential asthmatics based on the receipt of at least one canister of a SA β-agonist in a year.\textsuperscript{28,42} Theoretically, because one goal of asthma management is to minimize SA β-agonist use to less the 4 doses (8 puffs) per week or approximately 2 canisters per year, this has the potential to exclude the most well controlled asthmatics. In a study by Diette et al., SA β-agonists were the most frequently prescribed medication with 94.4% of moderate to severe asthmatics reporting use.\textsuperscript{43} Gaist et al. evaluated asthma medication utilization patterns in 20 to 44 year olds between 1991 and 1994 and found that in 1994, only 4.3% of asthmatics on moderate to high doses of ICS used the equivalent of less than 4 canisters of SA β-agonist.\textsuperscript{40} It is likely that less than one percent of these patients used less than one canister. Thus, although a theoretical consideration, the magnitude of this potential bias is minimal and unlikely to affect our findings significantly.

Because these results are based entirely on computerized prescription drug data of dispensed medications, they may not coincide precisely with the actual intake of the medications potentially resulting in some misclassification of drug use. It is also possible that some patients may acquire extra canisters SA β-agonist for security reasons.
Although this is a limitation of using administrative prescription data for any pharmacoepidemiologic study, the abundance of previous studies specifically in asthma using this methodology suggests that it is an acceptable limitation.\textsuperscript{2,3,6,28,44-49} Using annualized prescription data and assuming receipt of a prescription approximates usage patterns eliminates potential recall bias and attenuates any effect of seasonal variation in drug utilization. The large sample size and longitudinal analysis in this study should minimize the impact of this potential prescription bias.

This analysis demonstrates continued over-reliance on inhaled $\beta$-agonist medications, one measure of asthma control. Even though this is only a sample of the population, it provides disconcerting evidence of the potential magnitude of the problem. Although we have identified age, gender and socioeconomic status as potential contributing factors, other etiologic factors contributing to this inappropriate utilization remain to be elucidated. A recent survey of Canadian asthmatics suggested other potential causes such as inappropriate prescribing, lack of specialist referral, inappropriate asthma medication utilization, inaccurate patient and physician perceptions of asthma severity and control, and erroneous understanding of the role of $\beta$-agonist and ICS medications in asthma management.\textsuperscript{50} The explication of the physiologic, social, behavioral and control factors contributing to persistent excessive SA $\beta$-agonist utilization will facilitate the identification of patients prone to lack of control and the targeting of management resources to asthmatics most likely to benefit.
TABLE 4.1: ANNUAL NUMBER OF CANISTERS OF SA β-AGONIST RECEIVED

(Proportion of the sample in use group within year)

<table>
<thead>
<tr>
<th></th>
<th>Number of Canisters Prescribed</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 4</td>
<td>5-12</td>
</tr>
<tr>
<td>-------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>1996</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>35,251 (81.5)</td>
<td>4,999 (11.6)</td>
</tr>
<tr>
<td>1997</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>33,895 (81.1)</td>
<td>4,981 (11.9)</td>
</tr>
<tr>
<td>1998</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>27,515 (81.4)</td>
<td>4,114 (12.2)</td>
</tr>
</tbody>
</table>
FIGURE 4.1: TRENDS IN THE ANNUAL PREVALENCE OF NOT RECEIVING A PRESCRIPTION FOR AN ICS AMONG SA β-AGONIST USERS

** Mantel-Hantszel test for trend $p=0.0001$
FIGURE 4.2: TRANSITIONS BETWEEN RECEIVING AND NOT RECEIVING AT LEAST ONE ICS PRESCRIPTION
(by 1996 β-agonist Use Group)

NS = not significant; ** McNemar’s p<0.0001
### TABLE 4.2: FACTORS ASSOCIATED WITH INCREASING SA β-AGONIST USE – ‘CONTROLLED’ USERS IN 1996 (n= 5,563)

<table>
<thead>
<tr>
<th></th>
<th>Number Increasing (%)</th>
<th>Crude Odds Ratio (95% CI)</th>
<th>Adjusted Odds Ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n= 631</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 - 18 years</td>
<td>69/880 (7.8)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>19 - 34 years</td>
<td>221/1729 (12.8)</td>
<td>1.7 (1.3 - 2.3)</td>
<td>1.5 (1.1 - 2.0)</td>
</tr>
<tr>
<td>35 - 50 years</td>
<td>341/2954 (11.5)</td>
<td>1.5 (1.2 - 2.0)</td>
<td>1.4 (1.04 - 1.9)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>378/3734 (10.1)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Male</td>
<td>253/1829 (13.8)</td>
<td>1.4 (1.2 - 1.7)</td>
<td>1.7 (1.4 - 2.0)</td>
</tr>
<tr>
<td><strong>Plan</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plan E</td>
<td>133/1890 (7.0)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Plan C</td>
<td>484/3673 (13.2)</td>
<td>2.0 (1.6 - 2.4)</td>
<td>2.3 (1.8 - 2.9)</td>
</tr>
<tr>
<td><strong>ICS dose change</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>273/3790 (7.2)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;100 mcg/day ↓</td>
<td>69/784 (8.8)</td>
<td>1.2 (1.02 - 1.8)</td>
<td>1.4 (1.04 - 1.8)</td>
</tr>
<tr>
<td>100 - 400 mcg/day ↑</td>
<td>143/649 (22.0)</td>
<td>3.8 (3.0 - 4.8)</td>
<td>3.8 (3.1 - 4.8)</td>
</tr>
<tr>
<td>401 - 800 mcg/day ↑</td>
<td>77/217 (35.5)</td>
<td>7.6 (5.5 - 10.4)</td>
<td>7.8 (5.7 - 10.7)</td>
</tr>
<tr>
<td>&gt;800 mcg/day ↑</td>
<td>69/123 (56.1)</td>
<td>20.6 (13.8 - 30.8)</td>
<td>21.3 (14.3 - 31.8)</td>
</tr>
</tbody>
</table>

*Also adjusted for average daily ICS dose in 1996*
TABLE 4.3: FACTORS ASSOCIATED WITH INCREASING SA β-AGONIST USE - ‘UNCONTROLLED’ USERS IN 1996 (n=1,916)

<table>
<thead>
<tr>
<th></th>
<th>Number Increasing (%) n=584</th>
<th>Crude OR (95% CI)*</th>
<th>Adjusted OR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 - 18 years</td>
<td>56/200 (28.0)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>19 - 34 years</td>
<td>218/684 (31.9)</td>
<td>1.4 (0.96 - 2.0)</td>
<td>NS</td>
</tr>
<tr>
<td>35 - 50 years</td>
<td>310/1032 (30.0)</td>
<td>1.2 (0.86 - 1.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>321/1108 (29.0)</td>
<td>1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>263/808 (32.6)</td>
<td>1.2 (1.01 - 1.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Plan</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plan E</td>
<td>189/722 (26.2)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Plan C</td>
<td>395/1194 (33.0)</td>
<td>1.3 (1.03 - 1.6)</td>
<td>1.3 (1.01 - 1.6)</td>
</tr>
<tr>
<td><strong>ICS dose change</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>94/729 (12.8)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;100 mcg/day ↓</td>
<td>210/739 (26.5)</td>
<td>0.43 (0.33 - 0.57)</td>
<td>0.43 (0.33 - 0.58)</td>
</tr>
<tr>
<td>100 - 400 mcg/day ↑</td>
<td>129/238 (54.2)</td>
<td>3.4 (2.5 - 4.6)</td>
<td>3.5 (2.5 - 4.8)</td>
</tr>
<tr>
<td>401 - 800 mcg/day ↑</td>
<td>70/102 (68.6)</td>
<td>7.3 (4.5 - 11.6)</td>
<td>6.9 (4.3 - 11.2)</td>
</tr>
<tr>
<td>&gt;800 mcg/day ↑</td>
<td>81/108 (75.0)</td>
<td>9.6 (5.9 - 15.7)</td>
<td>8.9 (5.4 - 14.6)</td>
</tr>
</tbody>
</table>

*Adjusted for baseline SA β-agonist use
†Adjusted for baseline SA β-agonist and ICS use
4.7 REFERENCES


CHAPTER 5

USING ADMINISTRATIVE HEALTHCARE DATA TO RECRUIT STUDY SUBJECTS: EXPERIENCE WITH ‘CAMOUFLAGED SAMPLING’

5.1 FORWARD

This chapter is currently under review for publication in *Epidemiology* under the title “Using administrative health care data to recruit study subjects: experience with camouflaged sampling”. The candidate is first author of this manuscript which was co-authored by Leanne Warren, a programmer with the Ministry of Health who performed the data manipulation of the Pharmacare data, and Dr. Malcolm Maclure who developed the camouflaged sampling methodology. Drs. Aslam Anis and Peter Paré, co-supervisors of the candidate are also included as co-authors of the submitted manuscript.

The candidate’s role in this manuscript was the initial Pharmacare data manipulation, target population selection and stratification, co-ordination of study recruitment, development and performance of all statistical analysis, and the writing of the final manuscript.

5.2 INTRODUCTION

The utilization of even anonymous administrative health care data for health research has become a contentious issue, resulting in growing concern and regulations pertaining to the protection of privacy when using health care data for research purposes. This is a challenge for epidemiologic studies and clinical trials that require recruitment of individuals with a specific disease or health attribute.
Population-based sampling using media advertising or random digit dialing (RDD) typically reaches more ineligible than eligible subjects and is limited by the amount of background information that can be presented to potential participants. Recruiting through physician’s practices or specialized clinics may be more targeted but may not provide a representative sample of the general population. We utilized and evaluated a method of directly contacting individuals potentially eligible for a study, identified using an administrative prescription drug database.

The primary goal of the study was to identify factors associated with the excessive use of short-acting (SA) β-agonists, a marker for increased morbidity and mortality related to asthma.\textsuperscript{1-6} Previously, we analyzed asthma medication utilization and associated outcomes in British Columbia (BC) using BC Ministry of Health Services’ hospital programs, Medical Services Plan, and Pharmacare prescription drug databases.\textsuperscript{7} The results of these analyses lead to hypotheses about the determinants of inappropriate asthma management which necessitated that we contact patients directly; however, the privacy of administrative health data was a potential obstacle.

Our goal was to contact subjects in the Pharmacare database that had been included in our previous analysis, and to recruit a heterogeneous sample of SA β-agonist users. Because of the need to ensure the privacy of administrative health data, we used ‘camouflaged sampling’ to recruit subjects which permits patient contact while protecting their privacy and facilitates stratified sampling.

Camouflaged sampling involves using anonymized administrative data to compile a target sample, then ‘camouflaging’ the sample with a sufficient number of non-target patients before obtaining the names and addresses of potential study participants. The names and addresses of the mixed list of target and non-target patients are then obtained.
simultaneously to ensure the researchers know nothing about the health status of any individual on the list. Patients are then contacted, but do not provide any personal or health information until they consent to participate; the health status of those who decline to participate remains unknown.

We expected that using stratified sampling of a targeted population would result in a more heterogeneous sample than recruiting from the general population. In order to test this hypothesis, we also recruited a sample of the general population through media advertising. The objective of this analysis was to evaluate camouflaged sampling in terms of accrual rate, and to compare sampled patients to volunteers in terms of SA β-agonist use, demographics, socioeconomic status (SES), and asthma-related quality of life.

5.3 METHODS

Potential candidates for this study included asthmatics between 19 and 50 years of age who resided in the Greater Vancouver Regional District (GVRD). To accrue our sample we recruited subjects from two target populations: 1) BC Pharmacare clients, and 2) the general population of newspaper readers. Each patient assessment necessitated a clinic visit to undergo spirometry, complete a study-specific questionnaire, and provide a blood sample for genotype determination.

5.3.1 Pharmacare Target Population

A stratified random sample of all SA β-agonist users was identified using the BC Ministry of Health’s Pharmacare prescription drug database. Pharmacare is the BC government’s pharmaceutical reimbursement program which provides comprehensive coverage for all community-dwelling seniors (Plan A, ≥ 65years), all persons on social
assistance (Plan C), and the general population exceeding an $800 annual family deductible (Plan E). Once the $800 threshold has been reached, the individual becomes eligible for reimbursement of drug expenditures from Pharmacare and their entire drug profile, including drugs prescribed prior to their achievement of the threshold, is added to the database.

Using encrypted personal health numbers (PHNs), all Pharmacare Plan C and E beneficiaries between 19 and 50 years of age in 2000 who received the equivalent of at least one canister of SA β-agonist medication in 1998 were identified. We assumed that the receipt of the equivalent of at least one canister of salbutamol 100 µg/puff (200 puffs/canister), a SA β-agonist indicated for the management of acute asthma, would be an adequate indicator of physician-diagnosed asthma in this population.

To facilitate stratified sampling by the magnitude of SA β-agonist used, the amount of each SA β-agonist received by each patient was standardized to the number of canisters of salbutamol 100 µg/puff (200 puffs/canister) by metered-dose inhaler (MDI). Each patient was then classified as a low (≤4 canisters), intermediate (5-12 canisters), high (13 – 20 canisters), or excessive (>20 canisters) SA β-agonist user. This dosage standardization method has been utilized previously. Only those remaining in the database at the time our sample was drawn were retained as the ‘target population’.

5.3.2 Pharmacare Camouflage Population

A potential camouflage subject was any person who filled a prescription for a medication other than a SA β-agonist that was covered by Pharmacare Plan C or E in 1999, and was unlikely to have asthma. To minimize the probability of a camouflage subject having asthma or another chronic respiratory illness, patients were excluded if
they were in the target population, had received a prescription for any other asthma medication, antitussive, expectorant, anti-inflammatory drug, corticosteroid, or respiratory smooth muscle relaxant in 1998, 1999, or 2000, or filled a prescription under another medication-specific Pharmacare program.

Potential camouflage subjects were selected randomly from all remaining Pharmacare clients between 19 and 50 years of age in 2000 who lived in the GVRD and filled at least one prescription from the same physician as a target subject in 1999. To maximize the probability of reaching eligible subjects currently living in the GVRD, the target and camouflage subject lists were merged, and the postal code of each individual’s most recent address on record was obtained and used to identify those continuing to reside in the GVRD.

5.3.3 Target Sample Selection and Camouflaging of the Pharmacare Sample

A random sample of 500 low and intermediate SA β-agonist users, and all high and excessive users were selected to comprise the target population, and both target and camouflage subjects were grouped by prescribing physician. One camouflage subject was then selected for every four target subjects, with at least one camouflage subject selected per physician. Camouflage subject and target sample lists were then merged, the list identifiers removed, and the original lists destroyed.

Client names and addresses were extracted by government analysts not involved with the study. The final list of patients was then returned to study collaborators within Pharmacare for linkage with physician names and addresses, and recruitment letter production and mailing.
This camouflaged sampling methodology is in compliance with The Personal Information Protection and Electronic Documents Act (Pt 1, Div 1, 5.7.2(c)), The BC Freedom of Information and Privacy Act, and was approved by three independent ethics committees and the BC Ministry of Health’s Information and Privacy Branch.8,9

5.3.4 Indirect and Direct Patient Contact

Two different pathways of patient contact were evaluated. In the pilot phase, recruitment letters were sent to patients indirectly via each subject’s most frequent prescribing physician, identified using a unique practitioner identifier in the Pharmacare database. The general practitioner (GP) or internal medicine specialist (e.g. respirologist, allergist) from whom each patient filled the most prescriptions was selected. Patients who did not receive a SA β-agonist prescription from either a GP or an internist were excluded. A letter to each physician outlined the study rationale and recruitment methodology, and requested that they verify the patient’s address and forward the recruitment letter (provided in a stamped, pre-addressed, sealed envelope) to those they considered suitable study candidates. In the second phase, recruitment letters explaining the study rationale, enrollment procedures, and participation requirements were mailed directly to the remaining target sample and camouflage subjects.

5.3.5 General Population Recruitment

To facilitate the comparison of camouflaged sampling to recruitment from the general population, we also recruited volunteers using print media advertising. A total of
four advertisements were published in three newspapers: one advertisement in each of two newspapers with bi-weekly and daily GVRD circulation of approximately 50,000 and 200,000, respectively, and two in a newspaper with a daily circulation of approximately 250,000. The estimated readership of the two large circulation papers by 18-49 years olds living in the GVRD is approximately 30%.

5.3.6 Group Comparison and Statistical Analysis

The Pharmacare base population and the sample of participants recruited via camouflaged sampling were compared for differences in age, gender, and SES based on the receipt of social assistance. Sampled participants and volunteers were compared for differences in demographic, SES (income, education, and receipt of social assistance), asthma-related quality of life (QOL), pulmonary function, and asthma medication use.

Asthma-related QOL was measured using the Asthma Quality of Life Questionnaire (AQLQ), which elucidates QOL scores between 1 (poorest) and 7 (best) on four domains, and globally. Forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were measured in accordance with American Thoracic Society criteria and expressed as percentages of the value predicted by the patient’s height and gender. Differences between groups were compared using χ² tests for categorical variables and Student’s t-tests for interval data. All comparison variables were selected a priori.

The presence of a differential effect of SES on SA β-agonist use between sampled participants and volunteers was evaluated. Multivariate categorical modeling with SA β-agonist use group as the dependent variable was used to evaluate the interaction between the effect of SES and recruiting method on the magnitude of SA β-agonist use. The
presence of an interaction was determined by modeling the marginal probabilities of being in each SA β-agonist use category. All categories were defined \textit{a priori} or were dictated by the distribution of the data. Sensitivity analysis was performed on the income cutpoints.

5.4 RESULTS

5.4.1 Final sample

The compilation of the target sample and final mailing list is depicted in Figure 5.1. A total of 46,128 Pharmacare plans C and E clients received at least one prescription for a SA β-agonist in 1998. 14,650 patients would be between 19 and 50 years of age in 2000, of whom 9,566 resided in the GVRD. 2,386 were no longer in the eligible Pharmacare population, and an additional 82 did not have an identifiable internist or GP and were excluded from the target population. Of the remaining 7,098 patients, 7,065 were matched to 1,792 GPs (3.99 ± 4.18 patients/GP) and 33 to 30 specialists (1.2 ± 0.6 patients/internist). 557 remaining target subjects could not be matched to a suitable camouflage subject and were therefore also excluded, resulting in a final target population of 6,541.

The target sample consisted of the 500 patients randomly selected from the low and intermediate SA β-agonist use groups, 508 high users and 225 excessive users. 964 camouflage subjects were randomly selected from 877 and 11 corresponding GP and specialist practices, respectively, resulting in a final mailing list of 2,697 patients and a target:camouflage ratio of 1.8:1.
202 subjects were recruited for the study: 15 (7%) during the pilot phase, 94 (46%) using direct patient contact (Figure 5.2), and 93 who volunteered as a result of media advertising. Accounting for returned, undeliverable recruitment letters and an estimated positive predictive value (PPV) of identifying asthmatics in this age group based on the use of a SA β-agonist of approximately 0.85, camouflaged sampling recruitment rates were approximately 9% and 5% in the indirect and direct-to-patient mailing phases, respectively.

5.4.2 Group Comparisons

Because the final target population (n=6,541) and target sample (n=1,733) lists were destroyed once the final sample was compiled to ensure privacy protection, sampled participants were compared to the un-recruited target population (n= 9,311; 9,566 – 146 (received <1 canister of SA β-agonist) – 109 recruited). Although there was no difference in the distribution of gender, target sample subjects who enrolled in the study were less likely to be receiving social assistance and were, on average, older than patients in the target population from which they were drawn (Table 1).

Comparison between groups based on the stratification used for recruiting revealed that 75% of the target population received ≤4 canisters of SA β-agonist versus 62% of volunteers and only 24% of subjects recruited through camouflaged sampling (Figure 5.3). The distribution of SA β-agonist users was similar in the target population and volunteers, with the majority having received ≤4 canisters, and very few (2.9% and 4.3%, respectively) receiving more than 20 canisters. The distribution of the SA β-agonist use by sampled participants differed significantly from volunteers ($\chi^2 p<0.0001$),
and was more heterogeneous, ranging from 14% in the excessive use group to 43% in the intermediate use group. Sampling recruitment rates within each SA β-agonist use group (adjusted for the PPV, and assuming a proportional distribution of returned letters across groups) ranged from 5.0% in high users to 11.8% in intermediate users; 6.8% and 8.4% of low and excessive users, respectively, participated.

Although there was no difference in the distribution of gender or marital status, volunteers were younger, less likely to currently smoke or be receiving social assistance, and had more education and higher income. 29 participants declined to provide income information and were therefore excluded from the income analysis (Table 2). Volunteers also had better asthma-related quality of life on each domain of the AQLQ and better baseline pulmonary function; however, there was no difference in the reversibility of airway narrowing (FEV₁ and FEV percent change). Although volunteers were also less likely to have received an oral corticosteroid in the previous year, there was no difference in the daily use of an inhaled corticosteroid.

Table 3 illustrates the relationship between recruiting method, SES and the amount of SA β-agonist received. Independent of recruiting method and measure of SES, higher SES participants were more likely to have received ≤4 canisters and less likely to have received >12 canisters of SA β-agonist in the previous year than lower SES participants. Multivariate categorical modeling did not reveal any significant interactions between SES and recruiting method on the magnitude of SA β-agonist use ($\chi^2 p>0.05$). This suggests that the relationship between SES on SA β-agonist use was consistent between recruitment groups.
5.5 DISCUSSION

Our study of the determinants of excessive SA β-agonist use necessitated the accrual of a heterogeneous sample of SA β-agonist users. Although the distribution of SA β-agonist use was not representative of use in the general population, stratified camouflaged sampling provided a more heterogeneous sample of SA β-agonist users than did recruitment from the general population media advertising, as expected. The corollary of this lack of representativeness is the potential for selection bias to affect the study results if the association between SES and SA β-agonist use differed between recruiting methods; however, no differential association was found. The final estimated recruiting rate after accounting for undeliverable letters and the estimated incidence of prescribing of SA β-agonist for non-asthma indications was 9% when sent via a physician, and only 5% when mailed directly to the patient.

Given the hypothesis of our study that there is an association between socioeconomic status and SA β-agonist use, the differences we found in SES, demographic and asthma-related variables between groups were not unexpected. Previous studies comparing the SES and age of volunteers to randomly sampled study subjects have shown significant differences. In a study of depression in the elderly, Ganguli et al. found that volunteers had more education relative to subjects sampled from census data. Similarly, volunteers in a smoking cessation study had higher incomes, were less likely to be unemployed or employed in a blue collar occupation, and were more likely to receive the newspaper than participants sampled using random digit dialing. Admittedly, the base populations for each recruiting method used in this study were different, and thus differences between those recruited by each method could be
anticipated. Other than the difference in mean age between sampled participants and volunteers, all other differences were consistent with previously published studies.

Although we did not sample all potential asthmatics in the GVRD, Pharmacare provided a pseudo-population based source from which to compile our sampling frame. However, one consequence of using this database was an over-representation of potential study participants receiving social assistance in both the target population and consequently, the sampled participants (65% and 45%, respectively). The application of this methodology to a truly population-based data source should increase the representativeness of the sample.

Ideally, the determination of whether a selection bias is manifest in this sample should entail the calculation of the Selection Probability Ratio (SPR) for high vs. low SA β-agonist users recruited by each method and stratified by SES, similar to that done previously by Maclure and Hankinson. A selection bias can then be determined by calculating the ratio of SPRs. If the SPR, stratified by SES, for sampled participants is equivalent to the SPR for volunteers, i.e., SPR (sampled participants)/SPR (volunteers) = 1, then there is no bias, or at least the magnitude and direction of any bias is consistent between recruiting methods. Although ideal, this would require the knowledge of the distribution of both SES and SA β-agonist use in both denominator populations. These data are available for the sampled population but not for asthmatics exposed to media advertising. Therefore, although theoretically the best method, this cannot be practically applied in this instance. Direct comparison of the samples would be possible if we assume that the denominator populations had similar SES distributions, but this is not the case.
Alternatively, we tested the potential interaction between the effect of SES and recruiting method on SA β-agonist use. The absence of an interaction, despite differences in the distribution of SES and drug use between recruiting methods, suggests that the relationship between SES and SA β-agonist use was consistent between recruiting methods, that no selection bias existed, and that using camouflaged sampling exclusively could have yielded unbiased results.

The PPV of the factor used to identify subjects from an administrative database is an important consideration. Using IMSHealth Canada data (an independent pharmaceutical research firm) we determined that approximately 85% of prescriptions for SA β-agonists in this age group are prescribed for asthma, resulting in a PPV of 0.85 for SA β-agonist use an indicator of asthma in this age group. A German study determined that inhaled betamimetics were 2.6 (95% CI 1.28 – 5.14) times more likely to be prescribed for asthma than other respiratory diseases.\textsuperscript{18} Asthma experts have suggested that a PPV of 0.85 is an over-estimate which would result in even greater ‘true’ camouflaging of our sample and our estimates of recruitment rates being conservative. Using an identifying factor with a higher PPV would increase the efficiency of camouflage sampling.

The degree to which the target sample should be camouflaged (i.e. the \textit{a priori} established target:camouflage ratio) is based on the judgement of researchers, ethics committees, and data custodians of the risks and benefits of selecting or identifying target and camouflage individuals. For this study the \textit{a priori} target:camouflage ratio was set at 4:1. The methodological requirement of both a target and camouflage subject within each physician’s practice in the pilot phase resulted in a final target:camouflage ratio of 1.8:1.
Combined with a PPV of less than one, this may be too conservative to minimize intrusion and maximize the efficiency of recruitment.

The 14% undeliverable rate in the direct-to-patient mailing was higher than expected and reflects a lack of currency of the Ministry of Health's address information, which is maintained by voluntary reporting of address changes. The estimated response rates of 9% and 5% in the pilot and direct-to-patient mailing phases, respectively, were also lower than is normally considered acceptable, and may be partially attributable to the requirement that participants visit the clinic and provide a blood sample. This may be an acceptable consequence of using a population-based sampling frame given the resulting ability to estimate the response rate, compare respondents to the target sample, and stratify subject selection. Recruitment through physician's offices or specialized practices may minimize undeliverable letters and provide superior response rates but, as discussed, is fraught with the potential for physicians to impart their selection biases, thus negating one of the benefits of using camouflaged sampling.

Sampling yielded more participants than media advertising despite a circulation of more than 200,000 and an estimated 30% market penetration in this age group for 3 of the 4 published advertisements. Although the number of asthmatics who actually read each advertisement and declined to participate cannot be determined, we speculate that the rate of camouflaged sampling recruitment was significantly greater than the volunteer recruitment. This may be attributable in part to the ability to provide targeted subjects with more study details, or attributable to characteristics specific to individuals more likely to read the newspaper.

Until now, privacy and confidentiality concerns have prevented the contacting of patients identified anonymously using administrative health data; however, this recruiting
method was approved by three independent ethics committees and the provincial health privacy branch. Camouflaged sampling is a novel recruiting methodology applicable to studies of program evaluation and epidemiologic research that permits the contacting of a targeted sample of potential participants while protecting the privacy of an individual’s health status until they consent to participate. It minimizes unnecessary public intrusion, facilitates the estimation of response rates and comparisons to the base population, and permits stratified sampling. With further experience, methodologic improvements, and the utilization of truly population-based databases should come broader applicability and enhanced efficiency of camouflaged sampling as the sole method of recruitment.
FIGURE 5.1: DERIVATION OF TARGET SAMPLE AND FINAL MAILING LIST

Total Pharmacare Clients receiving SA β-agonist (1998)  
\[ n = 46,128 \]

Age 19 – 50 years residing in GVRD  
\[ n = 9,566 \]

Target Population  
\[ n = 7,098 \]

Final Target Population  
\[ n = 6,541 \]

Target Sample  
\[ n = 1,733 \]

Final Mailing List  
\[ n = 2,697 \]

- 2,183 not in database in 1999; 57 in LTC facility; 146 received <1 canister SA β-agonist
- 82 without GP or internist
- 557 without corresponding camouflage subject
- 964 camouflage subjects
**FIGURE 5.2: DERIVATION OF RECRUITING RATES FOR PILOT PHASE AND DIRECT-TO-PATIENT MAILING PHASE.**

**PILOT PHASE**

- Letters mailed: 200
- Undeliverable letters: 13
- N = 187
- N = 159
- Estimated Recruiting Rate: 9.4% (15/159)

**DIRECT TO PATIENT PHASE**

- Letters mailed: 2,497
- Undeliverable letters: 344
- N = 2,153
- N = 1,830
- Declined Participation: 28
- Estimated Recruiting Rate: 5.1% (94/1,830)

*PPV = positive predictive value. 0.85 represents the estimated proportion of SA β-agonist users who filled a prescription for a SA β-agonist specifically for asthma.*
TABLE 5.1: COMPARISON OF TARGET POPULATION WITH SAMPLED PARTICIPANTS

<table>
<thead>
<tr>
<th></th>
<th>Target Population</th>
<th>Camouflaged Sample</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 9,311</td>
<td></td>
<td>n=109</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>3,490 (38)</td>
<td>47 (44)*</td>
<td>NS</td>
</tr>
<tr>
<td>Social Assistance</td>
<td>6,069 (65)</td>
<td>49 (45)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>35.4 (9.0)</td>
<td>39.3 (8.3)</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

* One trans-gendered patient
FIGURE 5.3: THE DISTRIBUTION OF SHORT-ACTING β-AGONIST USE IN THE TARGET POPULATION, SAMPLED PARTICIPANTS, AND VOLUNTEERS

Sampled Participants vs Volunteers $\chi^2 p < 0.0001$
**TABLE 5.2: COMPARISON OF SAMPLED PARTICIPANTS TO VOLUNTEERS**

<table>
<thead>
<tr>
<th></th>
<th>Sampled Participants (n=109)</th>
<th>Volunteers (n=93)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (male)</td>
<td>47 (44)</td>
<td>34 (37)</td>
<td>0.3159</td>
</tr>
<tr>
<td>Age&lt;sup&gt;b&lt;/sup&gt;</td>
<td>39.3 ± 8.3</td>
<td>36.9 ± 8.7</td>
<td>0.04</td>
</tr>
<tr>
<td>Married/Partner&lt;sup&gt;a&lt;/sup&gt;</td>
<td>33 (30)</td>
<td>34 (37)</td>
<td>0.344</td>
</tr>
<tr>
<td>Smoker (Yes)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>47 (43)</td>
<td>19 (20)</td>
<td>0.0006</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years post-secondary&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.33 ± 1.8</td>
<td>3.0 ± 2.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diploma&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>18 (17)</td>
<td>11 (12)</td>
<td></td>
</tr>
<tr>
<td>Trades/High School</td>
<td>81 (74)</td>
<td>50 (54)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>University</td>
<td>10 (9)</td>
<td>32 (34)</td>
<td></td>
</tr>
<tr>
<td><strong>Annual Household Income&lt;sup&gt;b,c&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; $20,000 / year</td>
<td>46 (52)</td>
<td>22 (25)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$20 - $50,000 / year</td>
<td>22 (25)</td>
<td>27 (32)</td>
<td></td>
</tr>
<tr>
<td>&gt; $50,000 / year</td>
<td>20 (23)</td>
<td>36 (42)</td>
<td></td>
</tr>
<tr>
<td><strong>Receiving Social Assistance&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td>49 (45)</td>
<td>18 (19)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Asthma-related QOL&lt;sup&gt;a&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global</td>
<td>4.6 ± 1.1</td>
<td>5.1 ± 1.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Symptoms</td>
<td>4.3 ± 1.2</td>
<td>4.8 ± 1.3</td>
<td>0.004</td>
</tr>
<tr>
<td>Emotion</td>
<td>4.5 ± 1.4</td>
<td>4.9 ± 1.4</td>
<td>0.036</td>
</tr>
<tr>
<td>Environment</td>
<td>4.2 ± 1.3</td>
<td>4.8 ± 1.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Activity</td>
<td>5.0 ± 1.2</td>
<td>5.6 ± 1.0</td>
<td>0.0008</td>
</tr>
<tr>
<td><strong>Pulmonary Function&lt;sup&gt;a&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; %predicted</td>
<td>83 ± 22</td>
<td>89 ± 18</td>
<td>0.04</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; %change</td>
<td>11.9 ± 9.9</td>
<td>12.5 ± 13.3</td>
<td>0.7</td>
</tr>
<tr>
<td>FVC % predicted</td>
<td>99 ± 19</td>
<td>105 ± 15</td>
<td>0.03</td>
</tr>
<tr>
<td>FVC %change</td>
<td>5.8 ± 9.7</td>
<td>4.4 ± 8.8</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Drug use&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral steroid in previous year</td>
<td>36 (33)</td>
<td>19 (20)</td>
<td>0.04</td>
</tr>
<tr>
<td>Daily ICS use</td>
<td>61 (56)</td>
<td>44 (47)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

<sup>a</sup>number (%); <sup>b</sup>mean ± SD; <sup>c</sup>N = 173
TABLE 5.3: MULTIVARIATE CATEGORICAL MODELING OF THE INTERACTION BETWEEN THE EFFECT OF SES AND RECRUITING METHOD ON THE AMOUNT OF SA β-AGONIST USED

<table>
<thead>
<tr>
<th></th>
<th>Canisters of SA beta-agonist used in previous year</th>
<th>Chi-squared test of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 - 4</td>
<td>5 - 12</td>
</tr>
<tr>
<td><strong>Annual Income</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Ref = &lt;$20,000)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volunteers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$20,000 - $50,000</td>
<td>1.8 (0.57, 5.6)</td>
<td>1.1 (0.24, 5.3)</td>
</tr>
<tr>
<td>&gt; $50,000</td>
<td>4.3 (1.4, 10.2)</td>
<td>0.88 (0.22, 3.4)</td>
</tr>
<tr>
<td>Sampled Participants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$20,000 - $50,000</td>
<td>2.8 (0.9, 8.7)</td>
<td>0.39 (0.09, 3.5)</td>
</tr>
<tr>
<td>&gt; $50,000</td>
<td>0.72 (0.19, 3.0)</td>
<td>1.6 (0.5, 5.3)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Ref = No Diploma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volunteers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.4 (0.3, 5.9)</td>
<td>1.4 (0.6, 4.6)</td>
<td>0.18 (0.09, 0.90)</td>
</tr>
<tr>
<td>Sampled Participants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0 (0.75, 5.3)</td>
<td>2.2 (0.5, 9.8)</td>
<td>0.58 (0.15, 2.2)</td>
</tr>
<tr>
<td><strong>Social Assistance (SA)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Ref = Receiving SA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volunteers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.8 (0.63, 5.0)†</td>
<td>0.95 (0.24, 3.8)</td>
<td>0.6 (0.15, 1.55)</td>
</tr>
<tr>
<td>Sampled Participants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.3 (0.53, 3.3)†</td>
<td>1.4 (0.49, 1.4)</td>
<td>0.65 (0.12, 1.45)</td>
</tr>
</tbody>
</table>

* OR for being in that SA β-agonist use group, relative to the other two groups.

† N=173

Interpretation: Volunteers not receiving social assistance were 1.8 times more likely than volunteers receiving social assistance to have used ≤4 canisters of SA β-agonist. Sampled participants not receiving social assistance were 1.3 times more likely than sampled participants receiving social assistance to have used ≤4 canisters of SA β-agonist. There were no statistically significant differences in the odds ratios between recruiting methods for being in any SA β-agonist use group.
5.6 REFERENCES


CHAPTER 6

THE RELATIONSHIP BETWEEN SOCIOECONOMIC STATUS AND THE MAGNITUDE OF SHORT-ACTING β-AGONIST USE IN ASTHMA.

6.1 FORWARD

This manuscript is currently under review under the title "The relationship between proximate and contextual measures of socioeconomic status and the magnitude of short-acting β-agonist use in asthma" for publication in the Annals of Internal Medicine. The candidate is first author of this manuscript which is co-authored by Drs. Tony Bai, J. Mark FitzGerald, Andrew Sandford, Peter Paré and Aslam Anis, as well as Erin Kelly. Dr. Bai was involved in the development of the research plan and was included in the grant submitted to the BC Lung Association to fund this study. Dr. FitzGerald participated in developing the patient assessment plan and provided clinic facilities for the patient assessments. Dr. Sandford and Erin Kelly were responsible for the genotyping component of this manuscript. Drs. Anis and Paré are co-supervisors of the candidate.

The candidate’s role in this manuscript involved the development of the primary hypothesis and methodology, all data entry and statistical analysis, and the writing of the final manuscript.

6.2 INTRODUCTION

The association between the excessive use of short-acting (SA) β-agonists and greater asthma-related morbidity and mortality have been identified, raising significant concerns over their safety.¹ ² Specifically, asthmatics using excessive amounts of SA β-
agonist experience more frequent emergency room visits, have a greater likelihood of hospital admission, and are at greater risk of having a fatal or near fatal asthma exacerbation, independent of asthma severity. At least four prospective studies have also shown that the regular use of salbutamol and fenoterol is associated with poorer outcomes when compared to their use on an as needed or rescue basis.

Current asthma management guidelines define asthma control as requiring less than four doses (eight puffs) of SA β-agonist per week. In two previous studies, we identified a surprisingly high prevalence of SA β-agonist use above this threshold with little or no concomitant inhaled corticosteroid (ICS) suggestive of sub-optimal management. We therefore embarked on a study of factors related to the excessive use of SA β-agonists.

Similar to the adverse outcomes reported secondary to the excessive use of SA β-agonists, asthmatics of lower socioeconomic status (SES) also experience more frequent hospital admissions, emergency room visits, and physician visits, as well as greater asthma-related mortality. Although SES and excessive SA β-agonist use have been shown to be independently related to similar measures of asthma-related morbidity and mortality, their inter-relationship has not been investigated.

It has been posited that lower social class asthmatics experience greater morbidity as a result of more severe asthma. Another potential determinant of SA β-agonist use is β-receptor genotype. Specific genotypes are associated with greater β-agonist induced down regulation which could lead to increased tolerance and thus increased use. We hypothesized that the social gradient in asthma-related outcomes may be related to poorer asthma control. The objective of this study was to assess the relationship between SES
and the excessive use of SA β-agonists as a measure of asthma control, adjusting for asthma severity and β-receptor genotype.

6.3 METHODS

6.3.1 Patient Recruitment and Study Sample

This was a cross-sectional study of a sample of English-speaking asthmatics between 19 and 50 years of age residing in the Greater Vancouver Regional District of British Columbia (BC), Canada. 109 subjects were recruited from a random sample of SA β-agonist users identified using the BC Ministry of Health Pharmacare database. Pharmacare is the BC government’s pharmaceutical reimbursement program that provides comprehensive first-dollar coverage for all BC residents on social assistance (Plan C) and the general population under 65 years of age (Plan E) whose annual family pharmaceutical expenditure exceeds $800 per year. Ninety-three subjects were also recruited through media advertising. Each subject was assessed in a pulmonary research clinic by trained assistants, and received $25 to defray travel expenses. The institutional and university ethics review boards approved the study protocol, and informed consent was obtained from each participant.

6.3.2 Drug Utilization

The quantity of inhaled SA β-agonist and ICS used in the previous year was determined by questionnaire. To control for differences in potency, strength and formulation, the amount of each specific SA β-agonist used was standardized to the number of canisters of salbutamol metered dose inhaler (MDI) (100 μg/puff, 200
puffs/canister) and each dosage form of ICS was standardized to the equivalent dose of beclomethasone dipropionate (BDP) by MDI. This dosage standardization methodology has been applied previously.\textsuperscript{15,16}

6.3.3 \textit{Socioeconomic status and }\beta\textit{-receptor genotype determination}

Both individual (proximate) and population (contextual) measures of SES were used. Proximate measures were based on individually reported annual household income, education, and the receipt of social assistance. Annual household income was classified as less than $20,000, $20,000 to $50,000, and more than $50,000. Exploratory analysis accounting for family size based on the low-income cutoff was also performed.\textsuperscript{32} Education was classified based on the total years of post-secondary education, and highest level of education completed, categorized as none, high school diploma or trades certificate, or a university diploma.

Contextual socioeconomic factors were derived from the linkage of the postal code of each subject's current residence with the 1996 BC census data.\textsuperscript{33} Contextual SES characteristics included neighborhood median household income, unemployment rate, and proportion of residents having received a bachelor's degree. Blood was collected from each subject for DNA extraction from leukocytes. Genotyping for \(\beta\)-adrenergic receptor polymorphisms at positions 16 and 27 was done using PCR amplification of the region containing the two polymorphisms followed by restriction endonuclease digestion, as described previously.\textsuperscript{34} The association between genotype and the amount of SA \(\beta\)-agonist use were compared separately for each locus. Homozygotes for glycine at position 16 and for glutamine at position 27 were compared separately to all other individuals.
6.3.4 *Asthma Severity*

In general, 4 dimensions of asthma have been proposed as measures of asthma severity: symptoms, medication use, degree of airflow obstruction, and asthma-related morbidity (e.g. emergency room visit or hospital admission). Although numerous methods incorporating different combinations of these dimensions have been proposed, there is currently no gold standard for measuring asthma severity. Therefore, we used five different methods to facilitate comparison.

The Asthma Related Quality of Life Questionnaire with Standardized activities (AQLQ(S)) was used to measure asthma-specific quality of life (QOL). Specific components of the symptom domain (i.e. frequency of wheeze, cough, shortness of breath, and chest tightness) were extracted as measures of the proposed symptom-related dimensions included in each score. Pulmonary function was measured in accordance with ATS criteria. Forced expiratory volume in one second (FEV₁) and peak expiratory flow rate (PEFR) were expressed as percentages of the value predicted by the patients gender, age and height. Health care utilization was measured by self report.

An algorithm based on the Canadian Asthma Guidelines, encompassing whether or not asthma was controlled, asthma medication use other than SA β-agonists, degree of airflow obstruction, and symptoms, was used to classify severity as mild, moderate or severe. The magnitudes of asthma symptoms were derived from the scores on the symptom and activity domains of the AQLQ.

Three interval score measures of asthma severity, each based on different dimensions of asthma severity, were also used. The Asthma Symptom Sum (ASS) is a summed score of patient-rated severity of wheeze, SOB, cough, and chest tightness,
ranging from zero to 20. The Chronic Lung Disease severity index (CLDSI) is a validated summed score proposed for use in asthma, emphysema, and chronic bronchitis and ranges from 6 (least severe) to 27. It is derived from the frequency of shortness of breath, wheeze, cough and sputum production. Because each component of both the ASS and CLDSI are included in the AQLQ, these scores were derived from the corresponding AQLQ questions resulting in final severity scores ranging from 4 to 28, with higher scores representing less severe disease.

Ng proposed a score (referred to as the “Ng Score”) based on the frequency of daytime symptoms and nocturnal symptoms, and the percent of predicted FEV₁. Daytime symptom frequency and FEV₁ are each scored on a 3 point scale, and nocturnal symptoms on a four point scale resulting in a score ranging from three to ten. Final scores were reverse coded so that higher scores correspond to less severe asthma.

Finally, a specific model incorporating all variables related to each proposed dimension of asthma severity was developed with the amount of SA β-agonist use as the dependent variable. Initially, separate models were developed for the dimensions of symptoms, morbidity, airway obstruction, and asthma medication use (other than SA β-agonists) using forward stepwise multiple polychotomous logistic regression. All significant variables from each dimension model were then incorporated into a final forward stepwise regression model to yield a final model of all severity-related factors which best explained the magnitude of SA β-agonist use.

6.3.5 Statistical Analysis

The relationship between SA β-agonist use and SES, controlling for asthma severity, was evaluated using polychotomous logistic regression. The dependent
variable was the ordinally classified number of standardized canisters of SA β-agonist used in the previous year. Each individual was classified as a low (<4 canisters), intermediate (4-12 canisters) or high (>12 canisters) user. A cumulative logit model was used which assumes that the log cumulative odds are proportional, or that the odds of a response above a given response level are constant, independent of the cutpoint chosen. To ensure the greatest amount of the variance of SA β-agonist use attributable to asthma severity was accounted for, any dimension of severity not included in a specific severity score was added to the model using forward stepwise regression prior to adding the SES variable into the model.

The proportional odds assumption was tested for each model using a Score test. If the hypothesis of proportional odds was rejected (p<0.05), each group comparison (high vs. low/intermediate use and intermediate/high vs. low use) was modeled separately using dichotomous logistic regression.

Model fit was assessed based on the minimization of the -2 Log Likelihood and maximization of the adjusted $R^2$ ($R^2_{adj}$). Entry criteria for forward step-wise variable selection were set at p<0.10. Odds ratios and 95% CIs for having used a greater amount of SA β-agonist (i.e. ≤4 canisters versus >4 canisters, or ≤12 canisters versus >12 canisters) are reported for each association.

6.4 RESULTS

6.4.1 Univariate Analysis

The distribution and univariate analyses of factors postulated a priori to be potentially associated with SA β-agonist use are summarized in Table 6.1. The sample
was comprised of 50% more women than men, and age was normally distributed across the entire range (median 39.0, range 19 – 50 years).

The sample was well distributed across all levels of asthma medication utilization use and SES. 29 either didn’t know or preferred not to provide their annual household income and were therefore excluded from the analysis of income at the proximate level. Although 68/173 (47%) had an annual household income below $20,000, 38 reported incomes over $70,000, 18 of which exceeded $100,000. 120 (59%) completed at least one year of post secondary education (median 2.0) and 42 (21%) received at least a bachelors degree; 31 (15%) completed between 5 and 10 years of post-secondary education. The sample was also very contextually heterogeneous, with participants residing in neighborhoods with unemployment rates varying from 3% to 33% and the prevalence of having received a bachelors degree ranging from 3% to 53% (median=15%). This sample was also representative of all levels of asthma severity (Table 6.2). All three sum scores were normally distributed across the entire range of the score, with the Ng Score encompassing its entire range while the CLDSI and ASS ranged from 5 and 6 to 28, respectively.

There was no significant association between age, gender, or genotype and the amount of SA β-agonist used. Corticosteroid use, all indices and dimensions of asthma severity except having been hospitalized for asthma in the previous year, and all proximate and contextual measures of SES were significantly associated with SA β-agonist use.
6.4.1. **Multivariate analysis**

6.4.1.1 **Proximate SES Factors**

Independent of the method used for controlling for asthma severity, lower SES was associated with utilizing higher doses of SA β-agonists. Patients receiving social assistance were at least 2.5 times more likely to have used greater amounts of SA β-agonist (Figure 6.1). With the exception of the Canadian Guidelines ($R^2_{adj} = 0.22$), asthma severity and receipt of social assistance combined accounted for 33 to 37 percent of the variance of SA β-agonist use. The variance in SA β-agonist use accounted for in the models of income and education was similar to that described by asthma severity and plan (i.e. $R^2_{adj} = 0.24 - 0.36$) with the Canadian Guidelines and the stepwise model explaining the least and most variance, respectively. Adding genotype to each final model did not affect the parameter estimates for any variables and reduced the adjusted $R^2$ of each model and therefore these variables were not included in the final models.

Annual household income and level of education completed were both negatively and significantly associated with the magnitude of SA β-agonist used, with a consistent gradient across social classes. Adjustment for family size based on the low-income cutoff did not affect the results. Although the gradient based on education was consistent and the overall associations significant (p<0.05), the effect of having received only a high school diploma or trades certificate did not differ from unity in any model. However, subjects completing at least a bachelor’s degree were significantly less likely to have used higher doses of a SA β-agonist in the previous year than those not completing any formal education.
The hypothesis of proportional odds was only rejected in the models of years of post-secondary education. This association was therefore modeled separately (Table 6.3). Each additional year of post-secondary education resulted in approximately a 20% reduction in the odds ratio for having used more than 4 canisters of SA β-agonist in the previous year, and approximately a 35% reduction in the odds ratio for having used more than twelve canisters.

The final stepwise model that included both annual household income and years of post-secondary education explained the most variance of SA β-agonist use ($R^2_{adj} = 0.40$). In this model, for each year of post secondary education, the OR for using a greater amount of SA β-agonist was 0.82 (95% CI 0.71, 0.95), and although an annual household income of between $20,000 and $50,000 was not significantly different from an income less than $20,000 (OR 0.54; 95% CI 0.24, 1.2), income over $50,000 remained significant (OR 0.34; 95% CI 0.15, 0.75) and the gradient persisted.

### 6.4.1.2 Contextual SES Factors

The associations between all contextual measures of SES and the magnitude of SA β-agonist use were also significant and consistent in magnitude, independent of method of asthma severity adjustment. For every $1,000 increase in median neighborhood household income there was approximately a 10% decrease in the odds of using greater amounts of SA β-agonist (OR 0.91; 95% CI 0.84, 0.98), and nearly a 5% decrease with every 1% greater prevalence of having completed a university degree (OR 0.96; 95% CI 0.93, 0.99). The association between SA β-agonist use and neighborhood unemployment rate was consistent (OR 1.1; 95% CI 1.03, 1.2).
6.5 DISCUSSION

We identified a strong and significant association between lower SES and the use of excessive amounts of SA β-agonist medications by asthmatics, independent of asthma severity. This association was consistent across all proximate and contextual measures of SES, with gradients in the appropriate direction for interval measures. It has been postulated that poorer outcomes in poorer asthmatics are attributable to greater asthma severity which could explain the higher utilization of rescue medication. Three studies that have reported a higher prevalence of more severe asthma in children measured asthma severity based on symptoms alone and may therefore be demonstrating poorer control rather than greater severity.\textsuperscript{45-47}

The two studies that have attributed poorer outcomes in poorer asthmatics specifically to greater severity suffer from significant limitations.\textsuperscript{23,27} Using survey data, Littlejohns and McDonald found that adults in the lower two quintiles of SES based on the Registrar General’s classification of occupation were twice as likely to have ‘disabling asthma’ as those in the upper 40%.\textsuperscript{27} Disabling asthma was defined as “severe or frequent bouts of breathlessness, wheezing, or coughing which limit daily activities” which could also represent a lack of asthma control. Similarly, a Canadian study based on administrative health care data found that low income adults were admitted to hospital more frequently, had more physician contacts, and were less likely to be assessed by a specialist.\textsuperscript{23} There was no evidence of more fragmented care or higher prevalence of asthma in the lower classes so by deduction, without any metric of asthma severity, the authors concluded that lower income asthmatics must have had more severe disease. By directly assessing patients, we were able to overcome these limitations, and the negligible
differences in the crude and adjusted ORs for SES suggests that confounding by disease severity may be less than expected.

Only one previous study in adults has demonstrated an association between lower SES and poorer asthma control. Connolly et al. reported poorer asthma control based on a greater reversibility of airway disease in men in lower social classes. The only studies to assess differential pharmacologic management are two US studies done in children and adolescents, both of which concluded that asthma management may be inadequate in lower social classes. The likelihood that different factors impact asthma control in children and adults prevents the direct extrapolation of these results to adult asthmatics. Furthermore, class differences in access to health care between the US and Canada may mean a lesser likelihood of a social gradient in a Canadian population if access to health care is an important etiologic factor. The persistence of this gradient in participants receiving social assistance relative to those that do not suggests that barriers to health care are not the primary etiologic factor in poorer management, given that they receive all their asthma medications and health care services at no cost.

Previous studies have shown that specific mutations at amino acid positions 16 and 27 render these individuals prone to β-adrenergic receptor down-regulation with persistent use of SA β-agonists. Because this would render individuals with these genotypes less responsive to the bronchodilatory effects of SA β-agonists, we hypothesized that asthmatics homozygous for glycine at position 16 or glutamine at position 27 would be more likely to use greater amounts of SA β-agonists. However, there was no association between excessive use of SA β-agonist use and genotype at
either locus suggesting that social or environmental rather than genetic factors play a
more predominant role in determining the magnitude of SA β-agonist used.

By design, this sample was very heterogeneous in terms of asthma severity, SES, and drug utilization. Although the distributions of these variables are not representative of the population distributions, this methodology facilitated the recruitment of a smaller sample size to test this hypothesis. This does raise concerns of a potential volunteer bias, if uncontrolled asthmatics from either extreme of SES were more likely to participate. Evidence of differential health beliefs, health management strategies and perceptions of ability to control one’s disease suggest that uncontrolled asthmatics of higher SES would be more likely to participate in an attempt to increase their knowledge and achieve better control. This would result in conservative estimates of all ORs. The potential for the misclassification of SES to bias the results must also be considered. This most commonly manifests as upward misclassification of lower social classes, which would also result in conservatively biased estimates of the magnitude of the associations.

These results are dependent upon the accurate measure and adjustment of asthma severity. More than 25 years ago the World Health Organization recommended that a standard measure of asthma severity be adopted; however, a task force that reviewed the major severity classification schemes concluded that patients vary too much across dimensions to create a single severity measure, and therefore there is currently no gold standard for measuring asthma severity.\textsuperscript{36,51} For this reason, we applied five different methods of controlling for asthma severity. Not only were the results consistent across all measures of asthma severity, but the construct validity of each score was demonstrated by a positive association between each metric of asthma severity and the amount of SA β-agonist used.
Although each asthma severity measurement tool was not administered exactly as designed, we incorporated each component of each scale into a similarly summed severity score, measured over a similar time frame. Furthermore, because the measurement of asthma severity cannot be based solely on symptoms, each model included additional measures of any additional proposed dimension of asthma severity not incorporated into the score. This maximized the variance of SA β-agonist explained by all dimensions of severity prior to adding SES to the model. The consistency of this approach with the theoretical framework of quantifying asthma severity, of the results across all methods of severity adjustment, and of the relationship between each severity measure and the magnitude of SA β-agonist use, supports this methodology.

Identifying and understanding specific factors related to excessive SA β-agonist use and poor asthma control is a fundamental step in the continuum of research aimed at reducing asthma-related morbidity. We previously showed that SA β-agonist users receiving social assistance were more likely to increase their use over three years without adjusting for asthma severity. This study provides further evidence that lower SES asthmatics use greater amounts of SA β-agonist, and that this association cannot be attributed solely to disease severity as postulated previously, or to socioeconomic barriers to health care access.

An assumption of this analysis is that the excessive use of SA β-agonists is synonymous with asthma control, an assumption that is supported by the metrics of control included in the current asthma management guidelines, and by the components of the Asthma Control Questionnaire. These results support our hypothesis that the social gradient in asthma outcomes may be at least partially attributable to poorer control,
which consequentially leads to the hypothesis that improving asthma management in lower social classes may result in a narrowing of the gap in asthma-related outcomes. The determination of the SES-related etiologic factors of inadequate asthma management, such as health beliefs, health behaviors, self-esteem, motivation, knowledge, economic barriers, and medical system management will be the next step in developing programs and strategies to reduce the social gradient in asthma-related outcomes.
TABLE 6.1: UNIVARIATE ANALYSIS OF THE ASSOCIATION BETWEEN DEMOGRAPHIC AND SES FACTORS AND THE MAGNITUDE OF SA β-AGONIST USED IN THE PREVIOUS YEAR (n=202)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mean ± SD or Frequency (%)</th>
<th>OR (95% CI)</th>
<th>Adjusted R²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>38.2 (8.5)</td>
<td>1.02 (0.99,1.06)</td>
<td>0.02</td>
</tr>
<tr>
<td>Gender - Male</td>
<td>81 (40)*</td>
<td>1.3 (0.8, 2.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Drug Utilization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily Inhaled Corticosteroid Use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled Steroid Use in Previous Yr.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>34 (17)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≤4 canisters</td>
<td>94 (47)</td>
<td>0.87 (0.4, 1.8)</td>
<td>0.17</td>
</tr>
<tr>
<td>5 - 12 canisters</td>
<td>58 (29)</td>
<td>3.2 (1.5, 7.3)</td>
<td></td>
</tr>
<tr>
<td>&gt;12 canisters</td>
<td>16 (8)</td>
<td>11.5 (3.4, 39.8)</td>
<td></td>
</tr>
<tr>
<td>Oral Steroid in last year</td>
<td>55 (27)</td>
<td>2.4 (1.3, 4.2)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Proximate SES Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest Education Attained</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Diploma</td>
<td>29 (14)</td>
<td>1.0</td>
<td>0.08</td>
</tr>
<tr>
<td>High School/Trade Diploma</td>
<td>131 (65)</td>
<td>0.78 (0.37, 1.6)</td>
<td></td>
</tr>
<tr>
<td>University Diploma</td>
<td>42 (21)</td>
<td>0.24 (0.1, 0.59)</td>
<td></td>
</tr>
<tr>
<td>Years Post Secondary Education</td>
<td>2.1 (2.3)</td>
<td>0.76 (0.66, 0.86)</td>
<td>0.11</td>
</tr>
<tr>
<td>Receiving Social Assistance</td>
<td>67 (33)</td>
<td>2.8 (1.6, 4.8)</td>
<td>0.07</td>
</tr>
<tr>
<td>Annual Household Income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$20,000</td>
<td>68 (39)</td>
<td>1.0</td>
<td>0.11</td>
</tr>
<tr>
<td>$20,000 - $50,000</td>
<td>49 (28)</td>
<td>0.34 (0.17, 0.68)</td>
<td></td>
</tr>
<tr>
<td>&gt;$50,000</td>
<td>56 (32)</td>
<td>0.27 (0.14, 0.53)</td>
<td></td>
</tr>
<tr>
<td><strong>Contextual SES Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Neighborhood Income</td>
<td>$19,959 (444)</td>
<td>0.92 (0.86, 0.97)†</td>
<td>0.05</td>
</tr>
<tr>
<td>Unemployment (%)</td>
<td>10.0 (4.7)</td>
<td>1.1 (1.04, 1.2)</td>
<td>0.07</td>
</tr>
<tr>
<td>Bachelor’s Education (%)</td>
<td>18.4 (11.0)</td>
<td>0.95 (0.92, 0.98)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Genotype†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLY/GLY at position 16</td>
<td>35 (21)</td>
<td>1.2 (0.58, 2.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>GLU/GLU at position 27</td>
<td>60 (37)</td>
<td>1.03 (0.57, 1.8)</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*One transgendered
†OR for $1,000 increase
‡N=164

142
TABLE 6.2: UNIVARIATE ANALYSIS OF THE ASSOCIATIONS BETWEEN ASTHMA SEVERITY SCORES AND DIMENSIONS AND MAGNITUDE OF SA β-AGONIST USE.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mean ±SD or Frequency (%)</th>
<th>OR (95% CI)</th>
<th>Adjusted R²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severity Score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cdn. Asthma Guidelines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>42 (21)</td>
<td>Ref</td>
<td>0.13</td>
</tr>
<tr>
<td>Moderate</td>
<td>55 (27)</td>
<td>3.0 (1.3, 6.9)</td>
<td>0.13</td>
</tr>
<tr>
<td>Severe</td>
<td>105 (51)</td>
<td>6.0 (2.8, 12.9)</td>
<td>0.12</td>
</tr>
<tr>
<td>CLDSI (range 4-28)</td>
<td>16.5 (4.9)</td>
<td>0.88 (0.82, 0.92)</td>
<td>0.12</td>
</tr>
<tr>
<td>ASS (range 4-28)</td>
<td>17.6 (5.0)</td>
<td>0.87 (0.83, 0.92)</td>
<td>0.12</td>
</tr>
<tr>
<td>Ng Score (range 3-10)</td>
<td>7.0 (2.0)</td>
<td>0.72 (0.62, 0.83)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Severity-related Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency Room Visit</td>
<td>34 (17)</td>
<td>3.2 (1.6, 6.4)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>8 (4)</td>
<td>1.5 (0.4, 5.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FEV₁ % predicted</td>
<td>85 (20)</td>
<td>0.98 (0.97, 0.99)*</td>
<td>0.04</td>
</tr>
<tr>
<td>PEFR % predicted</td>
<td>102 (26)</td>
<td>0.98 (0.97, 0.99)*</td>
<td>0.03</td>
</tr>
</tbody>
</table>

* OR for a 1% increase
FIGURE 6.1: ASSOCIATION BETWEEN RECEIPT OF SOCIAL ASSISTANCE AND THE MAGNITUDE OF SA β-AGONIST, ADJUSTED FOR ASTHMA SEVERITY.

<table>
<thead>
<tr>
<th>Severity Index</th>
<th>Odd Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma Guidelines*</td>
<td></td>
</tr>
<tr>
<td>ASS†</td>
<td></td>
</tr>
<tr>
<td>CLDST†</td>
<td></td>
</tr>
<tr>
<td>Ng Score‡</td>
<td></td>
</tr>
<tr>
<td>Stepwise Model‡</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for: ER visit in previous year.
†Adjusted for: ER visit in previous year, daily ICS use (Y/N), daily ICS dose.
‡Model includes: ER visit in previous year, daily ICS use, frequency of daytime symptoms, and AQLQ symptom score.
FIGURE 6.2: ASSOCIATION BETWEEN ANNUAL HOUSEHOLD INCOME AND EDUCATION AND THE MAGNITUDE OF SA β-AGONIST USE IN THE PREVIOUS YEAR, ADJUSTED FOR ASTHMA SEVERITY.

Severity Index
- Asthma Guidelines
- ASS
- CLDS
- Ng Score
- Stepwise Model

Annual Household Income*

Education Completed†

Odds Ratio (95% CI)

* Reference category: < $20,000
† Reference category: None
‡ Adjusted for: ER visit in previous year (Y/N).
§ Adjusted for: ER visit in previous year (Y/N), daily ICS use (Y/N), and daily ICS dose.
‖ Model includes: ER visit in previous year (Y/N), daily ICS use (Y/N), frequency of daytime symptoms, and AQLQ symptom score.
### TABLE 6.3: ASSOCIATION BETWEEN THE NUMBER OF YEARS OF POST-SECONDARY EDUCATION AND THE MAGNITUDE OF SA β-AGONIST USE IN THE PREVIOUS YEAR, ADJUSTED FOR ASTHMA SEVERITY

<table>
<thead>
<tr>
<th>Severity Adjustment</th>
<th>High/Intermediate vs. Low Use OR (95% CI)</th>
<th>High vs. Intermediate/ Low Use OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian Guidelines</td>
<td>0.83 (0.72, 0.95)</td>
<td>0.66 (0.52, 0.83)</td>
</tr>
<tr>
<td>ASS†</td>
<td>0.80 (0.69, 0.93)</td>
<td>0.67 (0.53, 0.86)</td>
</tr>
<tr>
<td>CLDSI†</td>
<td>0.81 (0.70, 0.94)</td>
<td>0.67 (0.53, 0.86)</td>
</tr>
<tr>
<td>Ng Score†</td>
<td>0.78 (0.68, 0.91)</td>
<td>0.62 (0.48, 0.80)</td>
</tr>
<tr>
<td>Stepwise Model‡</td>
<td>0.82 (0.70, 0.94)</td>
<td>0.65 (0.50, 0.84)</td>
</tr>
</tbody>
</table>

*Adjusted for: ER visit in previous year (Y/N).

†Adjusted for: ER visit in previous year (Y/N), daily ICS use (Y/N), daily ICS dose.

‡Model includes: ER visit in previous year (Y/N), daily ICS use (Y/N), frequency of daytime symptoms, and AQLQ(S) symptom score.
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50. Togias A, Horowitz E, Joyner D, Guydon L, Malveaux F. Evaluating the factors that relate to asthma severity in adolescents. Int Arch Allergy Immunol 1997;113(1-3):87-95.


CHAPTER 7

THE RELATIONSHIP BETWEEN PROXIMATE AND CONTEXTUAL MEASURES OF SOCIOECONOMIC STATUS AND ASTHMA CONTROL.

7.1 FORWARD

This manuscript is currently under review under the title “The association between socioeconomic status and asthma control: are poor people treated more poorly?” in the Journal of Respiratory and Critical Care Medicine. The candidate is the first author of the manuscript with co-authored by Daphne Guh who provided statistical support, and Drs. Tony Bai and Mark FitzGerald, respiratory clinicians involved in the conceptualization of the study, the submission of the BC Lung Association grant, and the assessment of the patients. Drs. Aslam Anis and Peter Paré, co-supervisors of the candidate, were also co-authors on the manuscript.

The candidate’s role in the manuscript involved the development of the primary hypothesis and methodology, all data entry and statistical analysis, and the writing of the final manuscript.

7.2 INTRODUCTION

The total direct and indirect costs of asthma in Canada in 1990 were estimated to be between $504 million to $604 million.\(^1\) Among these, direct costs accounted for than 61% of total costs, the majority of which were attributable to drugs ($124M) followed by inpatient care, physician visits, and emergency room visits. Because significantly more expensive drugs have been introduced since 1990, current drug costs are considerably higher. Effective drug therapy is a necessary component of asthma control in a majority
of asthmatics. Much of the inpatient and emergency room asthma care may be the consequence of either the severity of asthma or poor asthma control.

Although asthma is a chronic disease associated with considerable morbidity and mortality, management in accordance with treatment guidelines should result in essentially complete asthma control in the majority of patients. Morbidity despite maximal therapy should occur in only the most severe, treatment resistant asthmatics, which account for only a very small proportion of all asthmatics. Poor asthma control in the majority of asthmatics is therefore likely related to inadequate drug therapy rather than severe disease.

Specific factors associated with greater asthma-related morbidity have been identified, one of which is socioeconomic status (SES). More frequent hospital admission and emergency room visits in lower SES asthmatics suggest that the less affluent experience greater asthma-related morbidity. This is not unexpected, and is consistent with the evidence of a general social gradient in health. In asthma, this social class gradient in outcomes and health care utilization has been attributed to more severe disease, without consideration of the complex inter-relationship between asthma severity and asthma control.

Attributing this class difference solely to asthma severity without considering a lack of control as an etiologic factor leads to acceptance of this gradient as unmodifiable, and perpetuation of the antiquated concept that symptoms, physiologic abnormalities, and frequent short-acting (SA) β-agonist use are to be expected rather than controlled.

It was is our hypothesis that the SES gradient in asthma-related outcomes could be attributed as much to poorer asthma control as greater asthma severity. Therefore, the
objective of this analysis was to evaluate the relationship between SES and asthma control.

7.3 METHODS

7.3.1 Study Sample

Two hundred and two English speaking adults between 19 and 50 years of age diagnosed with asthma by a physician and who resided in the Greater Vancouver Regional District (GVRD) were recruited into this cross sectional study. One hundred and nine subjects were recruited from a stratified random sample of SA β-agonist users identified using the BC Ministry of Health Pharmacare database, and 93 through media advertising. Pharmacare is the BC government’s pharmaceutical reimbursement program that provides comprehensive first-dollar coverage for all BC residents on social assistance (Plan C) and the general population (Plan E) whose annual family pharmaceutical expenditure exceeds $800 per year. Each subject providing consent was assessed at our research clinic at either St. Paul’s Hospital or Vancouver General Hospital, and received $25 to defray travel expenses.

The institutional and university ethics review boards approved the study protocol, and informed consent was obtained from each participant.

7.3.2 Measurement of Asthma Control

Asthma control was quantified in the entire sample using a control score derived from the Asthma Quality of Life Questionnaire with Standardized activities (AQLQ(S)), and also using the Asthma Control Question (ACQ) in a subset of participants. The ACQ is comprised of seven questions, five relating to asthma symptoms, and one each to the
magnitude of SA β-agonist use and forced expiratory volume in one second (FEV\textsubscript{1}), and has been shown to be valid and reliable, and possess both strong evaluative and discriminative properties.\textsuperscript{12} FEV\textsubscript{1} was measured by trained pulmonary research personnel in accordance with American Thoracic Society criteria and expressed as a percent of predicted FEV\textsubscript{1} based on the patient's age, height, and gender.\textsuperscript{13,14} Each question is scored on a seven point Likert scale ranging from zero to six, representing the best and worst possible asthma control, respectively. The mean score of the seven questions provides a quantitative measure of overall asthma control.

7.3.2.1 Derivation of Asthma Control Score from the AQLQ(S)

The AQLQ(S) consists of 32 questions, of which five of twelve symptom-related questions pertain to the same symptoms included in the ACQ. Each question is also measured on a seven point Likert scale ranging from one (maximal impairment) to seven (no impairment).

The five symptom-related questions of the ACQ are similar to, or verbatim of, five questions included in the AQLQ(S) and both questionnaires employ identically ranged scales (Table 7.1). We therefore hypothesized that, in conjunction with FEV\textsubscript{1} and SA β-agonist use, an asthma control score could be derived from the specific questions of the AQLQ(S) that pertain to the same symptoms deemed most predictive of asthma control by 100 asthma specialists and therefore included in the ACQ.\textsuperscript{12}

Responses to the AQLQ(S) questions were reverse coded and re-scaled to coincide with ACQ responses. Two asthma control scores were calculated for 56 (28%) participants who completed both the ACQ and AQLQ(S): one directly from the ACQ, and the second from the five selected AQLQ(S) questions, the frequency of SA β-agonist...
use and FEV₁. The two scores were compared within this subset to determine the validity of extracting a control score from the AQLQ(S) questions for the entire sample. Mean scores were compared using a paired Student’s test. Agreement and correlation between matched questions and final control scores were evaluated using a quadratically weighted kappa (κ) and Pearson’s product moment correlation coefficient (r), respectively. Patterns in the disagreement between matched questions and final scores were assessed by plotting the mean score against the difference for each individual.

7.3.3 Socioeconomic status

The association between SES and asthma control was tested at both the individual and population level of SES. Individual measures of SES were based on self reported annual household income, education, and the receipt of social assistance (Appendix II). Annual household income was classified as less than $20,000, between $20,000 and $50,000, and greater than $50,000. Analysis accounting for family size based on the low-income cutoff (LICO) was also performed. Education was classified based on the years of post-secondary education and highest level of education completed, ordinally categorized as less than high school, high school or trade, or at least a university bachelor’s degree.

Using a Postal Code Conversion file, we determined the census tract where each participant’s current residence was located. From this we determined the neighborhood characteristics related to SES for each participant’s current residence that could be derived from BC Census data. Census tract level variables deemed representative of SES included median neighborhood income, proportion of the population over 20 years of age completing at least a bachelor’s education, and unemployment rate.
7.3.4 Statistical Analysis

The dependent variable for all analyses was the AQLQ(S)-derived asthma control score. Univariate associations between control and all demographic, SES, and potential confounders were assessed using simple linear regression. Multiple linear regression using forward-stepwise variable selection was used to assess the relationship between SES and asthma control, adjusted for all potential confounders (p=0.10). Each SES variable was modeled separately. To control for differences in potency, strength and formulation, the amount of each specific ICS was standardized to the equivalent dose of beclomethasone dipropionate (BDP) by MDI, and the average daily utilization in the previous two weeks classified as low (<400 μg), intermediate (400 – 800 μg) or high (>800 μg). This dosage standardization methodology has been applied in two previous studies.17,18

Because we posited a priori that any social gradient in asthma control could be related to inadequate management, a secondary analysis of the associations between SES and both corticosteroid (inhaled and oral) and other add-on medication use was undertaken. Statistical comparisons were made using either a Student’s t-test or χ² test, where appropriate. All two-way interactions between SES and asthma medication use were also tested in the multiple regression models.

To evaluate the potential differential effect of social status within neighborhood, we tested the interaction between education and median neighborhood income. The impact of status inconsistency (i.e. the upward mobility of the lesser educated, or visa versa) on asthma control was also evaluated by comparing the mean control scores of participants in the upper quartile of education living in a neighborhood in the lowest
quartile of income to those in the lowest 25% for education but residing in a neighborhood in the upper median income quartile.

Regression coefficients (β) and standard errors (SE) are reported for each association. Model fit was assessed using $R^2$; standardized residuals were plotted against predicted asthma control score to assess each model for homoscedasticity.

7.5 RESULTS

56 subjects completed both the ACQ and AQLQ(S). Both scores were normally distributed and the sample was representative of all but the most poorly controlled. ACQ scores ranged from zero to 4.7, and AQLQ(S) scores from 0.3 to 5.1. Mean ACQ and AQLQ(S)-derived scores were $1.7 \pm 0.97$ and $2.1 \pm 1.10$ (p<0.05), respectively.

The agreement between ACQ and AQLQ(S) questions ranged from $\kappa=0.43$ to $\kappa=0.64$, and the correlation ranged from $r=0.74$ to $r=0.85$ (p<0.001) (Table 7.2). Good agreement ($\kappa=0.64$) and almost perfect correlation ($r=0.90$) occurred between the overall control scores (Figure 7.1). Mean versus difference plots for overall scores and matched questions revealed that discordant scores most often resulted from lower ACQ scores relative to the corresponding AQLQ(S)-derived scores across the entire range of the score.

An asthma control score was derived from the AQLQ(S) questions for 194/202 study participants; eight subjects were excluded due to missing pulmonary function data. The average age of the sample was $38.0 \pm 8.5$, and there were significantly more women (60%); there was no gender difference in age (p=0.43) (Table 7.3). The mean number of years since being diagnosed with asthma was $18.6 \pm 12.7$. 

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The sample was well distributed across all levels of SES and asthma medication utilization (Table 7.3). 28/194 participants did not report their annual household income and were therefore excluded from the income analysis at the individual level. Although 68 (39%) had an annual household income below $20,000, 37 reported incomes over $70,000, 18 of which exceeded $100,000. 114 (59%) completed at least one year of post secondary education (median 1.0) and 39 (20%) received at least a bachelors degree; 30 (15%) completed at least five years of post-secondary education. The sample was also very contextually heterogeneous, with participants residing in neighborhoods with unemployment rates varying from 3% to 33% (median = 9%) and the prevalence of having received a bachelors degree ranging from 3% to 53% (median=15%).

Unadjusted associations between demographic, SES and potentially confounding variables with asthma control are presented in Table 7.3. Although the relationship between age and control was not statistically significant (p=0.057) there was a trend for older asthmatics to have poorer control. On average, men were more poorly controlled than women (β=0.57 ± 0.16; p=0.005). Having visited an emergency department (p=0.015), use of an oral corticosteroid (p=0.0001), daily ICS use (p=0.03) and daily ICS dose (p=0.039) were all associated with less than optimal control, with a consistent gradient between ICS dose and asthma control.

A significant relationship between all proximate and contextual SES variables was also identified. Lower SES was consistently associated with poorer asthma control and a gradient in the expected direction occurred across proximate measures of both education and income. In the multivariate analysis, only gender and daily ICS use met the threshold (p≤0.10) for significant covariates.
In general, independent of how SES was measured, there was a consistent negative association between SES and asthma control score. On average, control scores of participants not receiving social assistance were 0.55 lower than those receiving social assistance, and 0.90 lower for those having completed at least a bachelor's education relative to those not completing any formal education (Table 7.4). Mean scores were also 0.11 lower for each year of post-secondary education with a consistent gradient in the appropriate direction across both income and education.

Contextually, on average, control scores were lower in individuals residing in more affluent neighborhoods (Table 7.4). Asthma control scores were negatively associated with median household income and the proportion of the neighborhood with a bachelor's education, and positively with neighborhood unemployment rate.

The prevalence of status inconsistency was approximately 10% in this sample. Although not significant, the thirteen subjects in the lowest quartile of education residing in a neighborhood in the upper quartile of median neighborhood household income were more poorly controlled than the seven in the upper quartile of education who lived in a neighborhood in the lowest quartile of income (2.5 ± 1.3 versus 2.0 ± 1.1, respectively; p=0.38). In the multiple regression model, although both years of post-secondary education and median neighborhood household income were significant, there was no significant interaction.

7.6 DISCUSSION

This study demonstrates a consistent and significant gradient between SES and asthma control in a sample of the population with universal health care and first-dollar medication coverage for residents receiving social assistance. In this sample, lower SES
asthmatics had more poorly controlled disease, independent of how SES was measured, either proximately or contextually. Furthermore, there was no SES difference in the magnitude of corticosteroid or other asthma medication use, suggesting that this difference is not attributable to a higher prevalence of more severe, treatment resistant disease in lower SES asthmatics.

In a previous study, we identified the association between inappropriate asthma management and a greater likelihood and greater frequency of hospital admission and emergent hospital admission, and more frequent physician visits.\(^1^7\) Two other Canadian studies found that asthmatics requiring treatment in emergency departments tended to be poorer and have less education and more social problems than those managed as outpatients; however, this could not be attributed to poorer care.\(^7,^9\) Additional studies have also demonstrated similar social class gradients in asthma-related mortality as well as health care utilization.\(^2,^6,^8,^19-^21\)

Prior to this study, social class differences in outcomes have been attributed to both a higher prevalence and more severe asthma in lower social class individuals.\(^9,^10\) Littlejohns and MacDonald concluded that, because lower SES adults in their study were more likely to have disabling asthma, defined as "severe or frequent bouts of breathlessness, wheezing, or coughing which limit daily activities", they had more severe disease.\(^10\) In a Canadian study, Erzen et al. found that low income adults were admitted to hospital more frequently, had more physician contacts, and were less likely to be assessed by a specialist than higher income adults.\(^9\) They could not attribute differences in outcomes to more fragmented care or a higher prevalence of asthma, and therefore attributed this to more severe asthma. In both studies, the outcomes evaluated could have been the result of inadequate control. This study is predicated on the assumption that
asthma severity and asthma control are different and can be quantified separately. To our knowledge, this study provides the first evidence that, even without any apparent barriers to health care, asthma control may be primary etiologic factor in the gradient in health outcomes.

We were able to identify a relationship between lower SES and poorer asthma control in 194 asthmatics, heterogeneous for SES, asthma control, asthma severity, and drug utilization. Although we performed numerous analyses thereby increasing the probability of a type I error, the results of all analyses were consistent and robust to the measurement of SES at both the individual and population levels, and showed consistent gradients in the expected direction. The strongest association identified was between education and control. Asthma control scores of participants completing at least a bachelor’s degree were almost one unit lower than those who did not complete any formal education (β=0.90 ± 0.23), and were 0.11 ± 0.03 lower for every year of post secondary education completed.

These results are consistent with two previous US studies. In a small study conducted in pediatrics, Beausoleil et al. found that males, minorities, and those of lower SES were more likely to use excessive amounts of SA β-agonist. The only adult study (n=630) designed specifically to evaluate the class – control relationship demonstrated that lower social class asthmatics had more reversible of airway disease, suggestive of a lack of control. Drug therapy was not assessed and how social class was defined is unclear.

Although asthma is a chronic, incurable disease, recent advances in pharmacotherapeutic management, if used appropriately, makes nearly complete control of symptoms possible in the majority of patients. As such, with ideal management only
those rare patients with the most severe asthma resistant to treatment should experience asthma-related morbidity, and neither a higher prevalence nor greater severity should result in significantly greater morbidity in lower social classes unless there is a concomitant lack of control. Based on a previous US study that found that adolescents in the lowest quartile of family income were less likely to be prescribed an ICS or a SA β-agonist, we expected that any social gradient in asthma control may be related to an underutilization of ICS by lower SES participants. If the hypothesis of a social gradient in asthma severity were correct and asthma management was optimal, we should have found greater ICS use in lower social classes, however there was no difference in ICS use between classes. Although this doesn’t preclude the possibility of a social gradient in asthma severity, it does suggest that the gradient may be amenable to improved management.

Based on previous studies and clinical experience, we also expected that participants using greater amounts of ICS would experience better asthma control. To the contrary, higher ICS doses were associated with worse control suggesting that ICS use may be a surrogate measure of asthma severity or treatment compliance. We therefore elected to include ICS use in the multivariate models. A significant SES – control relationship not only persisted in the multivariate models, but all regression coefficients for all SES variables remained essentially unchanged suggesting that the association between SES and asthma control is not confounded by either severity or gender. The lack of a significant interaction provides further evidence of a consistent effect of ICS use on control across all levels of SES.

The social status gradient in asthma control identified in the US studies may be related to barriers to health care access and drug coverage. BC residents receiving social...
assistance receive full coverage of all first-line asthma medications. If an economic barrier to asthma management was the primary etiologic factor of poor control in lower social classes, we would not have found an association between receipt of social assistance and asthma control, or a consistent gradient across income. However, participants receiving social assistance were more poorly controlled ($\beta=0.55 \pm 0.16$) despite complete coverage of drug therapy. The persistence of the gradient in a Canadian population with universal health care suggests that access is not the primary etiology, however other etiologic factors remain to be elucidated.

Education provides a static measure of social status and the number of years of post-secondary education can be measured most precisely. We therefore chose to evaluate status inconsistency based on this measure of proximate SES. Although the differences were not significant and no effect modification was identified, the better educated residing in poorer neighborhoods were more well controlled that those with less education living in more affluent neighborhoods. The lack of a significant difference may be due to a lack of power to detect a difference. This is not to say that education is the most important factor in asthma control, but is consistent with the status inconsistency theory of upward movement resulting in poorer outcomes than downward movement.

The primary limitation of this study was our inability to evaluate the entire sample with the ACQ. The ACQ and AQLQ(S) were both developed by Juniper et al. and are similar in theory and content. The five symptoms incorporated into the ACQ control score were selected based on expert opinion of 100 asthma clinicians. We therefore derived a control score from AQLQ(S) questions pertaining to the same symptoms and quantified on a scale of exactly the same range as the ACQ questions. Although the agreement between ACQ and AQLQ(S) control scores was lower than expected
(κ=0.64), discordance was consistently the result of lower scores on the ACQ questions. More importantly, the correlation between the two final scores was excellent (r=0.90). Although the difference in mean scores and only moderate agreement limits the external comparability of our control scores with other ACQ control scores in other studies, the excellent correlation reflects the internal validity of the AQLQ(S)-derived control score for relative comparison of subjects enrolled in this study.

As asthma 'severity' can be considered relatively unmodifiable, the complacent attribution of the social gradient in outcomes to asthma severity without good evidence precludes the need for corrective action. This study provides the best evidence thus far of a SES gradient in asthma control which cannot be attributed to more severe, treatment-resistant disease.

These data suggest that the social gradient in asthma-related morbidity and mortality may be at least partially attributable to worse control. The identification of the etiologic factors and subsequent investment in improving asthma control in the lower social classes rather than conceding to severity as the causative factor may lead to narrowing the social gradient in outcomes.
<table>
<thead>
<tr>
<th>ACQ Question</th>
<th>AQLQ(S) Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. On average, during the past week, how often were you <strong>woken by your asthma</strong> during the night?</td>
<td>24. In general, <strong>how much of the time</strong> during the last two weeks were you WOKEN at night by your asthma?</td>
</tr>
<tr>
<td>2. On average, during the past two weeks, <strong>how bad were your asthma symptoms</strong> when you woke up in the morning?</td>
<td>20. In general, <strong>how much of the time</strong> during the last two weeks did you wake up in the morning with asthma symptoms?</td>
</tr>
<tr>
<td>3. In general, during the past week, <strong>how limited were you in your activities</strong> because of your asthma?</td>
<td>32. Overall, among <strong>ALL THE ACTIVITIES</strong> that you have done during the last two weeks, how limited have been by your asthma?</td>
</tr>
<tr>
<td>4. In general, during the past week, <strong>how much shortness of breath did you experience because of your asthma?</strong></td>
<td>8. In general, <strong>how much of the time</strong> during the last two weeks did you feel short of breath as a results of your asthma?</td>
</tr>
<tr>
<td>5. In general, during the past week, <strong>how much of the time did you wheeze?</strong></td>
<td>10. In general, <strong>how much of the time</strong> during the last 2 weeks did you experience a WHEEZE in your chest?</td>
</tr>
</tbody>
</table>
TABLE 7.2: AGREEMENT AND CORRELATION BETWEEN ACQ AND AQLQ(S) QUESTIONS AND TOTAL ASTHMA CONTROL SCORES

<table>
<thead>
<tr>
<th>ACQ Question</th>
<th>AQLQ(S) Question</th>
<th>weighted kappa</th>
<th>Pearson’s correlation (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>0.59</td>
<td>0.85</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>0.43</td>
<td>0.81</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>0.66</td>
<td>0.79</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>0.48</td>
<td>0.74</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>0.51</td>
<td>0.78</td>
</tr>
<tr>
<td>Total Control Score</td>
<td></td>
<td>0.64</td>
<td>0.90</td>
</tr>
</tbody>
</table>
FIGURE 7.1: CORRELATION BETWEEN ASTHMA CONTROL SCORES DERIVED FROM ACQ AND AQLQ(S) QUESTIONS.

\[ r = 0.90 \]
<table>
<thead>
<tr>
<th>Factor</th>
<th>Mean ± SD or Number (%)</th>
<th>Regression Coefficient (SE)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>38.0 ± 8.6</td>
<td>0.02 (0.009)</td>
<td>0.057</td>
</tr>
<tr>
<td>Gender (Male)</td>
<td>77 (40)</td>
<td>0.57 (0.16)</td>
<td>0.0005</td>
</tr>
<tr>
<td><strong>Medical History and ICS use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years since diagnosis</td>
<td>18.6 ± 12.7</td>
<td>0.002 (0.006)</td>
<td>NS</td>
</tr>
<tr>
<td>No. of other chronic diseases</td>
<td>0.85 ± 1.24</td>
<td>0.09 (0.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Depression</td>
<td>35 (18)</td>
<td>0.28 (0.21)</td>
<td>NS</td>
</tr>
<tr>
<td>Any psychiatric disorder</td>
<td>49 (25)</td>
<td>0.28 (0.14)</td>
<td>NS</td>
</tr>
<tr>
<td>ER visit in previous year</td>
<td>34 (17)</td>
<td>0.53 (0.22)</td>
<td>0.015</td>
</tr>
<tr>
<td>Oral steroid in previous year</td>
<td>53 (27)</td>
<td>0.68 (0.17)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Daily ICS use</td>
<td>106 (55)</td>
<td>0.59 (0.17)</td>
<td>0.03</td>
</tr>
<tr>
<td>Average daily ICS dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>33 (17)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>&lt;400 μg</td>
<td>90 (46)</td>
<td>0.32 (0.22)</td>
<td></td>
</tr>
<tr>
<td>400 – 800 μg</td>
<td>55 (28)</td>
<td>0.55 (0.24)</td>
<td>0.039</td>
</tr>
<tr>
<td>&gt;800 μg</td>
<td>16 (8)</td>
<td>0.87 (0.34)</td>
<td></td>
</tr>
<tr>
<td><strong>Proximate SES Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receipt of social assistance</td>
<td>64 (33)</td>
<td>Ref</td>
<td>0.0017</td>
</tr>
<tr>
<td>Yes</td>
<td>130 (67)</td>
<td>-0.54 (0.16)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education Completed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>28 (14)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>High school/Trade</td>
<td>127 (65)</td>
<td>-0.17 (0.22)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Bachelors education</td>
<td>39 (20)</td>
<td>-0.90 (0.27)</td>
<td></td>
</tr>
<tr>
<td>Yrs. post-secondary education</td>
<td>2.1 ± 2.3</td>
<td>-0.12 (0.03)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Annual household income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ $20,000</td>
<td>68 (39)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>$20,000 – $50,000</td>
<td>49 (28)</td>
<td>-0.54 (0.21)</td>
<td>0.0009</td>
</tr>
<tr>
<td>&gt; $50,000</td>
<td>56 (32)</td>
<td>-0.73 (0.20)</td>
<td></td>
</tr>
<tr>
<td><strong>Contextual SES Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Neighborhood Income</td>
<td>19,907 ± 4,349</td>
<td>-0.51 (0.18)*</td>
<td>0.006</td>
</tr>
<tr>
<td>% Bachelors Education</td>
<td>18.2 (10.9)</td>
<td>0.22 (0.07)†</td>
<td>0.002</td>
</tr>
<tr>
<td>Neighbourhood Unemployment Rate</td>
<td>10.0 ± 4.4</td>
<td>0.55 (0.17)†</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Coefficient for a $10,000 increase;  
†Coefficient for a 10% increase
TABLE 7.4: RELATIONSHIP BETWEEN SES AND ASTHMA CONTROL, ADJUSTED FOR POTENTIAL CONFOUNDERS (N= 194)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mean Control Score ± SD</th>
<th>Regression Coefficient (SE)*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proximate SES Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receipt of social assistance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.6 ± 1.0</td>
<td>Ref</td>
<td>0.008</td>
</tr>
<tr>
<td>No</td>
<td>2.0 ± 1.1</td>
<td>-0.55 (0.16)</td>
<td>0.008</td>
</tr>
<tr>
<td>Education Completed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2.6 ± 1.1</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>High school/Trade</td>
<td>2.4 ± 1.1</td>
<td>-0.22 (0.22)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Bachelor’s degree</td>
<td>1.7 ± 1.1</td>
<td>-0.90 (0.25)</td>
<td></td>
</tr>
<tr>
<td>Years of post-secondary education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--</td>
<td>--</td>
<td>-0.11 (0.03)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Annual household income§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ $20,000</td>
<td>2.7 ± 1.0</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>$20,000 – $50,000</td>
<td>2.1 ± 1.1</td>
<td>-0.45 (0.20)</td>
<td>0.0011</td>
</tr>
<tr>
<td>&gt; $50,000</td>
<td>1.9 ± 1.2</td>
<td>-0.72 (0.19)</td>
<td></td>
</tr>
<tr>
<td><strong>Contextual (Neighborhood) SES Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Income</td>
<td>--</td>
<td>-0.45 (0.17)†</td>
<td>0.012</td>
</tr>
<tr>
<td>% Bachelors Education</td>
<td>--</td>
<td>-0.21 (0.07)‡</td>
<td>0.002</td>
</tr>
<tr>
<td>Unemployment Rate</td>
<td>--</td>
<td>0.45 (0.17)†</td>
<td>0.008</td>
</tr>
</tbody>
</table>

* Adjusted for gender and daily ICS use
§ n=166
† Coefficient for a $10,000 increase
‡ Coefficient for a 10% increase
7.7 REFERENCES


CHAPTER 8
GENERAL DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

8.1 SUMMARY OF STUDY FINDINGS

The results of this study provide significant insight into asthma management patterns and related outcomes in British Columbia, and more specifically, into the social gradient of asthma management and asthma control. More importantly, it provides evidence that not only is there a social gradient in asthma management, but that this gradient appears to be independent of the severity of the disease, and can not be attributed specifically to barriers to the access to health care.

In terms of the treatment patterns, we used a novel strategy to assess the relationship between inappropriate asthma management and health care utilization. Because the use of administrative data to study asthma is limited by the inability to delineate asthma severity and asthma control, we analyzed only a subset of Pharmacare clients that could be more definitively classified as appropriately or inappropriately managed without the benefit of clinical information. The results of this analysis showed that, in keeping with previous studies, patients treated with excessive amounts of SA β-agonist medication in conjunction with sub-optimal doses of inhaled corticosteroids were more likely to fill more prescriptions, visit more prescribing physicians, to be hospitalized, and be hospitalized more frequently.

Because this analysis was limited to administrative data, we were not able to determine the cause of this association, or even attribute it specifically to the excessive use of SA β-agonists. An alternative explanation may be that excessive SA β-agonist use
was a marker of poor asthma management, and it may have been that the under utilization of inhaled corticosteroids was responsible for the poorer outcomes. One can conclude, however, that these patients experienced greater asthma-related morbidity and generated more health care costs.

From these data, it was also not possible to determine if the inappropriate management was related specifically to physician or health system related factors, to patient related factors, or a combination of them both. Physician prescribing may have been inappropriate due to a lack of awareness of the guidelines, or because their practice is comprised predominantly of severe asthmatics. Conversely, patients may be non-compliant to appropriately prescribed management and may choose to rely on SA β-agonist medications. There is also some evidence of an "addiction"-like phenomenon to the β-agonist related side effects that may lead some individuals to use greater than the recommended doses despite the absence of symptoms. Economic barriers, a lack of knowledge of appropriate therapy, and behavioural or social factors may also have influenced an individual’s treatment decisions.

Regardless of the etiology of inappropriate asthma management, it was associated with the utilization of more health care resources, relative to patients treated appropriately, independent of disease severity. In actual fact, limiting the analysis to the extremes of asthma management in this population (i.e. excessive SA β-agonist use with sub-optimal doses of inhaled corticosteroid versus low dose SA β-agonist with high doses of inhaled corticosteroid), it is conceivable that appropriately treated patients may have actually had more severe asthma than in appropriately treated patients. As with other
studies using administrative data, asthma severity could not be accurately measured in this study.

These results were consistent with previous studies which have shown better asthma-related outcomes associated with the addition of inhaled corticosteroids to the asthma treatment regime and with overall asthma management in accordance with the guidelines. Inappropriately treated patients in this study would likely benefit from the addition or optimization of controller medications, specifically inhaled corticosteroids, which may have resulted in a reduction of their SA β-agonist use and ultimately their utilization of health care resources.

Prior to embarking on a study of factors associated with the excessive use of SA β-agonists, it was necessary to determine if, in the population to be studied, the over-utilization of SA β-agonists was a persistent problem that required investigation and intervention. Although in the previous analysis we found that more than 10% of the sample received more than nine canisters of SA β-agonist over twelve months, far exceeding the maximum recommended amount of two canisters a year, this analysis was based on 1995 data. Therefore, we hypothesized that as a result of the revision and re-publication of the asthma management guidelines in 1995 that asthma management should have improved subsequent to this, demonstrable by a decrease in SA β-agonist use and an increase in inhaled corticosteroid use between 1996 and 1998.

A longitudinal analysis of all SA β-agonist users between 1996 and 1998 identified in the BC Pharmacare prescription drug database showed that the excessive use of short-acting β-agonist medications persisted. Each year, more than 5% of the population received more than 12 canisters of SA β-agonist, half of whom filled...
prescriptions for more than 20 canisters. No general trends toward improved management were identified. To the contrary, asthma management appeared to be paradoxically deteriorating. This was demonstrated by an increasing prevalence of not receiving a prescription for inhaled corticosteroid, and a greater likelihood of not filling a prescription for an inhaled corticosteroid after having received one previously relative to filling a new inhaled corticosteroid prescription. The most disconcerting finding was that this decreasing inhaled corticosteroid use was most pronounced in excessive SA β-agonist users who are the most likely to benefit from inhaled corticosteroid therapy.

Exploratory analysis of factors related to increasing SA β-agonist use in Pharmacare clients who remained in the database in all three years revealed that in controlled users, adjusting for the other factors, those older than nineteen years of age were at least 1.4 times more likely to increase their use than those less than nineteen years of age, and men were 1.7 times more likely than women to increase their use. In uncontrolled patients, neither age nor gender remained significant.

The only factor associated with increasing SA β-agonist use in both controlled and uncontrolled patients was the receipt of social assistance. Pharmacare clients receiving social assistance benefits and considered controlled in 1996 were 2.3 times more likely to increase their use than those not receiving social assistance. The association was attenuated in uncontrolled SA β-agonist users, but remained significant (OR 1.3; 95% CI 1.01 – 1.6). This provided the first suggestion that in this population, asthmatics of lower SES may be more likely to rely on SA β-agonists to manage their asthma, and as a result, be more likely to use excessive amounts of SA β-agonist medications and be at a greater risk of adverse outcomes.
This estimate of the association between the receipt of social assistance and increasing SA β-agonist use is likely to be conservative considering the comparator group. All British Columbia residents receiving social assistance receive first dollar coverage for all first-line asthma medications, compared to those under 65 years of age and not covered by any other Pharmacare plan who were subject to a $600 family deductible up to April 01, 1998, and an $800 deductible therefore. Although the deductible may have been achieved as a result of a family member with another chronic disease, it is likely that a significant proportion of this group were responsible for the achievement of the deductible themselves. The implications of this are that those not receiving social assistance may have been the subset of the population with the most severe asthma, and thus, if those on social assistance were compared to the entire general population their risk of increasing use would be higher than estimated in this sample.

These preliminary analyses provided the necessary background evidence that: i) in the British Columbia Pharmacare population, inappropriately treated asthmatics utilize more health care resources, suggestive of greater asthma related morbidity and poorer outcomes; and ii) despite the dissemination of the asthma management guidelines in 1995, the excessive use of SA β-agonists persisted. Ultimately, this shows that in British Columbia there are a significant number of asthmatics at unnecessary risk for adverse outcomes, and in whom asthma management could be improved.

This longitudinal analysis also showed that the majority of SA β-agonist users (>80%) received less than four canisters in a year. Given the need for non-social assistance recipients to exceed their deductible before entering the Pharmacare dataset, the prevalence of low use of SA β-agonists in the general population is potentially even...
higher. Realizing that all patients filling a prescription for a SA β-agonist do not have asthma, using IMSHealth Canada data and a previously published study, we estimated that the positive predictive value of identifying asthmatics using this method is approximately 0.85. This means that approximately 15% of patients receiving a prescription for a SA β-agonist do not have asthma, but have another indication for a SA β-agonist such as bronchitis, or a post-viral cough, the majority of whom would fall into this low use group. This has significant implications for the recruitment of subjects into a study of factors relating to the magnitude of SA β-agonist use.

Recruiting only volunteers from the general population would likely result in a greater representation of low users, and thus, would necessitate the recruitment of a very large sample in order to accrue a sufficient number of excessive users to facilitate the analysis of factors related to excessive use. We hypothesized that the ability to recruit a stratified sample of SA β-agonist users using administrative data from the Pharmacare prescription drug database would overcome this problem. Despite the current climate of growing concern over data privacy and patient confidentiality, we proposed a method of recruitment through which we would use prescription data to identify a sample of potentially eligible study subjects and contact them without revealing their health status prior to their providing informed consent. This method was approved by three independent ethics review committees and the British Columbia Ministry of Health’s Information and Privacy Branch, demonstrating that it is possible to ethically utilize an individual’s health care information, in a blinded fashion, for health care research.

We employed camouflaged sampling, stratified by SA β-agonist use, in order to attempt to accrue a heterogeneous sample of SA β-agonist users. As expected, we found
that compared to media advertising, stratified camouflaged sampling resulted in a sample that was much more heterogeneous for SA β-agonist use. The response rates achieved through direct and indirect patient contact (5.1% and 9.4%, respectively) were both lower than desirable; however, the determination of this rate is directly related to the positive predictive value of using SA β-agonist use to identify asthmatics. Although we estimated a positive predictive value of 0.85, it has been suggested that this may be an overestimate, which would result in a conservative estimation of the recruiting rates. Furthermore, refinement of this recruiting method, including repeated patient contact, and applying it to a more population based database may increase its utility and efficiency.

A primary consideration in combining subjects recruited through different methods was the potential for differences in the association between socioeconomic status and the magnitude of SA β-agonist use between recruiting methods. Multivariate categorical modeling did not reveal any difference in this association between recruiting methods, suggesting that either method could have been used alone and would have resulted in the same conclusions, but using camouflaged sampling provided a more heterogeneous sample of SA β-agonist users. This result provided the necessary evidence to permit the combining of subjects recruited through both methods for the final analysis.

The primary hypothesis being investigated was that in asthma, lower socioeconomic status is associated with the excessive use of SA β-agonists. In accordance with the Asthma Management Consensus Report,4,5 and in keeping with the evidence of a greater risk of adverse outcomes with the excessive use of SA β-agonists,6 the magnitude of SA β-agonist was used as a measure of asthma control. These results show that lower socioeconomic status asthmatics do use greater amounts of SA β-agonist
relative to those of higher socioeconomic classes. This association was consistent, independent of the method used to measure socioeconomic status at both the individual and population levels and of method used to adjust for asthma severity. In the fully adjusted model with the best fit, SES and the dimensions of asthma severity explained 40% of the variance of SA β-agonist use. This was similar to the findings of Rose and Marmot that showed only 30% to 40% of cardiovascular disease could be explained by known risk factors. These results are consistent with previous studies that have shown poorer control in adults, and a higher prevalence of inadequate drug therapy in lower socioeconomic status adolescents and children. However, these previous studies were done in the United States where asthmatics in lower social classes are more likely to encounter barriers to access to health care compared to a similar population in Canada. The persistence of this social gradient in our sample suggests that barriers to health care are unlikely a primary etiologic factor in this socioeconomic class - asthma control gradient. The corollary to this is that universal access does not necessarily extrapolate to universal utilization.

The possibility that this association could have been related to asthma severity necessitated that it be controlled for in the analysis. Although previous studies claim to have shown a higher prevalence of more severe asthma in lower social classes, their measures of asthma severity were limited to symptoms and they were therefore unable to differentiate between asthma severity and control. Although it is expected that asthmatics with more severe disease use higher doses of SA β-agonist, the differences between the crude odds ratios and those adjusted for asthma severity for the association between socioeconomic status and SA β-agonist use in this study were negligible. This suggests
that there is minimal confounding of the relationship between social class and the magnitude of SA β-agonist use by asthma severity, and that other etiologic factors are having an effect.

These results become even more striking if one considers the magnitude of the association, and the potential for misclassification bias in terms of recall of drug use in the previous 12 months, and of socioeconomic status. Participants may have either under or over-estimated their drug use over the previous year. Because there is no reason to believe that there should be differential misclassification between social classes, this will result in a conservative bias of the association. Conversely, there is likely to be a differential misclassification of socioeconomic status as it is more common to have upward misclassification of those in lower social classes, which will further conservatively bias estimates of the association. The inherent inaccuracy of social classification in conjunction with the misclassification of drug use will result in the observed associations being conservative estimates of the true relationship.

Finally, using a previously validated measure of asthma control, we found that, consistent with the previous analysis, asthmatics of lower socioeconomic status were more poorly controlled, adjusting for gender and daily inhaled corticosteroid use. Once again, this association was consistent across all proximate and contextual measures of SES, with consistent gradients in the expected direction across categories of both income and education.

A secondary component of this analysis was the derivation of a measure of asthma control from questions included in the Asthma Quality of Life Questionnaire (AQLQ(S)). This analysis demonstrated that the symptom dimensions of the Asthma Control Questionnaire can be derived from the AQLQ(S) to yield an internally valid
measure of asthma control. The control scores derived in this manner were consistently higher than those derived directly from the ACQ, thereby limiting only the external validity, prohibiting the comparison of asthma control scores from this analysis to those from other studies.

The complex relationship between asthma severity and control and the difficulty in separating these effects is exemplified by the final two analyses. In the first analysis of the relationship between socioeconomic status and the magnitude of SA β-agonist use, because it wasn't possible to measure asthma severity in controlled patients only it was necessary to incorporate symptoms, add-on medication use and health care utilization into the model as a measure of asthma severity. Conversely, in the analysis of the relationship between SES and asthma control, symptoms in conjunction with SA β-agonist use and the reversibility of airway obstruction are included as a measure of asthma control. Thus, in the uncontrolled patient, the combination of symptoms and add-on drug therapy can provide a measure of asthma severity. Conversely, the Asthma Control Questionnaire aptly shows that, in conjunction with SA β-agonist use and pulmonary function, symptoms are representative of asthma control. Furthermore, subsequent analysis showed that symptoms alone provide a valid measure of control.

Considering both of these analyses together, from the first analysis it appears that at the same level of severity, lower SES asthmatics utilize greater amounts of SA β-agonist medication. From this one could conclude that symptomatically and functionally these patients may be fine, or at least no worse off than asthmatics in higher socioeconomic classes. However, if the theories of a direct causal association between the excessive use of SA β-agonists and adverse outcomes are correct, these patients are at
greater risk. Thus, an appropriate approach would be to increase their add-on medication use, either by increasing their inhaled corticosteroid doses or adding another agent to facilitate a reduction in dose of the SA β-agonist. Conversely, if this excessive use is merely secondary to the habitual use of the SA β-agonist independent of symptoms, this may be amenable to merely educating these patients on the appropriate management of their asthma.

The results of the second analysis provide further evidence of this, given the poorer control in poorer asthmatics with similar levels of inhaled corticosteroid use. An increase in an individual’s inhaled corticosteroid dose should theoretically result in an improvement in asthma control. Because SA β-agonist use is one of the components of the asthma control score, symptoms may actually be controlled and the improvement in control may manifest merely as a decrease in SA β-agonist requirements.

8.2 UNIQUE CONTRIBUTIONS, IMPACT, AND IMPLICATIONS

The manuscripts comprising this dissertation contribute significantly to the current body of literature both methodologically and through the findings as they relate to asthma management. Previous studies demonstrating a social gradient in asthma severity were limited by their metric for severity, which could have been equally representative of asthma control.\textsuperscript{11-14} This was also true for one of the studies reporting that poorer asthma-related outcomes in lower socioeconomic status asthmatics was directly related to greater asthma severity.\textsuperscript{18} The only other study to report this did not attempt to quantify asthma severity and reached this conclusion purely through deduction.\textsuperscript{19} To our knowledge, this is the first study to attempt to comply with the theoretical framework of the association
between asthma severity and asthma control, and attempt to measure both severity and control simultaneously to evaluate the social gradient in asthma management, independent of severity. Although previous studies have shown a social gradient in asthma management or asthma control,\textsuperscript{8-10} these were all performed in the US, and primarily in children and adolescents. This was the first study to investigate the social gradient in asthma management in adults in a population with universal health care, thus limiting the effect of access to care.

The implications of these findings are numerous. The most significant contribution of this study to the current knowledge relating to asthma management is the specific demonstration that not only is there a social gradient in asthma control, but that this gradient is independent of asthma severity. If one assumes that asthma is an unmodifiable chronic disease, the complacent attribution of the social gradient in asthma-related outcomes specifically and solely to asthma severity precludes the obligation for intervention. This study provides evidence that lower socioeconomic status asthmatics are more poorly controlled, an association that is amenable to change. This shifts the focus from acceptance of the gradient in outcomes to the need to improve management in poorer asthmatics to attempt to narrow the gap in outcomes, improve quality of life and productivity, and reduce health care resource utilization.

The persistence of this association in persons receiving social assistance relative to those that do not provides evidence that the gradient cannot be directly attributable to barriers to the receipt of appropriate medical care or prescription medications. However, although there are theoretically no macro barriers to the receipt of health care in this population in terms of the government policy and its egalitarian approach to the provision of health care, there may be barriers to the receipt of appropriate care at the
individual level. Lower socioeconomic status asthmatics may lack the means, either material or economic, to travel to the physician or to take time off work. There may also be knowledge or perceptual barriers, such as a belief that they don’t need treatment because their asthma is controlled or because they have a chronic disease and are therefore meant to feel unwell, or that any treatment will be ineffective. Thus, although there are theoretically no barriers, open access to health care does not necessarily extrapolate to appropriate utilization.

The association between β-adrenergic receptor genotype and the magnitude of SA β-agonist use in the clinical setting has not been investigated previously. Although this was not the primary hypothesis of this study, it was a necessary component given its potential relationship with the magnitude of SA β-agonist use. The fact that there was no association with the magnitude of SA β-agonist use in this sample may suggest that although there is a theoretical association, clinically it doesn’t appear to be an important factor, and that other etiologies of excessive SA β-agonist use have a stronger effect.

In addition to the clinical contribution, this study provides a number of unique methodologic contributions. Specifically and most importantly is the empirical evidence of the application and utility of camouflaged sampling using direct and indirect patient contact. By using and evaluating camouflaged sampling in conjunction with voluntary recruitment through media advertising, we were able to show that an individual’s administrative health care data can be used for the recruitment of study subjects without compromising data privacy if appropriate methodologic safeguards are used. The implications of these finding for future studies proposing to use administrative data, whether patient contact is involved or not, are far reaching.
Although Maclure and Warren\textsuperscript{20} currently have a manuscript under review that describes the theory of camouflaged sampling and make reference to one other study in which this recruiting method was used, they do not provide any details of its utility or the logistics of its use. This study provides the first detailed account of the camouflaged sampling process accompanied by objective empirical evidence of its effectiveness and applicability.

Finally, in all analyses, an original method of asthma medication dosage standardization was used. The amount of both terbutaline and fenoterol used was standardized to the equivalent number of canisters of salbutamol, and all inhaled corticosteroids were standardized to the equivalent dose of beclomethasone dipropionate based on available data of weight to weight comparisons in potency.\textsuperscript{21-34} Applying these dosage conversions allows for the combining of the amounts of all inhaled SA β-agonist agonists and inhaled corticosteroids into one composite amount that can be interpreted in a clinical context, as opposed to a 'defined daily dose' which has been used but is not as intuitively useful. We are aware of at least one study being developed by a different research group in which this dosage standardization methodology is being proposed.

The potential impact of the primary findings of this study may extend beyond the boundaries of asthma and pulmonary medicine into many other disease states. Given that the social gradients in outcomes extends virtually across all diseases with the exception of only a few, it can be postulated that lower social class individuals with other diseases, either acute or chronic, are also less like to be appropriately managed or well controlled. If such a gradient exists in other diseases such as diabetes or hypertension in which treatment can result in improved outcomes, the identification of social factors related to poorer management in asthma may be similar in other diseases. This could potentially
result in management interventions applicable to these other diseases and ultimately in improved management and a narrowing of the social gradient in more diseases than just asthma.

8.3 STUDY STRENGTHS AND LIMITATIONS

8.3.1 Strengths

This study has a number of specific strengths that enhance the credibility of the results. Firstly, different methods of analysis, evaluation, and measurement resulted in consistent results. Analysis of administrative data from Pharmacare showed an association between the receipt of social assistance and increasing SA β-agonist use which was consistent with the results of the cross-sectional component in which data was collected directly from patients which showed that poorer asthmatics use greater amounts of SA β-agonist.

Within the cross-sectional component of the study, there are a number of consistencies which provide support for the findings. The strength and the direction of the association were consistent across all measures of socioeconomic status at both the proximate and contextual levels. Because there is currently no gold standard for the quantification of asthma severity, five different methods of controlling for asthma severity were used to facilitate the comparison, which also resulted in consistent results. The previously proposed asthma severity scores don't include all of the proposed dimensions of asthma severity,\textsuperscript{35-37} such as controller medication requirement, airflow limitation, and morbidity.\textsuperscript{21,38} These additional dimensions of asthma severity were included in the multivariate models in this study resulting in the maximization of the
explanation of the variance of SA β-agonist use prior to adding socioeconomic status to the models. This method was consistent with the theory of measuring asthma severity proposed by Cockroft and Swystun,\textsuperscript{38} and was the best method available given that inability and impracticality of achieving asthma control in all patients prior to determining asthma severity. The combination of these dimensions consistently explained more than 30% of the variance of SA β-agonist use. Despite the fact that this was more than was expected \textit{a priori}, socioeconomic status remained significantly associated with the magnitude of use, and was consistent across all measures of asthma severity adjustment.

In contrast to some of the previous studies that relied on administrative data, the recruitment and direct evaluation of patients facilitated the separation of the effects of asthma severity and control. The population in which the study was performed was one in which there are theoretically no barriers to the receipt of health care. In contrast to previous US studies of social class and asthma control, this study limited this as a potential explanation of the association.

Finally, two separate analyses of the final results were undertaken using two separate, although related, metrics for asthma control. Given the evidence that, in all but the most severe, treatment recalcitrant patients, the magnitude of SA β-agonist is more closely related to asthma control than severity, it was employed as a single measure of control. Asthma control quantified from a composite score was used in a subsequent analysis yielded consistent results. All analyses were robust to methodological differences in measurement and consistently point towards poorer asthma control in poorer asthmatics.
These results are further supported by the strength and consistency of the association, considering the relatively small sample size and the potential for misclassification in a study of this nature. The quantities of asthma medications, including SA β-agonists, used over the previous year were measured by self-report. Although this results in the potential for misclassification due to the reliance upon subject recall, there is no reason to believe that there should be differential recall between individuals from different social classes.

There is also the potential for the misclassification of socioeconomic status, and it is more likely that subjects in lower social classes will upwardly misclassified.\textsuperscript{15} In this study, it would be more likely that an individual may report more education or income than less. The consistency of the association across all proximate and contextual measures of socioeconomic status suggests that any misclassification of socioeconomic status was likely minimal. In relation to the final results, the misclassification of SA β-agonist use and socioeconomic status will both result in conservatively biased estimates of the association and therefore, the true relationship may actually be greater than that which we identified.

\textbf{8.3.2 Limitations}

As with any study, this one is not without its limitations, none of which should significantly affect the findings. Pharmacare prescription data were used for the initial background analysis of asthma management in British Columbia. The BC Pharmacare database is not a population based database, and only includes approximately 20\% of asthmatics in British Columbia. Furthermore, it is biased towards those of lower socioeconomic status (Plan C) and, considering the need for non-social assistance
recipients to exceed their annual deductible before they enter the database, potentially toward those with more severe asthma. Although this limits the generalizability of the results, these studies still provide evidence of poorer outcomes associated with inappropriate management, a high prevalence of excessive SA β-agonist use in British Columbia, and a greater risk of increasing their use of SA β-agonists by asthmatics receiving social assistance.

These initial analyses rely on computerized prescription data to approximate drug use which may not coincide exactly with the actual intake of the drug resulting in some misclassification. This is a common limitation of pharmacoepidemiologic studies that rely on retrospective administrative prescription data. In this particular population, it is possible that some prescriptions are filled for security reasons, i.e. to have extra inhalers in numerous locations, and therefore the estimates of the magnitude of use may be overestimates. It is also possible that this may occur more frequently in patients receiving social assistance given their receipt of medications at no cost. This limitation was overcome in the cross sectional component of the study where participants were asked specifically how much medication they 'used' over the previous year.

Because this dataset is comprised of a greater proportion of lower socioeconomic patients and we have shown that this group appears to be more likely to use greater amounts of SA β-agonists, the prevalence of excessive use in the general population is likely less than we identified. However, the absolute number of over-users who are therefore at risk and for whom improved management would likely be beneficial is likely much larger. The non-representativeness of the Pharmacare database as the source of the target population for the camouflaged sampling may also have been an influential factor
on the results. The inclusion of a volunteer recruitment component and the demonstration of consistent association between SA β-agonist use and socioeconomic status in participants recruited through both methods revealed that this was not an issue.

In the longitudinal analysis of the Pharmacare data there was no evidence of any improvements in asthma management over the three years following the 1995 publication of the updated asthma management guidelines. Because individuals can enter and exit the database for reasons unrelated to drug use (i.e. income) it was not possible to compile an incident cohort of SA β-agonist users, an indication of a new diagnosis of asthma, and follow them over time. The ramifications of this are that this sample is likely comprised predominantly of prevalent asthmatics. It is therefore possible that newly diagnosed asthmatics are managed in accordance with the guidelines, whereas prevalent asthmatics that have been managed inappropriately have become reliant upon the immediate relief they receive from β-agonists, and are reluctant to alter their management despite the efforts of clinicians.

The cross-sectional component of the study is subject to two specific limitations, one of which has been addressed as a strength. This is a cross-sectional study that relied on self reported drug use and socioeconomic status, as opposed to prospective study in which drug use could be measured. Although a limitation, as discussed under strengths, the potential for misclassification is likely to conservatively bias the results and is therefore not a significant limitation of this study.

The biggest limitation of the study is the fact that it involves a sample of only 202 subjects of a population of asthmatics in British Columbia that is estimated to be greater than 200,000. Because this is not a population study of all asthmatics which would not be
feasible given the requirement of direct patient assessment, the results may be biased if poorly controlled asthmatics of lower socioeconomic status were more likely to volunteer than poorly controlled asthmatics of higher socioeconomic status. The potential for bias stems from the potential for differences in health behaviour, and whether there are differences in health behaviour between classes that might affect their likelihood of study participation. The only incentives for participation in the study were $25 compensation for travel and the provision of the results of the pulmonary function tests to the participant’s physician, at their request. There was no intervention or education offered that might improve their asthma control. Social class differences in health behaviours would suggest that uncontrolled asthmatics in higher social classes are more likely to seek care, and thus, may be more likely to participate if they perceived that the provision of their pulmonary function results to their physician would be beneficial.\textsuperscript{40,41} The $25 financial incentive would not be expected to provide differential incentive to controlled or uncontrolled asthmatics in lower social classes. Thus, it is more likely that uncontrolled higher social class asthmatics would volunteer to participate than uncontrolled lower social class asthmatics, which will further conservatively bias the results.

The results of this study do not suggest that the leveling of the social gradient in asthma control will result in an eradication of the gradient in asthma-related outcomes. However, despite the fact that modern medical care is not a primary determinant of health in modern society, differences in the utilization of effective medical therapy can contribute at least partially to the social gradient in outcomes.
8.4 RECOMMENDATIONS

This study gives rise to two primary recommendations. Firstly, further initiatives must be taken and efforts made to improve asthma management and reduce the reliance upon SA β-agonists as the mainstay of therapy for many patients. Secondly, further research needs to be undertaken to identify other factors related to poor asthma control, and to determine the specific etiologic factors related to poor asthma control in lower socioeconomic status asthmatics.

8.4.1 Improved Asthma Management

There are four primary reasons for studying population health: to describe, predict, explain, and control. Poorer outcomes in asthma have been described, and subsequent research has allowed the prediction of a greater likelihood of poorer outcomes in lower social classes. This study has attempted to address the next step of explaining the etiology for this gradient in health-related outcomes.

In conjunction with previously published studies, the background analysis to this study demonstrates that in British Columbia inappropriate asthma management persists and is related to poorer asthma-related outcomes and greater health resource utilization. This is occurring despite vast improvements in the knowledge and understanding of the pathophysiology of asthma and improvements in asthma management aimed specifically at these pathophysiologic processes rather than merely treating the symptoms as was done historically. It is therefore obvious that merely developing and disseminating management guidelines is not sufficient, which is not inconsistent with previous evaluations of the impact of guidelines.
The approach to asthma management in Canada, the United States, and other developed countries has been moving forward in a stepwise, incremental process. Over the past 40 years, we have evolved from the identification of the risks of over-reliance on SA β-agonists for asthma management, to understanding asthma as an inflammatory process and the development and marketing of specific pharmaceutical agents targeting the inflammatory process to a consensus on appropriate asthma management within the realm of current knowledge and available therapeutic modalities. Furthermore, we have established that non-compliance with the treatment guidelines results in poorer outcomes, and that the prevalence of inappropriate management remains significant. The next logical step in the cascade is to improve asthma management in those who are inappropriately managed.

Although this is not to suggest that the description and prediction of poorer health-related outcomes in asthma is complete, or that there aren’t more explanatory components of the social gradient that can be identified, the next step is to address the specific issue of poorer asthma management in poorer asthmatics. There are at least two separate facets to this next step.

Realizing that there is no single factor that will identify all asthmatics who are poorly controlled, a population-based intervention aimed at improving asthma management could be used. This is likely to be the least efficient approach, and it could be expected that it is not the asthmatics that are the most poorly controlled that will respond the most to the intervention. Conversely, specific interventions can be developed and targeted at the sub-groups of the population who are at the greatest risk for inadequate asthma control. These results point to one group, those of lower
socioeconomic status, who appear to be at greater risk of poor control and are therefore prime candidates for a targeted intervention aimed at improving asthma control.

Operationalizing this is not however a simple process. It will not be a matter of merely informing each patient of the appropriate approach to asthma management, but rather will require the identification of the specific etiologic factors responsible for this social gradient in asthma control. It appears that programs that focus entirely on asthma knowledge and do not adequately attempt to modify health-related behaviour have limited success. This consequently leads to the next recommendation of the areas of further research.

8.4.2 Further Research

In order for any program aimed at improving asthma management to be effective and efficient, it must target not only those most likely to benefit, but also the specific factors to which the association can be attributed. In this case, we have shown an association between socioeconomic status and inadequate control. Although it appears that economic barriers to the receipt of health care do not appear to be a primary consideration, we did not identify what others factors might explain the differences in asthma control.

Numerous hypotheses can be formulated about the etiologic factors. There may be non-patient related factors which need to be addressed. It may be that physician behaviour differs towards lower socioeconomic status patients. With an *a priori* assumption of non-adherence to prescribed therapy, physicians may be less likely to prescribe add-on medications or provide a referral to an asthma specialist. In the US, it
has been shown that hospitalization of patients is not entirely independent of the patient’s socioeconomic status, social capital, or their social safety net.51

Previous studies showing poorer asthma management in lower social classes have either used only administrative data or measured current utilization,9,47,48 resulting the inability to determine whether the patient had received a prescription for an inhaled corticosteroid or other controller medication that they didn’t fill, and for what reason. One study found that 30% of prescriptions written for asthma were not filled, and that patients in lower social classes were less likely than those in middle or high social classes to fill their prescriptions (OR 0.84; 95% CI 0.7 – 1.0).49 They did not differentiate between SA β-agonists and controller medications. Conversely, Saunders did not find any class differences in the frequency of not filling a prescription for asthma following a visit to an emergency room.50 In their study of the relationship between income and asthma care patterns, Erzen et al. concluded that higher income asthmatics were more likely to be referred to an asthma specialists,19 but because this study was based on administrative data they were not able to measure the frequency of having received a referral but not visiting the specialist. The contribution of continuity of care and greater likelihood of receiving treatment from more physicians or relying on the emergency department may also be a factor. Answering these questions is paramount to determining the physician’s role in the social gradient in asthma control.

Numerous patient-related factors must also be examined. Although it doesn’t appear to be a primary consideration as a barrier to the health care system or obtaining drug therapy, there may still be economic barriers. These may include the inability to afford to travel to the physician, to take time off work to visit the physician, or to make necessary changes to one’s living conditions. There are data showing that those in lower
social classes are more likely to be living in conditions which will exacerbate their asthma,\textsuperscript{9,51,52} however the ability to decrease their exposure requires financial resources. Denson-Lino et al. showed that in families in lower social classes, education alone did not result in dust mite control, but that economic factors also influenced decisions.\textsuperscript{53} This also shows that there are environmental factors contributing to the gradient, but many of the specific factors are likely to vary between populations.

Given the association between poor knowledge of asthma management and inadequate treatment,\textsuperscript{54,55} one of the most intuitive differences may be merely in education, knowledge and understanding of appropriate disease management. The actual nature of the association between social class and health is more likely cognitive opposed to material. There may also be differences in behaviour, lifestyle, and societal values within communities. It has been shown that the two major foci that can affect health behaviour are the ‘group’ characteristics including group membership, group norms and social status or stratification, and ‘network’ characteristics including social ties representative of an individual’s social capital or social safety net, and community linkages.\textsuperscript{40}

Specific differences in health beliefs within an individual’s social circle can have a significant influence. This is exemplified by the fact that prior to the knowledge of the adverse health effects of smoking there was no social gradient in smoking rates.\textsuperscript{56} This therefore becomes a social problem as opposed to individual one. The question becomes, “what drives those of lower social classes to continue to smoke?” This study leads to similar questions about the driving forces behind inappropriate asthma management in lower social classes.
The many health behaviour models also lead one to posit that specific attributes of self-efficacy, self-esteem, motivation, and psychosocial stressors may play a role. The psychosocial dynamics of social class and status within society may contribute significantly to the feelings of personal efficacy and one's personal belief in their ability to overcome or take control of their disease. An individual with few successes or victories in life will believe that they are unlikely to achieve one at any subsequent point, and therefore be less likely to attempt to. Personal self-efficacy can be both learned through life experiences and reinforced by one's social position or structural community. A study of overall health found that in Russia, poor health status was associated with dysfunctional social structures and a lack of a social equity, as well as a lack of perceived control over one's own health. Specifically in asthma, a focus group study of low income asthmatics uncovered a fatalistic acceptance of their asthma symptoms and a poor perception of the lack of asthma control.

Many of these factors have been related to poorer outcomes, however, their association with poorer control hasn't been established; it is likely that there is a relationship. It is important to determine the actual contribution of each of these etiologic factors to the poorer control before attempting to improve treatment, as merely gaps in knowledge and understanding will be much less difficult to overcome than inherent psychosocial differences between the groups. The latter will require much more complex and intensive interventions.

There is also some recent evidence showing that obesity may be an important risk factor for obstructive lung disease. In some instances it has been shown that obesity is associated with asthma, wheeze, and shortness of breath, but not necessarily with reversible airway disease. Studies showing an inverse association between social
class and obesity lend credibility to this hypothesis, but the direct association remains
to be tested.

The specific factors contributing to poor asthma control are likely to differ
between populations, depending on living conditions, health care system, social beliefs,
and societal and communal values. Although there are studies that have started to address
this question, none have been in Canada and further study in this area is required.

8.5 CONCLUSIONS

When socioeconomic status is studied in relation to health status, it has been
historically treated as a black box. Initially we needed only to know what went in and
what came out. Now it is necessary to deconstruct it to understand the social, political
and economic forces operating within the box. Only recently have we started to delve
into the black box of socioeconomic status and its relationship with health-related
outcomes to determine what factors related to social status are contributing to poorer
health in lower social classes. Although these results only begin to identify some of the
contents of the black box, they provide significant insight into one more potential
component of the social gradient in health outcomes. Although this data relates
specifically to asthma, it is likely that similar associations can be found in other diseases.

This study provides good evidence of a socioeconomic gradient in asthma control,
independent of asthma severity which has significant implications in the future direction
doing asthma management. Contrary to attributing the social gradient in asthma-related
outcomes specifically to asthma severity, a social gradient in asthma control is amenable
to some form of remedial action, and suggests that there is an attributable risk of poorer
outcomes related to poor control in less affluent asthmatics. A portion of adverse outcomes can therefore likely be prevented with improvements in asthma management.

An important consideration of this analysis is the understanding that there is not necessarily a causal association between any proximate or contextual measure of socioeconomic status and asthma control. Increasing an individual’s income or education is unlikely to result in improvements in asthma control. The key concept is that it is not necessarily material or economic deprivation or a lack of education that is important, but rather more likely that social deprivation is the primary dimension for which these measures of socioeconomic status act as surrogates. Using these surrogate measures of socioeconomic status merely suggests that there is something systematically different about the less well off that puts them at risk for poorer asthma control. The question now remains, what are these systematic differences?

The identification of the etiology of this gradient can permit asthma management programs targeted not only at those patients most likely to benefit, but at the primary causal factors of poor control. In turn, this has the potential to improve asthma management, and ultimately narrow the social gradient in asthma-related outcomes.
REFERENCES


27. Ebden P, Jenkins A, Houston G, Davies BH. Comparison of two high dose corticosteroid aerosol treatments, beclomethasone dipropionate (1500 micrograms/day) and budesonide (1600 micrograms/day), for chronic asthma. Thorax 1986;41(11):869-74.


37. Ng TP. Validity of symptom and clinical measures of asthma severity for primary outpatient assessment of adult asthma. Br J Gen Pract 2000;50(450):7-12.


APPENDIX I

DECLARATION OF CANDIDATES ROLE IN PUBLISHED MANUSCRIPTS
APPENDIX II

DETERMINANTS OF β-AGONIST USE STUDY:
ASTHMA ASSESSMENT QUESTIONNAIRE (SELF-ADMINISTERED)
The Determinants of 
β - Agonist Use Study:

ASTHMA 
ASSESSMENT 
QUESTIONNAIRE

Self Administered

SUBJECT ID# :
SECTION I: ASTHMA and HEALTH CARE USE ASSESSMENT

This first section starts by asking some general questions about yourself. Then there will be some questions dealing specifically with your asthma, your use of the health care system and complementary medicines, and about some of the expenses you might have incurred because of your asthma. You may decline to answer any question, however please remember that it is very important that we get the most accurate and complete information we can, and that all the information you provide is completely confidential.

HC1. What is your current marital status?

- Single
- Married
- Married and separated
- Common – law
- Divorced
- Widowed

HC2. What type of health insurance coverage do you have?

[Please check all that apply]

- I don't currently have medical insurance
- Plan C (Social assistance)
- Plan E (Basic MSP) – self paid
- Plan E (Basic MSP) – employer paid
- Extended medical – self paid
- Extended medical – employer paid
- Prescription drug plan (3rd party coverage)
- Other

If OTHER, please specify: ▶

HC3. When were you first diagnosed with asthma?

Approximate date of asthma diagnosis [month / year]

- I don't know
- I prefer not to answer this question

HC4. Do you currently, or have you previously, smoked cigarettes, cigars, or a pipe?

- Never smoked [Go to Question HC7]
- Currently smoke
- Quit smoking
- Other
- I prefer not to answer this question

If OTHER, please specify: ▶
HC5. If you have quit smoking, how long has it been since you last smoked?
- < 3 months
- 3 – 6 months
- 6 – 12 months
- 1 – 5 years
- > 5 years
- I don’t know

HC6. How much do you, or did you previously smoke?
- Amount smoked [per day, or per week]
  [specify pipe, cigarette, cigar]
- I don’t know
- I prefer not to answer this question

HC7. Approximately how frequently have you have felt symptoms of your asthma (such as cough, wheeze, shortness of breath, chest tightness) over the previous month?
- Constantly
- Daily (off and on throughout the day, every day)
- 3 – 6 times per week
- 1 – 2 times per week
- Never
- I don’t know

HC8. Approximately how frequently have you have felt symptoms of your asthma during the night (i.e. either you have been awakened by symptoms, or you are unable to sleep because of your symptoms) over the previous month?
- Frequently (≥ 2 times a week)
- Once / week
- Less than once a week, but more than once over the month
- Once
- Never
- I don’t know
- I prefer not to answer this question

HC9. Do you have symptoms of your asthma (cough, wheeze, have chest tightness, or feel short of breath) all year-around, or only at certain times?
- All year round
- Only at certain times of the year
- Only when I exercise
- Other
  If OTHER, please specify: 

HC10. Over the past year, have you seen a doctor because of your asthma, other than in the emergency department or hospital?
- Yes; How many times?
- No
- I don’t know
- I prefer not to answer this question
HC11. Over the past year, have you had to visit an emergency department in a hospital because of your asthma?

- Yes; How many times? □
- No
- I don’t know
- I prefer not to answer this question

HC12. Over the past year have you been admitted to hospital due to your asthma?

- Yes; How many times? □
- No
- I don’t know
- I prefer not to answer this question

[If NO, go to Question HC17]

HC13. Did any of these hospital admissions occur after being seen by a doctor in the emergency department?

- Yes; How many times? □
- No
- I don’t know
- I prefer not to answer this question

HC14. What was the total number of days you spent in the hospital because of your asthma in the previous year?

□ Total number of hospital days due to asthma in the previous year

- I don’t know
- I prefer not to answer this question

HC15. During any of these hospital admissions, were you admitted to a critical care unit [e.g. ICU or CCU] because of your asthma?

- Yes; How many times? □
- No
- I don’t know
- I prefer not to answer this question

[If NO, go to Question HC17]

HC16. During any of these admissions to a critical care unit, did you have to be placed on a life support system (e.g. a ventilator)?

- Yes
- No
- I don’t know
- I prefer not to answer this question
HC17. Over the past year, have you required any other services for your asthma such as physiotherapy, occupational therapy, social work, diet/nutrition counseling, or in-home services (e.g. home care)?

- Yes
- No
- I don’t know
- I prefer not to answer this question

[Go to Question HC19]

HC18. Could you specify the type of service(s) (e.g. physiotherapy, home care), the nature of the actual service(s) provided (e.g. physical conditioning, inhaler instruction, diet counseling) and number of visits?

<table>
<thead>
<tr>
<th>Type and Nature of Service</th>
<th>Number of visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td></td>
</tr>
</tbody>
</table>

HC19. Over the past year, have you had to rent or purchase any equipment (e.g. nebulizers, air purifiers, furnace attachments, special furniture or bed covers) related to your asthma?

- Yes
- No
- I don’t know
- I prefer not to answer this question

[Go to Question HC21]

HC20. Can you describe this equipment and its' cost?

<table>
<thead>
<tr>
<th>Type</th>
<th>Estimated Cost (total or per month)</th>
<th>Rented</th>
<th>Purchased</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HC21. Has it ever been recommended that you should use one of these pieces of equipment described above, but you decided not to purchase or rent it?

- Yes
- No  ➡️  [Go to question HC23]
- I don’t know
- I prefer not to answer this question

HC22. What type of equipment was it, and why did you decide not to acquire it?

Type of equipment

- I didn’t think it would help
- I couldn’t find one
- It was too expensive
- I don’t know
- Other

**If OTHER, please specify:**

HC23. Over the past year, have you had any out-of-pocket expenses for your asthma [such as child care, parking, travel to your doctor, hospital or emergency department, hotels, medical surcharges, prescriptions] that you have had to pay for?

- Yes
- No  ➡️  [Go to Question HC25]
- I don’t know
- I prefer not to answer this question

HC24. Can you list these out-of-pocket expenses? (e.g. parking, transit, childcare, etc.)

<table>
<thead>
<tr>
<th>Expense</th>
<th>Estimated annual cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>$</td>
</tr>
<tr>
<td>2.</td>
<td>$</td>
</tr>
<tr>
<td>3.</td>
<td>$</td>
</tr>
<tr>
<td>4.</td>
<td>$</td>
</tr>
<tr>
<td>5.</td>
<td>$</td>
</tr>
</tbody>
</table>

HC25. Over the past year, have you utilized any complementary methods of health care (e.g. herbal medications, homeopathic medications, acupuncture, healing touch) for the management of your asthma?

- Yes
- No  ➡️  [Go to Question HC27]
- I don’t know
- I prefer not to answer this question
HC26. Can you list these complementary methods of care and their estimated cost to you over the last year?

<table>
<thead>
<tr>
<th>Type</th>
<th>Estimated cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>$</td>
</tr>
<tr>
<td>2.</td>
<td>$</td>
</tr>
<tr>
<td>3.</td>
<td>$</td>
</tr>
<tr>
<td>4.</td>
<td>$</td>
</tr>
<tr>
<td>5.</td>
<td>$</td>
</tr>
</tbody>
</table>

HC27. Have you ever been enrolled in an asthma education program, or received specific instruction on asthma management from an asthma educator?

- [ ] YES
- [ ] NO

HC28. Have you ever used a peak flow meter to monitor your asthma?

- [ ] YES
- [ ] NO

HC29. Do you currently use a peak flow meter to monitor your asthma?

- [ ] YES
- [ ] NO

HC30. Do you have an emergency treatment plan for the initial management of an asthma attack?

- [ ] YES
- [ ] NO

HC31. Have you ever been tested for allergies using a skin test?

- [ ] YES
- [ ] NO

CONTINUE TO SECTION II
SECTION II: PERSONAL DATA

This section is made up of questions asking about yourself and anyone who might be living with you. This involves questions about education, income, and employment of yourself and anyone who might be sharing expenses with you.

P1. What was your main activity during the past 12 months? [Please check only one]
   - Working at a job
   - Looking for work
   - Unable to work due to health reasons
   - Going to school
   - Keeping house
   - Retired
   - Other
   If OTHER, please specify: ▶

P2. If your main activity was WORKING AT A JOB, what is your field of employment (e.g. secretary, nurse, laborer, store clerk, plumber, dentist)?
   Brief description: ▶

P3. If you worked, even if your main activity wasn’t WORKING AT A JOB, on average approximately how much did you work over the past 12 months?
   - Full time (>35 hours / week)
   - 30 – 35 hours / week
   - 20 – 29 hours / week
   - 10 – 19 hours / week
   - < 10 hours / week
   - Casual

P4. If someone in your field of employment lost the income from a missed work day, what would be the value of ONE days lost income (before deductions)?
   $ ▶ Value of one days lost income
   - I don’t know
   - Not applicable
   - I prefer not to answer this question

P5. Over the past year, have you had to miss work or school because of your asthma?
   - Yes
   - No ▶ [Go to Question P7]
   - Not applicable
P6. Can you estimate how many days of work and / or school that you have missed over the past two weeks and the past year because of your asthma?

<table>
<thead>
<tr>
<th>Days of WORK missed</th>
<th>Over the past TWO weeks</th>
<th>Over the past 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of SCHOOL missed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P7. Over the past year, has anyone else (e.g. spouse, partner, caregiver, friend) had to miss work or school because of your asthma?

- [ ] Yes
- [ ] No
- [ ] I prefer not to answer this question

[Go to Question P9]

P8. Can you specify the relationship of these individuals to you, and how many days of WORK or SCHOOL that they have missed in the previous year?

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Work days Missed</th>
<th>School days Missed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person 3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P9. Have you ever had to change jobs because of your asthma?

- [ ] Yes; What was your previous job? ▶
- [ ] No

P10. What is the highest grade (or year) of secondary (high school) or elementary school you have successfully completed?

- [ ] Never attended school, or attended kindergarten only
- [ ] I prefer not to answer this question

Number (1 – 13) of grades of secondary and / or elementary school successfully completed

P11. How many years of post-secondary education (after high school) have you completed?

- [ ] None
- [ ] Less than one year

Number of years of post-secondary education

223
P12. What certificates, degrees, or diplomas have you ever obtained?

[Please check all that apply]

☐ None
☐ High school diploma
☐ Trades or non-university diploma
☐ Undergraduate (bachelor’s) university degree
☐ Degree in medicine, dentistry, vet med, optometry, chiropractic, etc.
☐ Masters or Doctorate degree (M.A., M.Sc., Ph.D., D.Sc., D.Ed.)

P13. Is there another primary, non-dependent adult living in your household (e.g. a spouse or partner)?

☐ Yes ➔ [Go to Question P21]
☐ No

P14. What is this person’s relationship to you?

☐ Spouse / Partner
☐ Parent / Guardian
☐ Sibling
☐ Roommate
☐ Other

If OTHER, please specify: ▶

P15. What was this person’s main activity during the last 12 months?

☐ Working at a job
☐ Looking for work
☐ Unable to work due to health reasons
☐ Going to school
☐ Keeping house
☐ Retired
☐ Other
☐ I don’t know
☐ I prefer not to answer this question

If OTHER, please specify: ▶

P16. If this person’s main activity was WORKING AT A JOB, what is their field of employment (e.g. secretary, nurse, laborer, store clerk, plumber, dentist)?

Brief description: ▶

P17. If someone in this person’s field of employment lost the income from a missed work day, what would be the value of ONE days lost income (before deductions)?

$ ▶ Value of one days lost income

☐ I don’t know
☐ Not applicable
☐ I prefer not to answer this question
P18. What is the highest grade (or year) of secondary (high school) or elementary school this person has successfully completed?

Number (1 – 13) of grades of secondary and / or elementary school successfully completed

☐ Never attended school, or attended kindergarten only
☐ I don’t know
☐ I prefer not to answer this question

P19. How many years of post-secondary education (after high school) has this person completed?

Number of years of post-secondary education

☐ None
☐ Less than one year
☐ I don’t know
☐ I prefer not to answer this question

P20. What certificates, degrees, or diplomas have they ever obtained? (Please check all that apply)

☐ None
☐ High school diploma
☐ Trades or non-university certificate
☐ Undergraduate (bachelor’s) university degree
☐ Degree in medicine, dentistry, optometry, chiropracy, etc.
☐ Masters or doctorate degree
☐ I don’t know
☐ I prefer not to answer this question

P21. What was your approximate total household income from all sources for the previous year, before income tax deduction? [including only your family members, not roommates that you don’t share daily expenses with]

☐ less than $20,000
☐ $20,000 – $30,000
☐ $30,001 – $40,000
☐ $40,001 – $50,000
☐ $50,001 – $60,000

☐ $60,001 – $70,000
☐ $70,001 – $80,000
☐ $80,001 – $90,000
☐ $90,001 – $100,000
☐ greater than $100,000

☐ I don’t know
☐ I prefer not to answer this question

P22. Do you have any children?

☐ Yes
☐ No
P22. Continued:

**If YES:**

How many children do you have?

☐ Total number or children

How many children currently live with you?

☐ Number of children currently living with you

P23. How would you describe the type of dwelling that you currently live in?

☐ Single detached home
☐ Duplex or Townhouse
☐ Apartment or Condominium
☐ Mobile home
☐ Boarding room / Hotel / Rooming House
☐ Other
☐ I prefer not to answer this question

If OTHER, please specify:

P24. How many rooms does your current residence have, including kitchen, living room, bedrooms, finished rooms in the basement or attic, etc? (Do not count bathrooms, hallways, or rooms used exclusively for work).

☐ Total number of rooms

P25. How many of these rooms are bedrooms?

☐ Number of bedrooms

P26. How many adults and children (including yourself) live in your current residence?

☐ Total number of adults
☐ Total number of children

P27. Is your current residence:

☐ Owned by you or a member of household
☐ Rented [even if no rent is paid]
☐ Subsidized housing (you receive government rental assistance)
☐ Other
☐ I don't know
☐ I prefer not to answer this question

If OTHER, please specify:
The following are some general questions regarding your current residence and living conditions, which may have an effect on your asthma.

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P28.</strong> Are there any pets or animals living with you?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>P29.</strong> Is there anyone currently living with you that smokes?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>P30.</strong> Is there moisture or dampness in any room of your home?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>P31.</strong> Have you seen mold or smelled musty odors anywhere in your home?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>P32.</strong> Have you ever seen cockroaches in your home?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>P33.</strong> Do you use a humidifier in your home?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>P34.</strong> Is a wood-burning stove or fireplace used in your home?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>P35.</strong> Do you have carpet on the floors of your bedroom?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>P36.</strong> Do you have carpet on the floors anywhere else in your home, other than in your bedrooms?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>P37.</strong> Have you done any renovations or modifications to your home because of your asthma?</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

**CONTINUE TO SECTION III**
SECTION III: ASTHMA MEDICATION USE

This section asks some very specific questions regarding any asthma medications that you use. It is very important that we get the most accurate information that we possibly can. Some of the questions ask for very specific details, and deal with some things that may have happened over the past year, so please take your time and try and answer the questions as accurately as possible. Once again, please remember that any answers you give are completely confidential.

M1. Have you ever received a prescription for an asthma medication from your doctor that you have not had filled by a pharmacist?

☐ Yes; How many times?
☐ No
☐ I don't know
☐ I prefer not to answer this question

[If NO, go to Question M3]

M2. What was your reason for not filling the prescription?

☐ It was too expensive
☐ I didn't think I needed it
☐ I didn't think it would help
☐ I couldn't get to the pharmacy
☐ Other

If OTHER, please specify:

M3. Have you ever asked your family doctor for a referral to an asthma specialist?

☐ Yes
☐ No
☐ I don't know
☐ I prefer not to answer this question

M4. Have you ever been assessed by an asthma specialist for your asthma?

☐ Yes
☐ No
☐ I don't know
☐ I prefer not to answer this question

M5. Have you ever been referred to an asthma specialist but did not go to the specialist for an asthma assessment?

☐ Yes; How many times?
☐ No
☐ I don't know
☐ I prefer not to answer this question

[If NO, go to Question M7]
M6. What was your reason for not going to the specialist?

☐ I didn’t think it would help
☐ I didn’t think I needed to see a specialist
☐ I had no way of getting to his / her office
☐ It took too long to get an appointment
☐ Other

If OTHER, please specify: ▲

M7. In the past year, have you used a short-acting bronchodilator (blue) inhaler, such as Ventolin® or salbutamol, for the treatment of your asthma?

☐ Yes  ▶ ▶ [Go to Question M16]
☐ No
☐ I don’t know
☐ I prefer not to answer this question

You have indicated that you currently use, or have used, a bronchodilator (blue) inhaler for the treatment of your asthma. The next few questions ask specifically about this/these inhaler(s). Please try and answer all of the next few questions as they pertain to your bronchodilator (blue) inhaler only.

M8. Can you identify which bronchodilator (blue) inhalers you currently use, or have used in the past year? (please check all that apply)

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Currently use</th>
<th>Duration of use (months)</th>
<th>Used in past year</th>
<th>Duration of use (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>fenoterol (e.g. Berotec®)</td>
<td>☐</td>
<td></td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>salbutamol (e.g. Ventolin®, Ventodisk®)</td>
<td>☐</td>
<td></td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>terbutaline (e.g. Bricanyl®)</td>
<td>☐</td>
<td></td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>other; please specify:</td>
<td>☐</td>
<td></td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

M9. Is your bronchodilator (blue) inhaler a multi-dose inhaler, like a puffer, or a dry powder inhaler such as rotohaler capsules or disc, or do you use both types?

☐ Multi-dose inhaler (Puffer)
☐ Dry powder inhaler (capsule or disc)
☐ I use both types
M10. How regularly do you use your bronchodilator (blue) inhaler(s)?

☐ Every day
☐ Less than daily, but more than once a week
☐ Approximately once / week
☐ Less than once a week
☐ Only when I exercise
☐ Only when I have an asthma attack
☐ Other

If OTHER, please specify: ▶

Go to Question M12

M11. If you use your bronchodilator (blue) inhaler daily, how many puffs per day do you use?

☐ 1 – 2 puffs / day
☐ 3 – 4 puffs / day
☐ 5 – 8 puffs / day
☐ >8 puffs / day

M12. Approximately how many bronchodilator (blue) inhalers (canisters) in total have you used in the past month?

☐ ≤ 1
☐ 2 – 3
☐ 4 – 5
☐ 6 – 8
☐ > 8

M13. Approximately how many bronchodilator (blue) inhalers (canisters) in total have you used in the past year?

☐ ≤ 4
☐ 5 – 8
☐ 9 – 12
☐ 13 – 20
☐ > 20

M14. Do you keep extra bronchodilator (blue) inhalers at various locations, such as the office or in the car, just in case you forget to take your inhaler with you?

☐ Yes
☐ No  [Go to Question M16]
☐ I don't know
☐ I prefer not to answer this question

M15. Approximately how many extra bronchodilator (blue) inhalers do you have (that you are using) right now?

☐ 1 – 2
☐ 3 – 4
☐ 5 – 7
☐ >8
That is all the questions specifically about your bronchodilator (blue) inhaler. The next set of questions asks about a different type of inhaler.

M16. In the past year, have you used a steroid, anti-inflammatory (brown) inhaler, such as Beclovent®, Pulmicort®, or Flovent® for the management of your asthma?

- Yes
- No [Go to Question M25]
- I don’t know
- I prefer not to answer this question

You have indicated that you currently use, or have used, a steroid, anti-inflammatory (brown) inhaler for the treatment of your asthma. The next set of questions asks you specifically about this/these inhaler(s). Please try and answer all of the next few questions as they pertain to your steroid, anti-inflammatory (brown) inhaler only.

M17. Can you identify which steroid, anti-inflammatory (brown) inhaler(s) you have used over the previous year? (Please check all that apply)

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Currently use</th>
<th>Duration (months)</th>
<th>Used in past year</th>
<th>Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>beclomethasone (e.g. Beclovent®, Becloforte®, Beclodisk®, Vanceril®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>budesonide (e.g. Pulmicort®)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>flunisolide (e.g. AeroBid®)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fluticasone (e.g. Flovent®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>triamcinolone (e.g. Azmacort®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>other; please specify:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

M18. Is your steroid, anti-inflammatory (brown) inhaler a multi-dose inhaler, like a puffer, or a dry powder inhaler such as rotohaler capsules, or do you use both types?

- Multi-dose inhaler (Puffer)
- Dry powder inhaler (capsule or disc)
- I use both types

M19. How often do you use your steroid, anti-inflammatory (brown) inhaler?

- Every day
- Less than daily, but more than once a week
- Approximately once / week
- Less than once a week
- Only when I exercise
- Only when I have an asthma attack
- Other

If OTHER, please specify: ▶

231
M20. If you use your **steroid, anti-inflammatory (brown)** inhaler every day, how many puffs per day do you use?

- 1 – 2 puffs / day
- 3 – 4 puffs / day
- 5 – 8 puffs / day
- >8 puffs / day

M21. Approximately how many **steroid, anti-inflammatory (brown)** inhalers (canisters) in total have you used in the past month?

- ≤ 1
- 2 – 3
- 4 – 5
- 6 – 8
- > 8

M22. Approximately how many **steroid, anti-inflammatory (brown)** inhalers (canisters) in total have you used in the past year?

- ≤ 4
- 5 – 8
- 9 – 12
- 13 – 20
- > 20

M23. Do you keep extra **steroid, anti-inflammatory (brown)** inhalers at various locations, such as at the office or in the car, just in case you forget to take your inhaler with you?

- Yes
- No [Go to Question M25]
- I don’t know
- I prefer not to answer this question

M24. Approximately how many extra **steroid, anti-inflammatory (brown)** inhalers do you have right now that you are currently using?

- 1 – 2
- 3 – 4
- 5 – 7
- ≥ 8

M25. In the past year, have you used a **long-acting bronchodilator (green)** inhaler, such as Serevent® (salmeterol) or Oxeze® (formoterol), for the treatment of your asthma?

- Yes
- No [Go to Question M28]
- I don’t know
- I prefer not to answer this question

232
M26. How regularly do you use your Serevent® or Oxeze® (green) inhaler?

- Every day
- Less than daily, but more than once a week
- Approximately once / week
- Less than once a week
- Only when I exercise
- Only when I have an asthma attack
- Other

Go to Question M28

M27. If you use your Serevent® or Oxeze® (green) inhaler every day, how many puffs per day do you use?

- 1 – 2 puffs / day
- 3 – 4 puffs / day
- 5 – 8 puffs / day
- >8 puffs / day

M28. Do you ever have prescriptions for your inhalers filled and then share the inhalers with someone else, such as another member of your family or a friend?

- Yes
- No
- I don’t know
- I prefer not to answer this question

M29. Are you currently taking a steroid (such as prednisone tablets) by mouth to control your asthma?

- Yes; How long have you been taking it? months / years
- No
- I don’t know
- I prefer not to answer this question

M30. If you are not currently taking a steroid tablet by mouth, have you had to take any at any time over the previous year?

- Yes; How many times?
- No
- I don’t know
- I prefer not to answer this question

M31. Over the past year have you used, or are you currently using, any other medications for the treatment of your asthma?

- Yes
- No
- I don’t know
- I prefer not to answer this question
M32. Can you identify these medications? (Please check all that apply)

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Currently use</th>
<th>Used in past year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advair® (salmeterol/fluticasone Combination)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combivent® (ipratropium/salbutamol Combination)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cromolyn sodium (e.g. Intal®, Rynacrom®, Cromolyn®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ipratropium bromide (e.g. Atrovent®,)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>montelukast (e.g. Singulair®,) or zafirlukast (e.g. Accolate®,)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nedocromil (e.g. Tilade®,)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>theophylline (e.g. Theo-Dur®, Quibron®, Slo-Bid®, Uniphyl®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>other: please specify:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

M33. Do you use a spacer with any of your inhalers?

- [ ] Yes
- [ ] No
- [ ] I don't know
- [ ] I prefer not to answer this question

M34. Other than your asthma, do you have any other chronic diseases (such as high blood pressure, arthritis, diabetes, angina, depression) that have been diagnosed by your doctor?

- [ ] Yes
- [ ] No
- [ ] I don't know
- [ ] I prefer not to answer this question

M35. If you have other chronic diseases in addition to your asthma, can you list these diseases?

1. 
2. 
3. 
4. 
5. 
6. 
7. 
8.
M36. Overall, how would you describe the severity of your asthma?
[Please circle one]

1
Very Mild
2
Mild
3
Moderate
4
Severe
5
Very Severe

M37. Overall, how would you classify the control of your asthma?
[Please circle one]

1
Very Well
2
Well
3
Adequately Controlled
4
Not Well Controlled
5
Not Controlled At All

M38. Below is a line with '0' at the left-hand end and a '1' at the right-hand end. The '0' represents "death", the '1' represents "perfect health", and the area in between represents a state of health somewhere in between. Make a mark on the line at the point that you feel represents how you feel today.

CONTINUE TO SECTION IV
**SECTION IVa: WORK STRESSES**

The following is a series of statements that might use to describe their job and working environment. Complete this section only if you currently work at a job. If you have more than one job, respond to the statements as they would pertain to your main job. Please indicate if you STRONGLY AGREE, AGREE, NEITHER AGREE NOR DISAGREE, DISAGREE, OR STRONGLY DISAGREE with the statements. The answers are as follows:

1 = STRONGLY AGREE  
2 = AGREE  
3 = NEITHER AGREE NOR DISAGREE  
4 = DISAGREE  
5 = STRONGLY DISAGREE

<table>
<thead>
<tr>
<th></th>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Neither Agree nor Disagree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>WK1</td>
<td>Your job requires you to learn new things.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>WK2</td>
<td>Your job requires a high skill level.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>WK3</td>
<td>Your job allows you freedom to decide how to do your job.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>WK4</td>
<td>Your job requires you to do things over and over.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>WK5</td>
<td>Your job is very hectic.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>WK6</td>
<td>You are free from conflicting demands that others make.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>WK7</td>
<td>Your job security is good.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>WK8</td>
<td>Your job requires a lot of physical effort.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>WK9</td>
<td>You have a lot to say about what happens in your job.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>WK10</td>
<td>You are exposed to hostility of conflict from people you work with.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>WK11</td>
<td>Your supervisor is helpful in getting the job done</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>WK12</td>
<td>The people you work with are helpful in getting the job done.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
**SECTION IVb: SELF ESTEEM AND MASTERY**

This section is a series of statements that people might use to describe themselves. Please indicate if you STRONGLY AGREE, AGREE, NEITHER AGREE NOR DISAGREE, DISAGREE, OR STRONGLY DISAGREE. The answers to these statements are as follows:

1 = STRONGLY AGREE  
2 = AGREE  
3 = NEITHER AGREE NOR DISAGREE  
4 = DISAGREE  
5 = STRONGLY DISAGREE

<table>
<thead>
<tr>
<th></th>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Neither Agree nor Disagree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ES1</strong></td>
<td>You feel you have a number of good qualities.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>ES2</strong></td>
<td>You feel that you're a person of worth at least equal to others.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>ES3</strong></td>
<td>You are able to do things as well as most other people.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>ES4</strong></td>
<td>You take a positive attitude toward yourself.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>ES5</strong></td>
<td>On the whole, you are satisfied with yourself.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>ES6</strong></td>
<td>All in all, you're inclined to feel you're a failure.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>MS1</strong></td>
<td>You have little control over things that happen to you.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>MS2</strong></td>
<td>There is really no way you can solve some of the problems you have.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>MS3</strong></td>
<td>There is little you can do to change many of the important things in your life.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>MS4</strong></td>
<td>You often feel helpless in dealing with problems of life.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>MS5</strong></td>
<td>Sometimes you feel you are being pushed around in life.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>MS6</strong></td>
<td>What happens to you in the future mostly depends on you.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>MS7</strong></td>
<td>You can do just about anything you really set your mind to.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>Neither Agree nor Disagree</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>---</td>
<td>----------------</td>
<td>-------</td>
<td>-----------------------------</td>
<td>----------</td>
<td>-------------------</td>
</tr>
<tr>
<td>ES8</td>
<td>There are truly no effective treatments for asthma.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>ES9</td>
<td>Serious asthma symptoms can be prevented in most cases.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>ES3</td>
<td>Treatments available today can control asthma so that patients can lead normal, symptom free lives.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>