THE EFFECT OF EXCESS WEIGHT ON ASTHMA CONTROL AMONG CHILDREN

Gladys A. Osien, MSc Candidate
McGill University, Montreal
July, 2015

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science in Experimental Medicine

Table of Contents

Acknowledgements 4
Abstract 6
Résumé 8
1.0 Introduction 10
1.1 Background 10
Overview of the Problem: Asthma, Obesity and Asthma Control 10
Obesity and Asthma Control 11
1.2 Study Objective 13
2.0 Review of the Literature 14
2.1 Asthma Control 14
Asthma Control vs. Asthma Severity 14
Measuring Asthma Control 15
Medications 22
2.2 Asthma and Obesity 30
2.3 Effect of Excess Weight on Asthma Control 35
Research Gap and Impact of this Study 38
3.0 Methods 39
Study Design 39
Study population 39
Data Sources 40
Primary Outcome 42
Secondary Outcomes 43
Main Exposure – Excess Weight 44
Covariates 44
Asthma Severity 46
Statistical analysis 46
4.0 Results 48
Primary Outcome: Effect of Excess Weight on use of β_2 -agonist 53
Secondary Outcome: Effect of Excess weight on Acute Care Visits, Hospital Admissions and OCS Use 62
Sensitivity Analysis 65
5.0 Discussion 69
Secondary Outcomes (Acute Care Visits, OCS use, Hospitalization) 74
Composite Outcome 76
Limitations of Research 78
Conclusion 82
Possibilities for future research 83
Appendix I 98
Appendix II 100
Appendix III 102
Appendix IV 103
Appendix V 104

List of Tables and Figures

Tables

TABLE 2.1:SUMMARY OF VALIDATED SELF-REPORTING TOOLS THAT ASSESS ASTHMA CONTROL QUESTIONNAIRES. 21
TABLE 4.1:SAMPLE CHARACTERISTICS OF PARTICIPANTS WITH AND WITHOUT PUBLIC DRUG PRESCRIPTION COVERAGE 49
TABLE 4.2:BASELINE CHARACTERISTICS OF THE STUDY POPULATION 51
TABLE 4.3: HEALTH SERVICES AND OCS USE 52
TABLE 4.4: ASTHMA CONTROL STRATIFIED BY WEIGHT 54
TABLE 4.5: EXCESS WEIGHT AND POOR ASTHMA CONTROL: SUMMARY OF CRUDE EFFECTS 57
TABLE 4.6: EXCESS WEIGHT AND POOR ASTHMA CONTROL: SUMMARY OF ADJUSTED EFFECTS OF FINAL MODEL 58
TABLE 4.7: EXCESS WEIGHT AND POOR CONTROL: ADJUSTED EFFECTS STRATIFIED BY SEVERITY TYPE 61
TABLE 4. 8: EXCESS WEIGHT AND OCS USE, ACUTE CARE VISITS, HOSPITAL ADMISSION: SUMMARY OF CRUDE EFFECTS 63
TABLE 4.9: EXCESS WEIGHT AND POOR ASTHMA CONTROL: SUMMARY OF ADJUSTED EFFECTS OF FINAL MODEL 64
TABLE 4.10: EXCESS WEIGHT AND COMPOSITE POOR CONTROL: CRUDE EFFECTS OF COMPOSITE OUTCOME 67
TABLE 4.11– EXCESS WEIGHT AND COMPOSITE POOR CONTROL: ADJUSTED EFFECTS OF COMPOSITE OUTCOME 68

Figures

FIGURE 2.1: STEP-UP TREATMENT RECOMMENDATIONS TO MAINTAIN ASTHMA CONTROL. 24
FIGURE 2.2: STEP-UP TREATMENT RECOMMENDATIONS TO MAINTAIN ASTHMA CONTROL (CHILDREN 5 YEARS AND YOUNGER)..... 24
FIGURE 3.1: STUDY POPULATION SELECTION..... 40

FIGURE 4.1**:** DISTRIBUTION OF MEAN B_2-AGONIST DOSE PER WEEK.. 53
FIGURE 4.2:PATIENT PROFILE OF PARTICIPANTS 55
FIGURE 4.3: DISTRIBUTION OF MEAN B_2-AGONIST DOSE PER WEEK. SAMPLE DISTRIBUTION OF THE MEAN DOSE OF B_2-AGONISTS USED PER WEEK, STRATIFIED BY SEVERITY. 60
FIGURE 4.4: PATIENT PROFILE OF ACUTE CARE VISITS, HOSPITAL ADMISSIONS AND OCS USE PER WEIGHT GROUP. THIS INFORMATION WAS COLLECTED FROM DOCUMENTED ASTHMA RELATED VISITS IN THE MED-ECHO DATABASE. 62
FIGURE 4.5: PATIENT PROFILE OF PARTICIPANTS THAT WERE CATEGORIZED AS "POOR CONTROL" 66

Acknowledgements

I am extremely grateful for the opportunity to present this thesis. I would like to thank my co-supervisors Drs. Gillian Bartlett and Tracie Barnett for making this possible. I met Dr. Gillian Bartlett while working as Research Assistant. I was immediately drawn by her expertise and knowledge in the field of pharmacoepidemiology. Throughout my time at McGill, I was exposed to the tools, knowledge and experiences needed to succeed. I am grateful for not only the support, the countless editing and encouragement in completing this thesis but also the opportunity to engage in research and policy. Dr. Bartlett supported numerous opportunities for me to learn from peers by facilitating my attendance to Pharmacare 2020 Conference and two North American Primary Care Research Group Conferences (NAPCRG). And also by supporting my Pharmaceutical Policy Research Collaboration Fellowship as well as my travels to Taiwan to explore my interests in international health policy, both of which have been life-altering experiences. I truly believe that this thesis, and the opportunities and experiences that came alongside would not have been possible without Dr. Bartlett. I would also like to thank Dr. Tracie Barnett, who encouraged me throughout this process and spent countless time and effort to ensure that the final product is a true reflection of the effort that was put in. I would like to thank Dr. Barnett not only for her very close attention to detail, and her guidance throughout this but also for what I'd like to call her optimistic realism and always honest and constructive feedback. This project would not be possible without Dr. Barnett whose original proposal on the influence of neighborhood characteristics and obesity on asthma outcomes in children inspired this work.

I would like to thank Dr. Francine Ducharme. As a member of my thesis committee, Dr. Ducharme provided the clinical and analytical perspective that I needed to complete this project as well as the countless feedback in the writing of this thesis. In addition, the use of Dr. Ducharme's database was instrumental in completing this research. I would also like to thank Cristina Longo, as an honorary member of my committee. Cristina helped me tirelessly in the analysis portion, going above and beyond for me. In her capacity, she was my friend, lifeline, statistician,

SAS whisperer and mentor from start to finish. I am so grateful for the assistance and constant motivation that she has provided me with.

I would also like to acknowledge St. Justine Hospital, the Canadian Institute for Health Research for supporting Dr. Barnett's grant entitled: *Investigating the influence of neighbourhood characteristics and obesity on asthma outcomes in children and adolescents*, the Department of Family Medicine at McGill, the Experimental Medicine Division of the Department of Medicine and Dr. Elaine Davis at the Faculty of Medicine Research and Graduate Studies who supported me financially in the undertaking of this project and my graduate studies.

I would like to thank my parents, Andel and Nelly who teach me every day the importance of persistence and resilience. This was the ultimate test. Also, thank you to my siblings Neil, Murielle and Glen as well as my dear friend Betiel who always motivate and support me.

Abstract

Background: Asthma is the most common chronic pediatric illness in developed countries with nearly 10 million affected in North America. Patients affected with the disease can function without compromising their quality of life if the appropriate clinical treatment guidelines for optimal asthma management are used. However, 50% of patients fail to abide by the guidelines and in turn experience poor asthma control. Due to the physiological differences in overweight children with asthma, the effect of obesity on poor asthma control can lead to more serious outcomes. As a result of the documented physiological differences and pharmacokinetics, overweight children with asthma may experience poor asthma control.

Objective: The objective of the study is to determine to what extent weight affects asthma control among children in Quebec.

Methods: A retrospective historical cohort study was conducted from an existing *Régie De L'Assurance Maladie du Québec* (RAMQ) dataset generated from a population-based follow-up study. The sampling frame consisted of children aged 2-12 presented at the Montreal Children's Hospital Asthma Center (Canada, Quebec) between January 1st 2002 and December 31st 2007, a final sample of 817 was obtained. Data was collected from information documented in the RAMQ, *the Quebec Provincial Drug Plan* and the *MED-ECHO database.* Study participants were classified under normal weight (BMI < 85th percentile) and excess weight (BMI 85th > percentile).

Data Analysis: Basic descriptive statistics were produced to describe the study sample and test relationships of key variables with weight and asthma control. Univariate and multivariate logistic regression analyses were performed to test the hypothesis that excess weight children with asthma experience poor asthma control in comparison to normal weight children as indicated by predictors. The primary indicator was measured as the use of short-acting b2-agonists (SABA) defined by North American and International standards. The secondary outcome was measured as the rate of asthma related acute care visits, hospital admission

and use of oral corticosteroids (OCS) during the one-year follow up.

Results: Excess weight was found not to be associated with the use of b_2 agonists and by extension, asthma control (OR=1.15, 95% CI 0.83-1.58). In addition, excess weight was not associated with acute care visits, hospital admission or the use of OCS.

Conclusion: An association between excess weight and the use of SABA and by extension, asthma control was not observed, these results are congruent with some published literature. However, we speculate that with a larger sample size we would be able to make more accurate inferences in the extent to which excess weight affect the use of $ß_2$-agonists.

Résumé

Contexte : L'asthme est la maladie chronique la plus fréquente en pédiatrie dans les pays développés avec près de 10 millions de personnes touchées en Amérique du Nord. Les patients qui souffrent de l'asthme peuvent fonctionner sans compromettre leur qualité de vie pourvu qu'ils suivent les directives de traitement clinique approprié. Cependant, 50% des patients ne parviennent pas à respecter les lignes directrices et ont du mal à contrôler leur asthme. A cause des différences physiologiques entre les enfants en surpoids et ceux en poids normal qui souffrent d'asthme, l'effet de l'obésité sur le contrôle de l'asthme peut conduire à des conséquences graves. Pourtant nous pensons que les enfants en surpoids, à cause des différences physiologiques et pharmacocinétique documentées, ont plus de difficulté à maîtriser leur asthme.

Objectif: L'objectif de l'étude est de déterminer dans quelle mesure le poids affecte le contrôle de l'asthme chez les enfants au Québec.

Méthodes: Une étude de cohorte historique a été menée à partir d'un ensemble de données existant du Régie de l'assurance maladie du Québec (RAMQ) généré à partir d'une étude de suivi basée sur la population. La base de sondage comprenait des enfants âgés de 2-12 présentés à l'Hôpital de l'asthme Centre de Montréal pour enfants (Canada, Québec) entre le 1er Janvier 2002 et le 31 Décembre 2007 nous avons eu un total de 817 participants. Les données ont été recueillies à partir des informations documentées dans la RAMQ, le régime d'assurance médicaments provincial du Québec et de la MED base de données -ECHO. Les participants ont été classés dans le poids normal (IMC < 85 ème percentile) et l'excès de poids (IMC 85ème > percentile).

Analyse des données: les statistiques descriptives de base ont été produites pour décrire l'échantillon de l'étude et les relations de test des variables clés de poids et le contrôle de l'asthme. Analyses de régression logistique univariée et multivariée ont été réalisées pour tester l'hypothèse que les enfants de poids en excès n'ont pas un bon contrôle de leur asthme comparé aux enfants de poids normal, comme

indiqué par des prédicteurs (ou indices?). L'indicateur principal a été mesuré comme l'utilisation de β_2- agonistes définies par les normes nord-américaines et internationales. Le résultat secondaire a été mesuré comme le taux de visites de soins liées à l'asthme, admission à l'hôpital et l'utilisation de corticostéroïdes par voie orale au cours d'une année.

Résultats: Nous avons trouvé que l'excès de poids n'est pas liée à l'utilisation d'agonistes β_2 (OR=1.15, 95% CI 0.83-1.58), ni les visites de soins liées à l'asthme, admission à l'hôpital et l'utilisation de corticostéroïdes par voie orale.

Conclusion: Aucune association entre l'excès de poids et l'utilisation du médicament β_2- agonistes n'a été observé. Ces résultats sont comparables avec ceux de la littérature publiée sur cette recherche. Cependant, nous pensons qu'avec une population d'étude plus large, nous serions en mesure de tirer des conclusions plus précises entre l'effet du poids sur le contrôle de l'asthme.

1.0 Introduction

1.1 Background

Overview of the Problem: Asthma, Obesity and Asthma Control

Asthma can be defined as a chronic inflammatory disorder of the airways. The disease is associated with airway hyper-responsiveness causing wheezing, chest tightness and coughing [1, 2]. Asthma is the most common chronic pediatric illness in developed countries with nearly 10 million affected in North America [1]. In 2007, approximately 15.6% Canadian children between 4 and 12 years of age were diagnosed with asthma [3]; an escalation from 13% reported in 2001 and 11% reported in 1999 [4]. This disease has a significant impact on the quality of life of patients and their families due to significant morbidity and mortality [1, 3]. In addition, asthma carries a significant economic burden. Chronic lung diseases, including asthma, cost $13 billion with $3.4 billion in direct health care costs and $8.6 billion in indirect costs in Canada [5]. Costs include hospitalizations, medications, and loss of potential earning in parents due to loss of work days to care for children and school absenteeism [4].

Asthma control commonly measures the adequacy of asthma management and is directly related to the burden asthma imposes on children and their families. Asthma control is defined as the extent to which the various manifestations of asthma have been avoided or reduced by treatment [6]. The Canadian Pediatric Asthma Consensus Guidelines have issued clear recommendations to gauge the level of asthma control in children using six clinical and a lung function test criteria [7]. Clinical level of asthma control is gauged from features such as daytime and nighttime asthma symptoms, use of rescue β_2-agonists, and the extent to which the patient, in this case the child, can carry out activities of daily living, school absenteeism, and the frequency and severity of asthma flare-ups. Asthma control also includes the risk of future adverse events including the inadequate control exhibited by exacerbations and a decline in lung function [8, 9, 10, 11]. Severe exacerbations more commonly occur in children with poorly controlled asthma [8]. In addition to

long-term poor health outcomes, a lack of asthma control has also been associated with increased health care utilization [8, 9, 11, 12]. Suboptimal management interferes with quality of life and is associated with increased use of rescue asthma medications[i] [6] and thus increased use of health care resources [9]. The lack of asthma control in childhood may also carry long-term consequences in adulthood with irreversible limitations in lung function [8].

The Canadian Pediatric Asthma Consensus Guidelines provide evidence-based recommendations for the optimal management of asthma in children [10]. The management of preschool-aged children is more challenging in part due to the difficulty in accurately distinguishing those with intermittent versus persistent asthma without standard lung function testing that is only feasible in children aged 6 years and over. In general, however, the Guidelines recommend the use of daily low-dose controller asthma medications for all children with persistent asthma, with the exception of those with very mild symptoms. Inhaled corticosteroids (ICS) are the gold standard treatment for controller medications, with leukotriene receptor antagonists (LTRA) serving as a second option for monotherapy in children aged 2 years and above [10]. While it is important that children with asthma receive adequate treatment to help with asthma control; there are other factors that may impede achievement of asthma control.

Obesity and Asthma Control

One of the factors that has begun to be linked to asthma incidence in children is excess weight. The prevalence of obesity amongst children has been on the rise since approximately 1970. Approximately one third (31.5%) of 5-17 year olds are overweight or obese in Canada. Between the years 2009-2011, this translated to approximately 1.6 million children, of which 19.8% were classified as overweight, while 11.7% were categorized as obese [13]. More importantly, obesity is becoming an increasingly prevalent in pediatric asthma [14]. In a longitudinal study of 3 792 children by Gilliland et al, the risk of new onset asthma was higher among children who were overweight (relative risk, RR=1.52, 95% CI: 1.14, 2.03) or obese

[i] *Rescue asthma medications* are also known as reliever medications and are used for quick relief of asthma symptoms. Rescue asthma medications usually act within minutes to temporarily relieve symptoms.

(RR=1.60, 95% CI: 1.08, 2.36) than the risk among normal weight children [15]. These results were found in several other longitudinal studies [16, 17, 18].

There has also been an increasing amount of evidence linking excess weight to a rise in asthma morbidity [15, 16, 19-33]. The link between excess weight and asthma morbidity in children that has been documented [14] is very complex and the mechanism underlying this relationship remains elusive [34, 35, 36]. Asthma is an inflammatory disease of the airways and the proposed physiological indications linking asthma and obesity have been largely attributed to the inflammatory nature of excess adipose tissue in obese individuals. More precisely, hormones such as leptin, that is present in higher concentration in obese people, also have pro-inflammatory effects that exacerbate the inflammatory response in individuals with asthma. The link between excess weight and asthma morbidity is supported by the finding of substantial improvements in asthma morbidity that have been observed following weight loss [37, 38].

Given these findings, overweight and obese children with asthma may constitute a unique asthma type that is more difficult to manage [19]. Overweight children with asthma have been found to be more resistant to available steroid treatments requiring more medication [19, 39, 40]; to experience more frequent hospitalizations; and to have more asthma symptoms when compared with normal weight children with asthma [15, 16, 41, 21]. Pediatric obesity has also been associated with several other indicators of poor asthma control, including increased perceived asthma severity, higher rates of school absenteeism, lower pulmonary function and a greater number of prescribed asthma medications [23, 42, 43].

While some indicators of asthma control have been investigated, there is a need for a more systematic and thorough investigation into the association of asthma control for children with and without excess weight after controlling for other factors that can impact asthma control. The focus on asthma control is specifically of interest as it affects both short-term and long-term asthma morbidity. Children who achieve asthma control are less likely to suffer negative health outcomes as adults thus, potentially decreasing current and future asthma-related expenditures [6]. Investigating the effect of excess weight on asthma control in children within a large cohort while controlling for other factors affecting asthma control, such as reported

severity, sex, gender, and co-morbidities can provide initial information for the development of more targeted initiatives to achieve optimal asthma control.

1.2 Study Objective

The primary objective of this study is to determine, among children diagnosed with asthma, the extent to which being overweight or obese affects asthma control as measured primarily by the use of β_2-agonists (rescue medication), and secondarily by markers of moderate or severe exacerbations which include the use of oral corticosteroids, emergency department (ED) visits and the occurrence of hospital admissions.

2.1 Asthma Control

Asthma control has been shown to be suboptimal in the majority of Canadians despite available effect pharmacological treatments and evidence-based practice guidelines [44, 45, 46, 47, 48]. In a population survey across Canada targeting more than 26, 000 households, of 893 asthmatic patients, 53% were found to have uncontrolled asthma [44]. Suboptimal asthma control is associated with reduced quality of life, [44, 49] more asthma symptoms, and an increased risk of exacerbations and mortality [50, 51, 44]. An overview of the literature will provide information on current studies on asthma control and the potential impact of obesity.

Asthma Control vs. Asthma Severity

Asthma control and asthma severity are often used interchangeably [8], despite there being a distinction between the two [8, 9, 49, 52-55]. Severity can be defined (1) by the intensity of therapy required to maintain good control [8] or (2) measured by the level of asthma control in the absence of treatment [56, 8]. For the first definition, when asthma is well controlled on a low dose of controller medication (inhaled corticosteroids, ICS), the severity is considered to be mild; if it requires either moderate dose ICS or low ICS dose with adjunct therapy (e.g. leukotriene receptor antagonist, or long acting ß$_2$-agonists) it is considered to be moderate; and if high dose of ICS with or without adjunct therapy is needed, the patient's asthma is considered to be severe. This interpretation of severity is highly dependent on patient adherence to therapy, which is often over reported by patients which has led to severity being routinely overestimated. Consequently, since the year 2009, the use of the term 'severity' with this definition has been on the decline. For the second definition, asthma severity refers to the severity of symptoms experienced daily and/or the clinical severity of acute exacerbations. The severity of an acute exacerbation where the use of rescue β_2-agonists alone is sufficient usually indicates a mild exacerbation; an emergency department visit and/or use of rescue oral steroids signals a moderate exacerbation; and a hospital admission is a marker of a severe

exacerbation. In this case, severity is referring to the intensity of asthma exacerbations [57].

Asthma control, in contrast to asthma severity, can be measured by lung function; intensity and frequency of symptoms; and interference with daily activities. Asthma control can be measured irrespective of therapy or adherence to therapy. The Canadian Asthma Consensus Guidelines define good control as daytime symptoms fewer than four times a week, night time symptoms less than once a week, no limitations on physical activity, mild and infrequent exacerbations, no absences from school or work and fewer than four doses a week of short-acting-β_2-agonists. Exceeding the limits set for two or more these criteria would constitute uncontrolled asthma [58].

The level of control is a short-term evaluation of the patient's management; most instruments for assessing control use the previous 7 or 30 days as a time frame. Although increasing severity is commonly associated with poorer control, it is possible for a patient to have severe asthma that is well controlled using an appropriate amount of medication. The reverse is also true; one can have mild asthma severity with poor control due to insufficient medication intake (either due to poor technique or poor compliance), ongoing exposure to triggers, or other co-morbidities. When investigating associations between risk factors for asthma, it is thus of interest to measure both the severity of exacerbations and at the same time ascertain the level of asthma control.

Measuring Asthma Control

An important step towards the improvement of asthma control is an accurate assessment in the patient; this includes perceived and non-perceived limitations due to asthma [59]. In the current literature, clinical asthma control is measured mostly by questionnaires that are completed by patients [59]. A more objective assessment of asthma control, however, is to measure lung function, known as the FEV_1 [60, 61, 62]. The Canadian Guidelines recommends 6 clinical criteria of asthma control in addition to measurement of lung function. The two measures (clinical criteria of asthma control and lung function) are complementary and provide a more complete perspective on asthma control. There is some evidence, however, suggesting that lung function does not relate well to the asthma symptoms experienced in children [63,

57]. The FEV_1, however, at less than 60% predicted, is a strong predictor for the risk of experiencing exacerbations. When a normal or high FEV_1 (indicating good lung function) is found in patients with frequent asthma or respiratory symptoms other possible causes for the respiratory symptoms such as cardiac disease are usually investigated [57].

Despite this, lung function is infrequently assessed in children with asthma. A substantial proportion of parents have indicated that their child never received a lung function test, thus making questionnaires the most frequently used tool for the assessment of asthma control in the pediatric population [59, 64, 65, 66]. This is supported by the fact that there are age-related differences in the ability to cooperate with lung function testing, standard lung function tests (spirometry) are less likely to be performed in children below the age of 6 years because of difficulty in cooperating with the forced expiratory maneuver [67]. Often preschoolers are excluded from therapeutic studies due to their inability to perform accurate and replicable spirometry. Other measures such as the respiratory resistance have been found to be effective in preschoolers. The method measures respiratory systems using the forced oscillation (Rfo)[ii] technique. It is reported to be as sensitive as values obtained by spirometry [68]. Peak expiratory flow (PEF)[iii] may be used to assess response to treatment after a diagnosis, to evaluate triggers and derive action plans [57]. Fluctuations in the PEF are associated with sub-optimal control and increased risk of exacerbations in adults [69]. The Canadian Guidelines do not recommend home monitoring of peak expiratory flow (PEF) in children [10] because routine PEF monitoring has poor accuracy in children [64, 70].

Global Initiative for Asthma (GINA) guidelines state that if the tool used to measure asthma control includes symptom items, then it can outweigh the differences in lung function [71]. Therefore, there is value in using merely questionnaires to evaluate asthma control. Despite providing a subjective perspective on asthma control

[ii] Forced oscillation (Rfo), non-invasive technique in which respiratory resistance is measured. This is done by taking the measure of stable tidal breathing and imposing small pressure waves. The resistance of the respiratory system is calculated based on the change in flow generated by the pressure waves.

[iii] Peak expiratory flow (PEF), also called the peak expiratory flow rate (PEFR), is an individual's maximum speed of expiration (airflow) during a forced expiration beginning with the lungs fully inflated. The value is measured by a hand-held device called peak flow meter which is a tool used to monitor an individual's ability to breathe out air.

[72], questionnaires are widely used; they are cost-efficient and practical in clinical use [59]. In fact, several questionnaires have been developed to determine at which level a child may be considered to have controlled versus uncontrolled asthma. This is particularly important as parents, when asked about their child's asthma; tend to underestimate the severity while overestimating the degree of asthma control [59]. Studies have identified a disparity between actual and perceived asthma control when comparing proxy or self-reports and assessment questionnaires [64]. This discordance may be attributed to the different interpretations of the term "control" which are defined differently by parents, health professionals and children [57]. In a study by Rabe and colleagues conducted in Western Europe, only 52 % of children that were considered to have controlled asthma by their parents had good asthma control as assessed by questionnaires while 35% and 14% had poor and moderate asthma control respectively [64]. Similar findings have been found in a Canadian study where parents were found to overestimate the quality of their child's asthma control, with 47% reporting their child's asthma as well controlled when questionnaires revealed that their child's asthma was poorly controlled [73]. Questionnaires have an added benefit of being able to provide the parent and child's perspective, which might be discrepant. While Lara et al demonstrated that children reported symptoms that correlated better with FEV_1 testing and observed symptoms than parent reported symptoms [74], another study by Guyatt et al reported the opposite finding. Children younger than 11 years reported symptoms that highly correlated with quality-of-life measures while parents' report of asthma symptoms showed better correlations with the FEV_1 values [75]. Despite the reported poor correlations between the symptoms reported by children versus their parents [76, 77, 78, 74, 75], children and parental reporting should not be discounted.

Validated instruments for assessing asthma control in children include the Asthma Therapy Assessment Questionnaire, the Asthma Control Questionnaire, the Global INitiative for Asthma (GINA) Questionnaire as well as the Asthma Quiz for Kidz and Childhood Asthma Control Test which cater specifically to children and account for the perspective of a caregiver. These questionnaires will be explored in detail in the section that follows.

Asthma Therapy Assessment Questionnaire (ATAQ)

The Asthma Therapy Assessment Questionnaire (ATAQ) for children and adolescents (5-17 years) provides a multidimensional measure of asthma control over a period of a year [79]. The ATAQ assesses control based on a brief series of seven dichotomously scored questions. It is based on four dimensions that consist of nocturnal wakening, interference with activities, overuse of reliever medications and self-perception of poor control in the past month or past 12 months. The ATAQ control index shows a striking correlation with generic as well as asthma-specific measures of quality of life with self-reported, short-term health care utilization indicated by cross-sectional study of over 5 000 patients [8, 9, 33]. The ATAQ that is specific to children is intended to be completed by parents of children aged 5 to 17 years and also includes questions on patient-provider communication as well as questions on attitudes and behaviours [79]. This questionnaire has not been validated for pre-school aged children. This is important to note, as preschool aged children constitute more than 50% of all children presenting to the emergency department with acute asthma and account for a substantive proportion of children seen in the clinic setting [68].

Asthma Control Questionnaire

The asthma control questionnaire (ACQ) reported by Juniper et al [80, 81] has been shown to be a useful tool in measuring asthma control. The ACQ consists of 7 questions that explore multiple dimensions of control including nocturnal awakening, daytime symptoms, interference with activities, and overuse of reliever medication and lung function. Each of the questions are coded on a 7-point scale and are averaged to obtain an overall score in a 7-day time period for school-aged children [81, 80]. The questionnaire however is limited in that it is only for children above the age of 12. However, it does simplify the complexity of control into a short questionnaire and also provides a short recall.

Asthma Control Test

The Asthma Control Test (ACT) measures 5 dimensions of asthma control: the impact of asthma on role functioning, patient's rating of asthma control, shortness of breath, nighttime awakenings, and rescue medication use [82]. The ACT was developed as a population-screening and monitoring tool. The self-administered

survey is designed for patients that are 12 years or older. The ACT sums the responses for each of the five items referring to the past 30 days, to produce a final score ranging from 5 (poor control) to 25 (complete control). A score less than 19 indicates that a patient's asthma may not be controlled. Studies have demonstrated a correlation between ACT score and changes in asthma control as measured by physician global ratings as well as the FEV_1[iv] values. The ACT has been shown to also identify high-risk adolescent patients [83]. In addition, an adjusted ACT has been created for children of 4-11 years, often referred to as the C-ACT. The C-ACT, refers to the Childhood Asthma Control Test. It was developed based on the framework developed from the National Asthma Education and Prevention Program (NAEPP) guidelines, GINA guidelines as well as the input from 10 childhood asthma and allergy specialists. The questions were formatted and derived from the participation of 22 children with asthma as well as 14 caregivers of diverse ethnicities. In a cross-sectional validation study, the C-ACT has been shown to reliably measure and assess asthma control in children 4-11 years [84]. In addition to covering all components of the recommended GINA and NAEPP guidelines, the C-ACT considers the perspective of the guardian/parent.

Global Initiative for Asthma (GINA) Questionnaire

Bateman et al proposed a formal measure of control in adults based on the Global Initiative for Asthma (GINA) 1991 guideline [53]. The Global Initiative for Asthma (GINA) is a collaborative international initiative organization that provides international guidelines on asthma. GINA describes the goal of asthma control as the prevention of troublesome symptoms, the prevention of future risks (which includes exacerbations), the achievement of normal pulmonary functions and the ability to lead a productive, physically active life [57]. While testing the reliability of the instrument, Bateman concluded that reliance on individual measures of control is likely to result in significant overestimation of true control and thus they must be

[iv] FEV_1 is the forced expiratory volume in the first second. It is the volume of air that can be forced out in one second after taking a deep breath. It is a measure of pulmonary function. The FEV_1 is converted to a percentage of normal where FEV_1>80% is normal; FEV_1 of 60-79% of predicted indicates mild obstruction; FEV_1 of 40-59% of predicted indicates moderate obstruction, while FEV_1 less than 40% of predicted indicates severe obstruction (National Heart, Lung, & Blood Institute).

considered together [53]. The aforementioned questionnaires have been modified to target children; the changes are most noted by the expression of children's activities within the survey. For example, instead of work absenteeism, the term "school absenteeism" is used.

Asthma Quiz for Kidz

An asthma 6-item validated questionnaire for children named "*Asthma Quiz for Kidz"* was developed to be used for children aged 1 to 17 years. The study in which the quiz was introduced tested the concordance between the parents' and child's perception of asthma control based on the quiz against a physician assessment of asthma control [80]. Previous studies have demonstrated that the quiz had good internal consistency (Cronbach alpha=0.73) and inter-rater reliability was strong with an overall 0.3 Kappa (0.77 to 0.88, 95% CI). The "Asthma Quiz for Kidz" is a questionnaire that offers a reliable and responsive measure of asthma control. The "yes" or "no" questionnaire correlates with the physician assessment of asthma control that incorporates the adult instruments (the Asthma Therapy Assessment Questionnaire and the Asthma Control Questionnaire). The Asthma Quiz for Kidz includes the measure of: (1) daytime symptoms less than four days per week, (2) night time symptoms less than one night per week, (3) use of β_2-agonist more than four times per week and (4) normal physical activity in the past well as the exacerbations and absenteeism in the past month [72].

The properties of the different questionnaires are summarized in Table 2.1.

Table 2.1: Summary of validated self-reporting tools that assess asthma control questionnaires: Asthma Therapy Assessment Questionnaire (ATAQ), Asthma Control Questionnaire (ACQ), Asthma Control Test (ACT) and the Global Initiative for Asthma (GINA) survey and Asthma Quiz for Kidz.

	ATAQ	ACQ	ACT	C-ACT	GINA	Asthma Quiz for Kidz
Age Specific Validation, y of age	5-17	≥12	≥12	4-11	≥12	1-17
Recall time period	30 days and past year	7 days	30 days	30 days	7 days	7 days
Parameters:						
Daytime Symptoms	✓	✓	✓	✓	✓	✓
Night-time Symptoms	✓	✓	✓	✓	✓	✓
Physical Activity limits	✓	✓	✓	✓	✓	✓
Exacerbations					✓	✓
Use of rescue medication	✓	✓	✓	✓	✓	✓
Self-perceived control	✓		✓	✓		✓
Absence from school	✓			✓		✓
Lung function (FEV_1 or PEF)		✓			✓	?
Adverse events					✓	?

The questionnaires described here are widely used in the assessment of asthma control [8] despite the fact that self-administered tests are often subject to response bias. In the assessment of asthma control among children, there is an additional challenge as the parent often completes the questionnaires for the child. Encouraging children to contribute to survey responses has been shown to increase validity [72]. It is also important to note that in tools made specifically for children the recall period is shorter to provide a more accurate account since asthma control may fluctuate from week to week but also to accommodate the shorter recall memory of the surveyed children [72]. There are also other aspects to consider as the

administration of these asthma control measurements often come with age restrictions. Whereas adult asthma control questionnaires can be applied to individuals 18 years of age and above, asthma control instruments cannot be used in children of all ages, which restricts the application of these tools in pediatric studies.

Despite standards in measures of asthma control, evidence suggests that physicians also may overestimate control in children [85]. In a Canadian study, 266 physicians were surveyed, of those, 81% believed they had obtained optimal control of their patients' asthma, when in fact 52% of the children had poorly controlled asthma [86]. It was hypothesized that differences in physician-perceived and actual asthma control may partly be due to variations in the criteria used to assess asthma control as outlined in Table 2.1 [87].

Although there are defined parameters in clinically categorizing a child as having controlled versus uncontrolled asthma, some have argued that some parameters may be more indicative of control than others. In a study by FitzGerald et al, the majority of Canadian physicians identified "frequency/amount of medication used" as a better indicator of asthma control than the use of questionnaires alone [44].

Medications

The 2010 Canadian Asthma Guidelines have issued evidence-based recommendations for the optimal management of asthma in children and adults in regards to medication [58]. In addition, the Canadian Pharmacists Association provides detailed pharmaceutical options in the management of asthma in children, which are slightly different from the adult recommendations. The goal of asthma therapy in infants and children is to prevent asthma symptoms from interfering with daily activities, physical exercise, school attendance or sleep. The ultimate goal of management is to maintain control with the lowest effective dose of controller medication. Clinically, the therapy should provide the child or infant with normal measures of expiratory airflow, for example, peak flows and pulmonary function [10].

Pharmaceutical Interventions for Asthma Control

In terms of achieving control, asthma medications are essentially classified under two types: reliever and controller medications that have distinct roles in the

treatment and management of asthma. Despite their differences, there is considerable confusion among patients between reliever medications and controller medications [88]. In fact, 32% of parents in the American Lung Association believed that asthma should be treated only when symptoms appear instead of prevented with daily controller medications [89] and 26% of parents in the pediatric Asthma Pan European Survey Study incorrectly believed that reliever medications were controller medications [88].

Another distinctive feature of asthma treatment is that it can be increased by steps in order to achieve control and once control is achieved, treatment can then be stepped-down to lowest possible level (the minimal effective dose) specific to the patient to maintain control; the medication will be stopped down to [59]. See figure 2.1 and 2.2 for an illustration of this process. As indicated by figures 2.1 and 2.2, several types of medications can be used to obtain control and are categorized as reliever medications, controller medications and add-on treatments [57]. Figure 2.2 is specific to individuals that are 5 years and younger. The options for controller medications are less in the 5 years and younger age group. There are only four steps in figure 2.2, compared to the five in the first figure (2.1). In addition, there are no recommendations for the use of long acting $ß_2$-agonists (LABA) in children 5 years and younger.

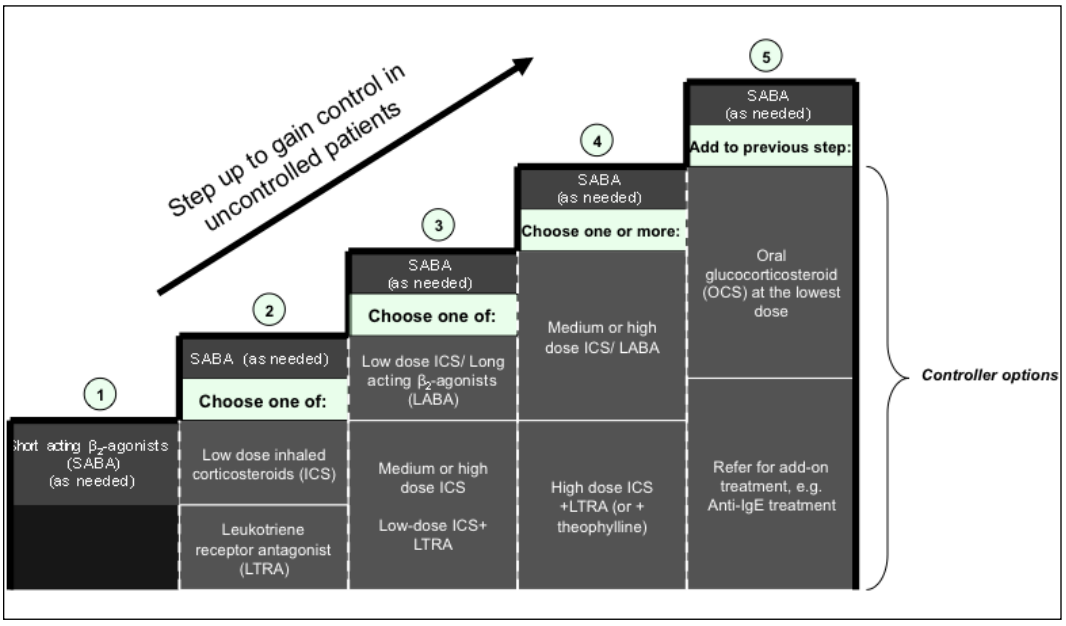


Figure 2.1: Step-up treatment recommendations to maintain asthma control adapted from Step Recommendation from the 2014 Global Initiative for Asthma (GINA) Asthma Management and Prevention guide [90].

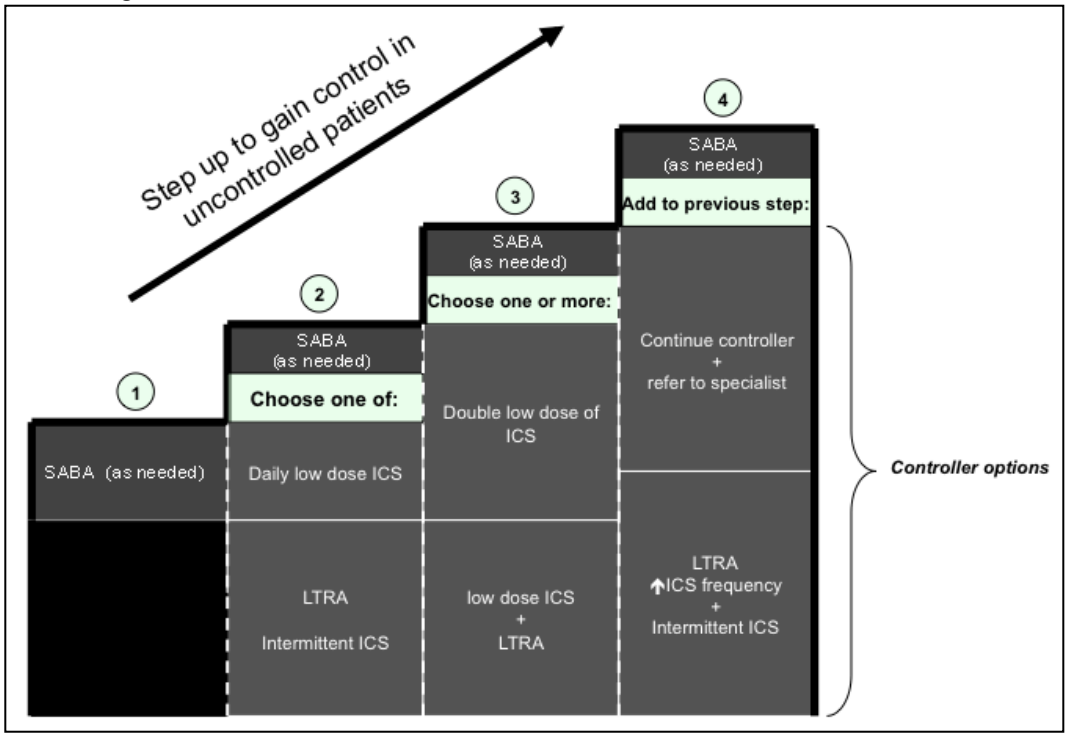


Figure 2.2: Step-up treatment recommendations to maintain asthma control adapted from Step Recommendation from the 2014 Global Initiative for Asthma (GINA) Asthma Management and Prevention guide specific to children 5 years and younger [90].

Reliever Medications

Reliever or rescue mediations provide rapid relief to asthma exacerbations by relaxing the airway smooth muscles and decreasing airway obstruction due to bronchoconstriction. The current Canadian guidelines propose inhaled short acting β_2- agonists (SABA) as the reliever drug of choice in asthma. They have been shown to be the most effective bronchodilators because of their functional antagonism of bronchoconstriction and exhibit minimal side effects [91]. When inhaled, they have a rapid onset with a duration of action of approximately 3-4 hours although this is less in severe asthma [91]. SABA have been shown to be effective in controlling asthma symptoms by improving peak expiratory flow rates and reducing asthma related symptoms [91]. The use of β_2-agonists as monotherapy is recommended as an "as-needed" basis instead of a prescribed schedule [91, 57].

The frequent use of reliever medications is often an indication of inadequate asthma control [59, 92, 93]. In a study by Lozano, 33% of patients used reliever medications at high frequency, defined as ≥3-4 doses per week [93]. This may be explained by the fact SABAs bring a rapid sense of relief to patients or the confusion between reliever medications and controller medications [59].

Controller Medications

Maintenance therapies or controller medications in asthma are anti-inflammatory agents that target the part of airway obstruction due to inflammation and secretions. These medications must be taken daily to reverse airway inflammation and prevent exacerbations and death. There are three main classes of maintenance therapy currently used in the treatment of asthma in children: inhaled corticosteroids (ICS), leukotriene receptor antagonists and long acting β_2-agonists (LABA) which are used with inhaled corticosteroids [91].

ICS are used in the treatment of many pulmonary inflammatory diseases. Corticosteroids were introduced in the treatment of asthma in the 1950s, thus they are relatively new. Inhaled corticosteroids are safe and effective for long-term use in children with asthma at recommended dosing [94-98]. Recent guidelines recommend that ICS should be used regularly by all patients with persistent asthma [58] and thus are considered first-line therapy in patients with persistent asthma. They are the most effective controller therapy available in the treatment of asthma [91]. ICS may be

used in children in the same way as in adults although used at doses of 200 ug/day of HFA beclomethasone-equivalent or more may be associated with suppressed growth in children [99, 100]. Regular use of ICS minimizes the need for reliever or rescue medications by increasing asthma control [59]. Once asthma control is achieved, recommendations state that the dose of ICS should be slowly reduced to minimal effective dose to prevent growth suppression [101, 102].

Cysteinyl-leukotrienes are increased in asthma and have significant effects on airway function, inducing bronchoconstriction, airway hyper responsiveness, and eosinophilic inflammation [103]. Blocking the leukotriene pathways with leukotriene receptor antagonists has been shown to prevent asthma symptoms. In patients diagnosed with mild asthma, LTRAs have caused a significant improvement in lung function and asthma symptoms as well as a reduction in the use of reliever medications. Despite these findings, LTRAs are considerably less effective than ICS in the treatment of asthma [57] therefore are not considered as the first treatment option [104]. On the other hand, LTRA treatment often has better compliance than ICS [105]. Consequently, the use of LTRA compared to ICS as controller medications has been found to lead to less impaired asthma control and lower risk for hospitalizations due to asthma related exacerbations [106].

Methylxanthines have been used in the treatment of asthma since 1930 and are widely used in developing countries due to their decreased cost. Despite being inexpensive, the frequency of side effects and limited efficacy has led to their reduced use in many countries. The role of methylxanthines such as theophylline is mainly to provide an additional bronchodilator effect when maximum effective doses of β_2-agonists have already been given [107]. Thus theophylline may be added to maintenance therapy [91]. Popular in the 1980's, they are no longer recommended in the chronic management of children with persistent asthma.

Unlike SABA, LABA have a bronchodilator action lasting more than 12 hours and thus protect against bronchoconstriction for a similar amount of time [108]. LABA have been shown to improve asthma control if given in appropriate dosage, compared with regular treatment with SABA which must be used four to six times daily [91]. LABA improve symptoms, exercise tolerance and exacerbations in adults but the effect is less impressive in children [109, 110]. Because of increased mortality

rates when taken alone, it is recommended that LABAs be used in combination with ICS [91]. They are recommended as one of the step-up therapies in children aged 4 years and older.

Health Canada has approved several combinations of ICS and LABA. Only one of these combinations is approved for use as both maintenance and rescue medicine such that extra inhalations can be used in the event of sudden decrease of asthma control instead of using a SABA [111]. The *Symbicort* drug is a combination of the corticosteroid (budesonide/Pulmicort®) plus a long-acting bronchodilator (formoterol/ Oxese®), and has been used mainly as an asthma controller medicine to reduce symptoms over time. Other combination therapies are recommended for use once or twice daily as maintenance therapy only. The available medications are summarized in Table 2.2.

The Canadian Thoracic Society appraised articles addressing the changes that were made in the asthma guidelines, specific to the management of asthma in preschoolers and children [58]. One of their key findings was that there was less information in the treatment recommendations for children below the age of 6 years. It was recommended that individuals above the age of 12 years that are not achieving asthma control on low doses of ICS would benefit from a combination therapy with LABA rather than an increased dose of ICS. For children aged 6-11 years that have not achieved control on low doses of ICS, it is recommended to increase ICS to a medium dose before considering adding another therapy. In the absence of head-to-head comparisons, and based on systematic review of randomized controlled trial, the best adjunct therapy to a medium ICS dose could be either a LTRA or a LABA in children [109, 110, 112-116].

Despite the availability of effective controller medications and these recommendations, many children with asthma are undertreated [59]. In particular, there is evidence of controller medications being underused in children while there is an over-reliance on reliever medications [117]. In the National Health and Nutrition Examination Survey (NHANES) study, it was found that 74% of children with moderate to severe asthma were inadequately treated, only 8% had received ICS, and only 26% had received any type of controller medication. The underuse of ICS is likely a factor contributing to poor asthma control, placing children at increased risk

of asthma exacerbations and need for emergency care [118]. Among children previously hospitalized for asthma, only 35% were reported to be receiving controller medications [119]. High use of ICS has been associated with reductions in hospitalization rates for asthma, and asthma related morbidity [120]. Studies have also shown that the over-reliance on reliever medications was reflected in the ratio of reported ICS use to SABA use which was found to be a ratio less than one for children partaking in a European study [121]. These findings were similar from that of a US study in children over the age of 5 years. A study on prescription medication use patterns in Canada demonstrated that patients who use excessive amounts of SABA together with low amounts of ICS experienced greater asthma-related morbidity and use of more medical services [122].

Table 2.2: Prescribed Asthma Medication in Children in Canada categorized by class, along with drug name and trade name.

Class	SABA	LABA	Inhaled Corticosteroids	Leukotriene Receptor Antagonist	Combination Therapy
Medication	*Salbutamol* Airomir® Ventolin® generics *Terbutaline* Bricanyl® Turbuhaler®	*Formoterol fumarate* Foradil® *Formoterol fumarate dihydrate* Oxeze® Turbuhaler *Salmeterol* Serevent®	*Beclomethasone* Qvar® *Budesonide* Pulmicort® Turbuhaler, Pulmicot®, Nebuamp® *Ciclesonide* Alvesco® *Fluticasone* Flovent® *Mometasone furoate* Asmanex®	*Montelukast* Singulair®, generics *Zafirlukast* Accolate®	Advair® (budesonide/ formoterol) Symbicort® (Fluticasone/ Salmeterol)

The device in which medication is delivered also plays an important role in its therapeutic effect and the overall management of asthma. Pressurized metered dose inhaler combined with a holding chamber is the best system for inhalation anti-asthmatic medication in preschool children [123, 124]. Hydrofluoroalkane (HFA)[v]

[v] Hydrofluoroalkane (HFA) and chlorofluorocarbon (CFC) are propellants. Propellants are key components of the pressurized metered dose inhalers (pMDI). The propellants provide the

have supplemented chlorofluorocarbon (CFC)[vi] propellants in pressurized metered dose inhalers (pMDI)[vii] because they are environmental friendly and yield good lung deposition [125]. Drug deposition in infants and young children, however, remains relatively low and thus may require similar doses as in adults [126]. In children that are above five years of age, the inhalation device may be a dry powder system, such as Diskus, Turbuhaler or a pMDI. The nebulizer is an alternative that according to GINA should be reserved for the minority of children that cannot be taught how to effectively use a spacer device [57]. The nebulizers are relatively more difficult to adhere to due to the portability, time and cost of using the device, and are rarely used in Canada [41]. In the step-wise treatment of asthma, health providers are advised to consider the appropriate use of the inhalation device first [57]. The use of the device, and thereby the intake of medication is critical for asthma management [57].

The type of asthma medication that is used by children varies with age and has often been found to not always be in accordance with guideline recommendations. Studies that measure the use of medication indicate that children experiencing poor control typically show increased use of SABA and underuse of ICS [26, 103] resulting in a low ratio of reliever to controller medications. Another marker of poor control resulting in exacerbation is the use of systemic oral corticosteroids [127]. In a recent cross-sectional study by Barbato et al, preschool children (aged $\leq$ 5 years) received significantly more oral corticosteroids and nebulized short-acting bronchodilators than older children who are more likely to receive aerosol preparations [128].

There is clear evidence that suboptimal management of asthma (notably low intake of daily controller medication) interferes with quality of life is associated with increased use of rescue asthma drugs [6] and health care resources [129] and results in severe exacerbations [8]. Although lack of asthma control in children may impact children over the long term, the regular use of ICS for children with uncontrolled persistent asthma has been associated with systemic adverse effects [99]. In a systematic review of 25 trials of which 8 471 children were examined, the regular use

---

force needed to generate aerosol and are also the medium by which the active component is suspended or dissolved for delivery.

[vi] chlorofluorocarbon (CFC) see above.

[vii] Pressurized metered dose inhalers (pMDI)[vii]- device that delivers medication into the lungs by inhalation.

of ICS at low or medium daily doses produced a reduction in linear growth velocity[viii] of 4.8 cm/y (95% CI –0.65 to 0.30) and change in height from baseline of 0.61 cm/year (95% CI -0.83 to -0.38) during a one year treatment period [99]. The effect of ICS appears to be dose-dependent. In a meta-analysis of 10 trials and 3394 children, results indicated that children in the higher ICS dose group had a lower growth velocity (0.2 cm/y) compared to those in the lower dose ICS [101].

The side effect of ICS, however, may be outweighed by the effect uncontrolled asthma on lung development. Longitudinal studies reveal a consistent average deficit in FEV1 in adolescents and adults who experienced asthma symptoms before the age of six versus those that did not [105]. This may in part be due to critical remodelling of the airway that subsequently causes irreversible long term-effect on the growth and function of the lung. This has been further illustrated by studies demonstrating airway remodelling with thickening and inflammation documented in children aged 1-3 years [84, 77, 78]. The age at onset, severity and intensity of asthma symptoms in early childhood has great impact on long-term asthma morbidity in adulthood [105]. Several studies have explored the inability to achieve control in childhood may continue to carry consequences into adulthood [74, 75].

Given the complexity of medication treatment and the that the long term effects of uncontrolled asthma can lead to irreversible damage to children that persists into adulthood, it is critical to explore other factors that contribute to asthmas severity, control and treatment. One important factor may be excess weight.

2.2 Asthma and Obesity

Obesity and asthma are considered “endemics” in developed countries and “epidemics” in developing countries [28, 130]. Overall asthma and obesity are amongst the most significant pediatric health problems in the world and represent worldwide public health priorities [131, 14]. Even a marginal increase in the mean population’s body mass index (BMI), a measure of excess weight that adjusts for height, may translate into significant changes in the incidence of asthma in

[viii] Linear growth velocity – measure obtained by measuring the height at a number of time points during the study and performing a linear regression of height over time. The resulting slop gives linear growth velocity that is expressed as cm/year.

individuals of all ages. Yet studies have found the asthma and obesity link to be very complex, as there are still conflicting ideas about the precise mechanism linking these conditions [34, 35, 36].

There are still questions on the temporality of the two diseases, meaning that it is unclear whether obesity precedes asthma or the reverse [19, 14, 26, 29, 132]. As some evidence suggests, the unclear association may be attributed to multifactorial characteristics of both asthma and obesity, as both involve genetic and environmental factors [20, 26, 32, 133]. For example, in a cross-sectional study by von Mutius et al conducted in 7 505 children aged 4 to 7 years, asthma prevalence rates were related to BMI increases. Besides finding a positive association between asthma and BMI (OR =1.77), it was also found that the increase in weight resulted in a pro-inflammatory state similar to that of asthma determined by a skin prick test [134].

In addition, factors that relate to asthma such as lifestyle habits can in turn have an effect on quality of life and may make asthmatic children more prone to less physical activities and more sedentary behaviors which subsequently play a role in the incidence of obesity [26]. The literature has also shown that non-specific respiratory symptoms of obesity can imitate symptoms of dyspnea that can be associated asthma. These include symptoms such as shortness of breath due to the elevation of the diaphragm caused by excess abdominal fat.

This has led to the hypothesis that the increased incidence of asthma seen with increased rates of obesity may be due to a misdiagnosis of asthma in obese children. This hypothesis was refuted by Aaron et al in a longitudinal study of adult non-obese (BMI 20-25) and obese (BMI $\geq$ 30) individuals. The study investigators observed that 31.8% of individuals have been misdiagnosed with asthma [135] but they found no conclusive evidence linking the misdiagnosis of asthma to obesity. A retrospective chart review of over 2 000 children referred to a pediatric pulmonologist for asthma showed a strong concordance between physician and specialist diagnosis of asthma. These findings were not affected by BMI, implying that physicians do not erroneously diagnose asthma in children due to higher BMI [19, 132]; however, it is possible that obesity creates management difficulties for asthmatic children.

Biological mechanisms have been proposed in order to associate excess weight with decreased asthma control. The physiological functions that have been

attributed to asthma as well as excess adipose tissue will be reviewed in this section.

The majority of the literature points towards leptin having a pro-inflammatory effect and thus accentuating asthma's central feature of airway inflammation. Thus, studies suggest that obesity may cause or worsen asthma though an inflammatory mechanism. The suggested mechanism is that excess adipocytes enhance systemic inflammatory activity in obesity, as the presence of leptin, an adipokine[ix] that is central to obesity and energy balance, significantly enhances the allergic and non-allergic airway responses [19, 136, 137]. Although studies have not specifically experimented with this mechanism in humans, there is evidence of an association between leptin, asthma and obesity. One particular study in children sought to evaluate the role of leptin in asthma. The crossover study of 23 participants with 20 matched controls demonstrated an association between asthma and hyperleptinemia[x]. In fact, children with asthma showed an elevated level of serum leptin (19.3 $\pm$ 5.1 ng/mL (SD)) than those of controls (9.8 $\pm$ 1.6 ng/mL(SD), $p<0.001$). A four-week treatment with inhaled corticosteroids normalized leptin levels to that of children without asthma as there appeared to be no significance between that of treated asthmatic children (10.6 $\pm$ 1.6 ng/mL) and healthy controls (9.8 $\pm$ 1.6 ng/mL) [138]. Mai et al also demonstrated this in a case-control study of 172 children with obesity and asthma, where a low serum concentration of leptin was protective for the development of asthma. The median levels of leptin serum were significantly higher in overweight children (18.1 ng/mL) than in non-overweight children (2.8 ng/mL). Hence, they concluded that high leptin concentration have an effect on the development of asthma [139].

Obesity has also been associated with systemic oxidative stress, and researchers have proposed that oxidative stress due to obesity may cause airway oxidative stress and inflammation that can lead to asthma [19]. A cross-sectional analysis by Sood et al assessed oxidative stress by plasma F2-isprostane[xi] concentrations, while measuring obesity using BMI and DEXA. It found that asthma was associated with higher plasma F2-isoprostanes and obesity [19, 140]. Research has also shown that long chain fatty acids and anti-oxidants have been found to

[ix] Adipokines are cytokines, cell signaling proteins that are secreted by adipose tissue.

[x] Hyperleptinemia is the presence of higher than normal levels of leptins in the blood stream.

[xi] F2-isprostane is a marker of lipid peroxidation, meaning the degradation of lipids, a process that results in cell damage.

reduce the risk of asthma, while polyunsaturated fats, often found in obese children, have been associated with an increased risk of asthma. Physiological variations between obese and normal weight children appear to make children that carry excess weight more prone to asthma. Therefore, there are biological interactions, such as the higher concentration of F2-isprostane that would suggest that asthma manifests in excess weight individuals in a different way than in non-excess weight individuals indicating that further exploration into asthma in excess weight individuals is necessary.

A study by Huang et al proposed that obesity might affect the atopic status, essentially, the immunologic mediated response status of an individual, which could explain the link between obesity and asthma. The increased susceptibility to allergy and its relationship to excess weight and asthma have been demonstrated in a number of studies [141, 142]. In a cross-sectional study of 1 459 children, researchers found an association between atopy and BMI quintiles in children aged 13-15 years [142]. The mean BMI for atopic girls (20.8 ± 3.55) was higher than that for non-atopic girls (20.01 ± 3.13, $p<0.001$). Similar findings were found in adult studies [143, 144]. A larger cross-sectional study conducted by Jarvis et al with a sample of 15 454 participants aged 20-44 years did not find an association between sensitization to allergens (based on IgE[xii]) and BMI [145]. Whereas Huang et al, found a relation between bronchial hyper-responsiveness and BMI only in an atopic sub-group. The study by Jarvis was not able to replicate the findings of Huang et al. that illustrated an interaction between BMI and atopy in terms of inflammatory symptoms larger population sample [142]. Jarvis et al. found instead that the relation between BMI and the symptoms related to asthma were stronger in non-atopic participants [145]. This result was also validated by Schachter et al. [42]. Overall, the literature is inconclusive on whether immunological process associated with asthma affect BMI status or conversely whether BMI affects atopy.

Studies suggest a genetic pleiotropy[xiii] between asthma and obesity. In fact, some genes have been identified that may contribute to the control of both asthma

[xii] IgE, Immunoglobin E is an antibody that when exposed to an allergen release mast cells along with mediators that cause inflammation. When IgE binds to mast cells, it triggers a cascade of allergic reaction.

[xiii] Pleiotropy—when one gene influences multiple unrelated phenotypic traits.

and obesity [146, 147]. More specifically, a study by Szczepankiewicz et al has shown a significant association between polymorphism in the leptin gene and asthma, although there were no associations with polymorphisms in the leptin receptor or ghrelin gene [146]. Other studies have found single-nucleotide polymorphisms (SNPs) in the PRKGA gene (protein kinase C alpha) that were associated with both BMI and asthma [147], The PRKGA maps to 17q22-q23.2, a location on chromosome 17 that has been linked to BMI. The PRKCA has associated with the proliferation of smooth muscle; increased protein kinase-C has been tied to asthma pathogenesis as an inducer of airway inflammation and mucous production induced by nitric oxide [147]. In addition the PRKCA has been shown to regulate proteins associated with airway remodeling and mediate leukotriene signaling, adding to the small but growing body of literature suggesting a genetic underpinning to obesity and asthma.

The presence of obesity poses a mechanical complication that has been linked to asthma [27]. Studies often cite the increase in abdominal and thoracic fat as a cause for altered lung volume, breathing capacity and peripheral diameter [26, 27]. Excess weight has an influence in obese children's functional residual capacity, the volume of air in the lungs, increased risk of airway obstruction and increased resistance of the chest wall. Other studies have focused on different mechanics, such as the possibility that increased weight has an impact on the overall function of muscles. Researchers found that the decrease in the functional capacity of the lung volume in obese children can cause a decrease in smooth musculature movements, meaning the muscle contractions [26, 58]. Other researchers have discredited the theory of chest tightness by noting that "tightness" cannot be explained by the increased work of breathing [27, 22]. Obese children had a reduced functional residual capacity (FRC)[xiv] due to the increased resistance of the chest wall to distension during breathing [148]. It was also found that it may also be attributed to the low tidal volumes experienced by obese individuals that lead to airway stiffness and consequently lead to a narrowing of the airway [30].

While several mechanisms have been postulated linking asthma incidence,

[xiv] Functional residual capacity (FRC) – the volume of gas that remains in the lungs after a normal expiration. Mathematically it is the sum of the expiratory reserve volume and residual volume.

severity and control, the evidence is still conflicting. Improvements in asthma exacerbations has been observed following weight loss interventions [37, 38] and in the stepwise treatment procedures illustrated in figures 2.1 and 2.2, GINA guidelines recommend that physicians address weight issues in treatment [57]. Although weight-loss and bariatric surgery studies among adults with asthma have shown that reduction of severe or moderate obesity is helpful in improving objective lung function parameters and reducing the frequency and severity of respiratory symptoms [29] these studies may be susceptible to selection bias [149]. Weight loss can improve chest wall compliance by reducing the mass loading effect of fat accumulation in and around the chest wall. Leptin, the pro-inflammatory molecule found to be elevated in obese individuals [136, 137], was found in reduced levels after weight loss [150]. Conversely, in a study by Dias-Junior et al., the doses of rescue medication were higher in the treatment group that succeeded in meeting target weight loss but no data were presented comparing the reduction in rescue medication across the weight loss intervention group in comparison to the control group. Very little, if any, investigations have been done investigating the impact of weight loss in children.

Several studies have investigated whether obesity amplified symptoms in asthmatic children. A study by Mai et al [139] from 2003, including 161 Swedish children with current wheeze, found that the number of wheezing episodes was significantly greater in the previous 12 months among overweight children versus children of normal weight. In the NCICAS prospective study among children in the inner city with asthma, obese children had a higher mean number of days of wheeze per 2-week period and of unscheduled emergency department visits than non-obese children [43]. Overall, however, there was no independent relation between BMI and atopy. The study concluded that increased BMI in children with asthma may be mediated by the increased regulation of inflammatory mechanisms instead of allergic eosinophilic inflammation of the airway [134]. These findings were similar to other studies in children investigating asthma and obesity [151].

2.3 Effect of Excess Weight on Asthma Control

The effect of excess weight on asthma control has been thoroughly discussed in the literature for adult populations [21, 31, 152, 153, 154, 155, 156, 157, 158, 159]

[160, 161, 162]. There is a large disparity between the amounts of literature on the topic of asthma control as it relates to obesity in adults versus those in children. Table 2.3 summarizes relevant literature on the effect of pediatric obesity where the primary outcome is asthma control published in the last ten years.

Prospective studies in adults show that overweight and obese patients are significantly less likely to achieve asthma control over time [33]. In a study among inner-city adolescents, higher BMI and body fat were associated prospectively with more days of asthma symptoms, more asthma exacerbations, and poorer lung function—all of which are indicators of poor asthma control [43]. A study by Luder et al reported significant increases in the likelihood of missing 30 or more days of school (OR=2.2), use of reliever (rescue) medication (OR=2.0), and low forced expiratory flow (OR=6.3) in overweight versus non-overweight children [151]. The National Health and Nutrition Examination Survey shows that overweight asthmatic children had significantly poorer asthma control including more school days missed, more lifetime hospitalizations and emergency department visits, and greater activity limitation. Finally, Clougherty *et al.* observed that environmental interventions aimed at improving asthma symptoms, thereby symptoms and quality of life, were less successful in overweight children than in children of normal weight.

More recent studies have attempted to define asthma control as a whole versus components of asthma control such as increased exacerbations, emergency department visits and night-time symptoms, which were looked at separately as indicators of asthma control in the aforementioned studies. This provides an overall and perhaps more relevant perspective of the achieved control relative to excess weight. Similar to previous findings that isolated asthma control components, researchers found that increase in BMI percentile in children also increased the risk of worsened overall asthma control [139, 134, 151, 163]. Further investigation is necessary there are still inconsistent findings for the role of severity, control and excess with a low number of studies that explore asthma control and obesity in children.

Table 2.3: Summary of findings related to asthma control where BMI is the primary exposure and "asthma control" is the primary outcome. Studies are from the last ten years.

Reference	Study Design	Exposure Measure	Setting, *n*	Age (years)	Primary Outcome Measure	Main Findings
Borrell et al., 2013 [164]	Retrospective cohort	BMI	United States, *2,791*	8-19	Asthma control using modified survey by American Thoracic Society Division of Lung Disease Epidemiology Questionnaire	Obese boys had 33% greater chance of poor asthma control (OR=1.33, 95% CI, 1.04-1.71) Direction of Association among girls depended on race
Quinto et al., 2011 [39]	Retrospective cohort	BMI	United States, *32,321*	5 - 17	Asthma control measured by B-agonist canister and nebulizer units dispensed	Children with high BMI more likely to have increased B-Agonist dispensed (OR=1.15,95% CI, 1.02-1.27) and increased corticosteroids dispensed (OR=1.21, 95% CI, 1.13-1.29)
Kwong et al., 2006 [165]	Retrospective cohort	BMI	United States, *1,196*	2-18	Asthma control National Asthma Education and Prevention Programs Guidelines for the Diagnosis Management of Asthma NAEPP/EPR2)	Obesity not a factor in achieving asthma control
Kattan et al., 2010 [166]	Randomized, double blind, parallel group	BMI and DEXA	United States, *368*	12-20	Asthma control measured by the Asthma Control Test (ACT)	Increased BMI is associated with poorer asthma control in adolescent females
Giese, 2013 [167]	Retrospective chart analysis	BMI	United States, *576*	7-18	Asthma control was measure using: daily controller medication by review of prescription in EMR, asthma exacerbation based on systemic corticosteroids administration based on EMR, spirometry measure (FEV_1) and spirometry measures of forced expiratory volume in one second	No association between increased BMI and asthma control

Research Gap and Impact of this Study

Few studies specifically address asthma control and severity in the Canadian pediatric population with a focus on children who with excess weight.

There is substantive literature on the effect of weight on asthma control in adult populations. In children this has yet to be explored to the same depth as the adult population but initial studies have shown similar results on the impact of weight on asthma control in children. The current literature that specifically addresses the effect of obesity and asthma control in children is inconsistent, reporting no association or only sex-specific associations. It is also important to note that the current literature, although using large samples with sufficient power, targets very specific populations that may not be representative of the pediatric population. Furthermore, the children-specific research on asthma control and obesity rely on self-reported questionnaires to measure asthma control. As noted in the review of the questionnaires, these measures often do not provide an objective measure of asthma control. There is a need to objectively ascertain the effect of body weight on asthma control and severity in a heterogeneous sample of children.

The objective of this thesis is to increase our understanding of the role of obesity in asthma control in children. The specific research question is to what extent does excess weight influence asthma control among children aged 4-12 years? The hypothesis of this study is that children with asthma who are overweight will experience poorer asthma control than their non-overweight counterparts as demonstrated by an increase of β_2-agonist use and increase use of medical services.

3.0 Methods

Study Design

This is a retrospective cohort study based on an existing database consisting of children who presented to the Asthma Center of the Montreal Children's Hospital (MCH), a tertiary care pediatric hospital in Montreal, Canada. Patients that presented at the clinic were referred for diagnosis and management either following an emergency department visit, hospital admission or by community pediatricians or general practitioners or were self-referred (less than 20%).

Study population

The original cohort consisted of all patients presenting at the Asthma Centre between January 1, 2000 and December 31, 2008. For this study cohort, patients that presented specifically between January 1, 2002 and December 31, 2007 were included to ensure adequate history and follow up time. For this specific study, the inclusion criteria consisted of: age 2-12 years at the initial visit, a confirmed diagnosis of asthma by a pediatric asthma specialist, measured height and weight and a minimum of one year of follow-up available following the initial visit. A total of 4,621 patients contributed 15,147 visits to the clinical database of the original study. Figure 3.1 illustrates the study population selection for this study. In the first step, only patients that had a physician confirmed diagnosis of asthma were included, eliminating 14.5% of the sample. An asthma diagnosis can be determined by the lung function test, however in its absence, a physician considers: the frequency of asthma symptoms or exacerbations. The diagnosis is supported by signs of airflow obstruction by either objective measures or in the case of children, parent reports. In diagnosing asthma in children the physician considers that there is no other alternative diagnosis for the airflow obstruction and notes a reversibility of difficulty breathing with the use of SABA. Setting the timeframe between January 1 2002 and January 1 2007 eliminated another 25.9%. Framing the analysis around children aged 2-12 years further reduced the sample by 21.4%. Excluding patients with missing

weight or height values further reduced the sample by 7%. The final sample of 2,141 pediatric patients included those with and without Quebec public drug insurance plan.

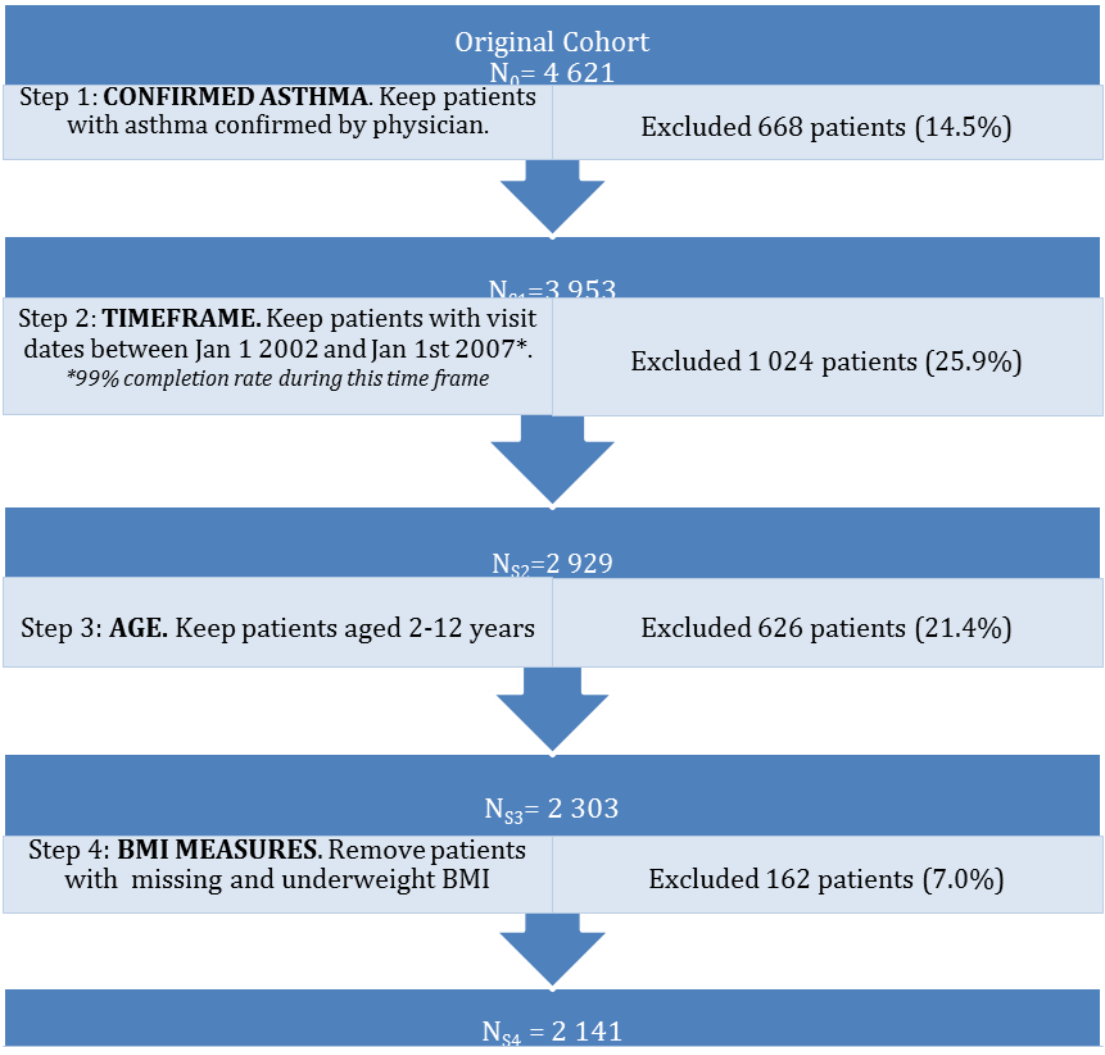


Figure 3.1: Study Population Selection

Data Sources

A clinical database was constructed from the patients attending the Asthma Center at the MCH. The center adopted a structured intake to create electronic health records using automated data entry with pre-programmed protocols to verify the quality of the data entry by flagging data entry values that are missing or out of range for verification by the treating physician within 24-48 hours of the visit. Between the years 2002-2007, the Asthma Centre electronic health records contained 99% of all visits to the center. All clinical encounters at the Asthma Center were with pediatric asthma specialists, such as, pediatricians, allergists, immunologists, and respirologists. The electronic health record, hereinafter referred to as the clinical database, contained patient demographics, physician assessment of asthma diagnosis, asthma phenotype, severity and control measures, lung function (when applicable) and prescribed medication.

The clinical database was linked with data from three health administrative provincial databases, specifically: the Régie de L'Assurance Maladie du Quebec (RAMQ) billing, the provincial drug plan administered by RAMQ, and the Med-ECHO database for hospital discharge summaries [90]. The RAMQ Medical services database contains information on demographics, service date, site of dispensation (clinic, emergency department, or hospital), ICD-9 diagnostic codes, and physician's specialty for all medical services dispensed by the 96% of Quebec physicians on a fee-for-service reimbursement scheme. The provincial drug plan database provided information on prescription claims including dates of coverage, drug code, product name, unit dose, form, duration, quantity prescribed and served, and dispensation date, type of prescription (new or refill), number of prescription refills, prescription renewals of all prescription filled and the encrypted identification of those covered. The Med-ECHO databases of hospital admissions included information on acute care hospital admission, discharge diagnoses coded in the International Classification of Disease (ICD) 9^{th} version until April 1, 2006 and 10^{th} version thereafter, the duration of the hospitalization. The patients' encrypted unique identifier was used to link all three administrative databases with the clinical database.

The RAMQ provides medical coverage to all Quebec residents therefore the Med-ECHO database ensures a detailed capture of all health-related utilization. Pharmaceutical coverage is limited to individuals who do not have access to a private

insurance plans individuals receiving social assistance, and elderly residents (≥ 65 years). Information was available on prescription medications dispensed for any children under the age of 18 for individuals covered by the public plan [168].

In the study cohort, all children were linked to their hospital admissions and medical services information, and 42% were covered by the Quebec Provincial Drug Plan information. The validity of these administrative databases for health research has been established [169] and were considered highly reliable [170, 171]. More specifically, information in the RAMQ database used to identify asthma diagnoses and prescriptions has been validated [172, 173, 174, 175].

Primary Outcome

B-2-Agonist Use

The use of short β_2-agonist as an indicator of asthma control was used as the main outcome measure. As per the Canadian Consensus, North American guidelines ≥4 doses/week of short acting β_2-agonist was considered indicative of poor control [176]. The mean number of doses of β_2-agonists per week was computed as the cumulative number of doses from all preparations dispensed during the follow-up divided by the length of the follow-up. To allow comparison, one dose of inhaled β_2-agonist was assumed to equal two inhalations of 100 μg salbutemol, one inhalation of 0.5 mg terbutaline or one nebule of salbutemol, the latter irrespective of dose. The number of doses was calculated according to the proportion of the follow-up time that was covered by last dispensed prescription. The start date used was the initial dispensed date. The baseline mean number of doses of β_2-agonist per week was calculated similarly using the period covered by RAMQ services up to one year before the initial visit date.

The duration of the previous prescription was used to impute the duration of the last dispensed prescription when the last prescription occurred just prior to the end of the available follow-up on December 31, 2008. The imputation algorithm was based on two rules: 1. If the patient had only one dispensed prescription, the duration by the median time between two prescriptions was imputed, 2. For patients that have two or more dispensed SABA prescription, the duration of the previous prescription

was carried forward. If the last prescription ended before the last day of RAMQ coverage, the imputed duration to this point was extended. The imputed durations had to be shorter than the shelf life for the SABA medication.

Secondary Outcomes

Secondary indicators of asthma control included the rate of rescue oral corticosteroids, acute health care visits and of hospital admission per year.

Rate of Rescue Oral Corticosteroids

Use of rescue oral corticosteroids (OCS) was used as a marker for moderate or severe exacerbations resulting from poor asthma control. The use rescue OCS per annum included any short-term oral preparation of corticosteroids, usually oral prednisone or prednisolone. For each group the drug identification number (DIN) as summarized in Appendix II.

The number of OCS prescriptions for each child was counted for the duration of follow-up. If several prescriptions of OCS were identified within a seven-day interval for a given child, they were counted only once assuming that they were prescribed for the same exacerbation. A search was conducted for visit within 24-48 hours of the OCS prescription being dispensed and the billing code was identified. Those OCS prescriptions that had a physician visit with a billing not related to a respiratory condition, such as anaphylaxis and mononucleosis were not included as in the rate calculation. The rate of OCS use was calculated per year.

Rate of Acute Care Visits

The number of acute health care visits was defined as emergency department (ED) visit (institutional code 0X7) or a clinic visit with repeated medical examinations where asthma was one of the billing codes. This information was collected from provincial administrative health databases and the MCH clinical database. The majority of visits (97.8%) appeared in both the health administrative databases and the clinical database, demonstrating high accordance. A small number of visits only appeared in the clinical database and is likely explained by other modes of physician remuneration (namely salary) that would result in an absence from the RAMQ medical visits database. Visits were considered the same visit (counted as one

visit) if they occurred on the same day; within one calendar day (4.4%) or if there were several emergency department visits or acute care visits within an interval of seven days for the same child. The rate of ED visits was calculated separately for (i) asthma, (ii) respiratory conditions associated to asthma (see Appendix I) and for (iii) all diagnoses. The rate of acute care visits was calculated by summing the number of distinct events divided by the length of follow up.

Rate of Hospital Admission& Hospitalization

Hospital admissions were defined as admissions to an acute care hospital facility with a primary diagnosis of asthma or asthma as secondary diagnosis but with an asthma complication as primary diagnosis (see Appendix I). Hospitalization data were obtained from the provincial hospital discharge (Med-ECHO). Children with a primary diagnosis of asthma or a secondary diagnosis of asthma were identified, provided the primary diagnosis was a complication or co-morbidity of asthma. If several hospitalizations happened within seven days for the same child, only one hospitalization was counted for the year.

Main Exposure – Excess Weight

Excess weight was defined using body mass index (BMI). A nurse or respiratory technician documented weight and height each visit in the clinical database. Using the measurements from the index visit, weight classifications for children were calculated using BMI percentile to account for changes due to age and sex. Crude BMI was calculated by taking the quotient of the individual's measured body weight and square of the height in meters. Percentiles where based on the World Health Organization (WHO) international growth standard chart for children from birth to age 19 years [177]. The growth chart provides the distribution of BMI values at each age. Children whose BMI falls between the 85^{th} and 94^{th} percentile for a specific age and sex were considered overweight and those who had a BMI percentile equal or greater than 95^{th} were considered obese [177].

Covariates

A wide variety of potential confounding variables were identified from the literature and include sociodemographic variables (age, sex, ethnicity, socioeconomic

status), lifestyle risk factors (exposure to tobacco smoke), and other comorbidities. For the purpose of the study, neighborhood factors including socioeconomic status were amalgamated into a social deprivation factor. The RAMQ beneficiary demographic database provides data on postal-code linked data on income, status and education based on Statistics Canada enumeration area mapping that allowed the calculation of the social deprivation index [178]. Social deprivation refers to relationships among individuals in the family, the workplace and the community. The variables used to calculate the social deprivation index are directly obtained from census information from Statistics Canada. The variables include: 1) the proportion of the population aged 15 and older who are separated, divorced or widowed, 2) the proportion of the population that lives alone and 3) the proportion of the population that has moved at least once in the last five years. Based on these variables, a factor analysis is calculated by distribution area to create the index. Once factor scores are calculated and ranked, the distribution is further divided into quintiles, where quintile 1 represents the least deprived segment of the Quebec population and quintile 5 represents the segment that is most deprived. This is index has been mainly used in Quebec and provides further insight into the health and social wellbeing of the participants. To our knowledge, it has never been used in the context of asthma control, although other indices of socioeconomic factors are associated with asthma prevalence and morbidity.

Data on cigarette smoke exposure was obtained from the baseline clinical database, this was measured based on whether children were exposed to parental smoking in the home. This self-report of behavioral tendencies was the most feasible measure for the study.

Relevant comorbidities identified for this particular study included: eczema; allergic rhinitis; conjunctivitis; food allergy; recurrent otitis; recurrent sinusitis; recurrent pneumonias; gastro-esopheageal reflux; broncho-pulmonary dysplasia; obstructive sleep apnea; vocal cord dysfunction; bronchopulmonary aspergillosis and swallowing dysfunction [92, 179]. The conditions of interest were systematically documented on the initial visit to the clinic and thus identified using clinic records. To account for potential discrepancies in the reported condition, the RAMQ administrative database on medical service claims as well as the MED-ECHO

database on hospital visits was searched for ICD-9 and ICD-10 codes corresponding to the co-morbid conditions.

Asthma Severity

Asthma severity was ascertained by participating physicians. Children were categorized as mild, moderate or severe based on the Physician Global Assessment that encompasses the intensity and frequency of symptoms and/or the amount of daily medications required to achieve control [90]. Physicians also considered the level of treatment required to control asthma and the difficulty in controlling asthma with treatment [6]. In patients with no medication, severity was determined by the severity of exacerbations with mild severity defined as no emergency department visits or OCS prescriptions; moderate as ED visit with OCS and severe as an asthma-related hospital admission. For patients with medications, mild severity was defined as use of a leukotriene receptor antagonist (LTRA) or low doses of inhaled corticosteroids (ICS) (< 200 µg/day), moderate asthma was defined as requiring between 200µg/day and 400 µg/day of hydrofluoroalkane-beclometasone dipropionate (HFA-BDP). Unlike our primary outcome, asthma severity was not determined by the use of SABA.

Statistical analysis

Basic descriptive statistics were calculated using means or counts with percentages. Unadjusted estimation of associations between key variables was assessed using means or chi-square tests. Overall, the association between the identified predictors and the impact on asthma control were evaluated using linear or logistic regression. All multiple regression models were built using a combination of backward and stepwise selection techniques. The final models included all covariates that were significant, and decreased the c statistic, or increased the AIC significantly once removed. Weight category (main exposure), age, sex, and ethnicity were forced into all models regardless of significance, as these are central to the theoretical framework underlying the research question. Once the regression models were finalized (i.e. main effects models), subgroup analyses stratified by asthma severity were performed. Severity groups for this stratification were: i) mild vs ii) moderate to

severe; moderate and severe groups were merged since a large proportion of the sample had “mild” asthma.

For the first objective, to estimate, among children aged 2 to 12 years of age, diagnosed with asthma, the extent to which having excess weight has an effect on asthma control as indicated primarily by the rate of SABA use per week, linear regression models were used. Crude and adjusted effect estimates were obtained for all potential confounders and covariates using the primary outcome, poor control, as indicated by mean ß$_2$-agonist doses per week, during follow-up using both the North American and International standards as a means of comparison. The former defined poor control as 4 or more mean doses of ß$_2$-agonists during follow-up, while the latter defined poor control as 2 or more mean doses of ß$_2$-agonists during follow-up. The exposure, BMI percentile, was considered categorical and classified as either: normal weight or excess weight, where excess weight combined overweight and obese individuals as per the WHO percentile cut-offs.

For the second objective, to estimate whether excess weight had an effect on other markers of asthma control such as health care visits and use of oral corticosteroids, logistic regression was used. Analyses were performed for secondary outcomes such as number of acute care visits, OCS courses obtained, and hospitalizations for asthma during follow. The average number of acute health care visits and hospitalizations were calculated per year. Baseline characteristics of the participants with and without the outcome (asthma control, determined by dosage of SABA per week) were compared using chi-square.

All analyses were done using SAS version 9.2. Ethics approval for this study was obtained from Montreal Children’s Hospital and Sainte-Justine University Health Centre.

4.0 Results

In the final sample of 2 141, 37.1 % had a BMI indicating excess weight. In the cohort, only 817 children were covered by public drug insurance and 1,324 (61.8%) had no medication information available. The characteristics of patients with and without drug insurance are presented in Table 4.1.

Since the primary and secondary outcomes require tracking the prescription of study participants, patients without continuous medical insurance and public drug coverage for the duration of our follow-up were removed. The final sample of 817 was used in the primary analysis with asthma control defined on the basis of $ß_2$-agonist use and the secondary analysis for hospitalization, acute care visits and the use of oral corticosteroids as indicators of asthma control. Within the sample of children with public drug insurance (*n*=817), 294 participants (36.0%) were categorized as having excess weight: 128 (15.7%) were overweight (BMI 85th-95th percentile) and 166 (20.3%) were obese (BMI > 95th percentile).

Table 4.1: Sample Characteristics of Participants with and without Public Drug Prescription Coverage

Table 4.1. Sample characteristics (n=2 141). Descriptive characteristics and frequencies of cohort that includes children with (n=817) and without (n=1 324) drug prescription coverage.

	Covered N=817	**Not covered N=1 324**	**Total N=2 141**
Age (y), mean (SD)	9.0 (2.4)	5.0 (2.8)	6.5 (3.2)
Female, n (%)	308 (37.7)	543 (41.0)	851 (39.8)
Weight Category, n (%)			
Normal	494 (60.5)	853 (64.4)	1 347 (62.9)
Excess	323 (39.5)	471 (35.6)	794 (37.1)
Ethnicity, n (%)			
Caucasian	453 (55.5)	661 (49.9)	1 114 (52.03)
Black	76 (9.3)	98 (7.4)	174 (8.13)
Asian	49 (6.0)	111 (8.4)	160 (7.47)
Other	35 (4.3)	97 (7.3)	132 (6.17)
Missing	204 (24.9)	357 (27.0)	561 (26.20)
Exposure to smoke, n (%)			
No	435 (53.2)	863 (65.2)	1 298 (60.63)
Yes	58 (7.1)	51 (3.9)	109 (5.09)
Missing	324 (39.7)	410 (30.9)	734(34.28)
School Absenteeism in past year, n (%)			
No	348 (42.6)	448 (33.8)	796 (37.18)
Yes	172 (21.1)	147 (11.1)	319(14.90)
Missing	297 (36.3)	729 (55.1)	1 026(47.92)
Physician Assessment of Asthma Severity, n (%)			
Mild	518 (63.4)	768 (58.0)	1 286 (60.07)
Moderate	187 (22.9)	305 (23.0)	492 (22.98)
Severe	39 (4.8)	111 (8.4)	150 (7.01)
Missing	73 (8.9)	140 (10.6)	213(9.95)
Reported Asthma Control, n (%)			
Good	202 (24.7)	243 (18.4)	445(20.78)
Satisfactory	184 (22.5)	268 (20.2)	452(21.11)
Poor	61 (7.5)	95 (7.2)	156(7.29)
Missing	370 (45.3)	718 (54.2)	1 088(50.82)
Social Deprivation Index, n (%)			
1 (lease disadvantaged)	26 (3.2)	54 (4.1)	80(3.74)
2	67 (8.2)	144 (10.9)	211(9.86)
3	64 (7.8)	148 (11.2)	212(9.90)
4	130 (15.9)	334 (25.2)	464(21.67)
5 (most disadvantaged)	75 (9.2)	137 (10.3)	212(9.90)
Missing	*455 (55.7)*	*507 (38.3)*	*962(44.93)*
Comorbidities*, n (%)			
Yes	338 (41.4)	593 (44.8)	931(43.48)
No	479 (58.6)	731 (55.2)	1 210(56.52)
Medical visit reported in past year, n (%)			
Yes	456 (55.8)	931 (70.3)	1 387(64.78)
No	315 (38.6)	318 (24.0)	633(29.57)
Missing	*46(5.6)*	*75 (5.7)*	*121(7.01)*
Hospital Admission in past year, n (%)			
Yes	306 (37.4)	684 (51.7)	990 (46.24)
No	458 (56.1)	543 (41.0)	1 001(46.75)
Missing	*53 (6.5)*	*97 (7.3)*	*150(7.01)*
Intensive Care Unit visit in past year , n (%)			
Yes	16 (2.0)	42 (3.2)	58 (2.71)
No	686 (84.0)	1 044 (78.8)	1 730 (80.80)
Missing	*115 (14.0)*	*238 (18.0)*	*353 (16.49)*
Previous use of OCS in past year, n (%)			
Yes	152 (18.6)	360 (27.2)	512 (23.91)
No	572 (70.0)	798 (60.3)	1 370 (63.99)
Missing	*93 (11.4)*	*166 (12.5)*	*259 (12.10)*

*The comorbidities include atopic conditions (food allergy, allergic rhinitis, eczema, conjunctivitis); upper-respiratory tract conditions (swallowing dysfunction, vocal cord dysfunction, recurrent sinusitis and recurrent otitis); and lower-respiratory tract conditions (bronchopulmonary aspergillosis, recurrent pneumonias, bronchitis and gastroesophageal reflux disease

Table 4.2 illustrates the characteristics of the study population with public drug prescription coverage stratified by weight category. The average age of the study sample was 6.1 years (3.1 SD) and 6.9 (3.2 SD) years among normal and excess weight children, respectively, with older children being more likely to have excess weight (Table 4.2). Children who experienced absenteeism were statistically more likely to be overweight or obese (Table 4. 2).

Table 4.2: Baseline Characteristics of the Study Population

Table 4.2. Baseline Characteristics of the Study Population (n=817). The table describes the baseline characteristics of the study participants (n=817). Data was collected from index visit. The p-value represents the significance in differences between the weight group, α=0.05.

CHARACTERISTICS	**N (%)**			*p-value*
	Normal (N= 523)	**Excess Weight (N=294)**	**Total (N=817)**	
Age				
2-6	327(62.5)	155 (52.7)	482 (59.0)	*<0.01*
7-12	196 (37.5)	139 (47.3)	335 (41.0)	
Gender				
Male	322 (67.6)	182 (61.9)	504 (61.7)	*0.92*
Female	201 (38.4)	112 (38.1)	313 (38.3)	
Ethnicity				
Caucasian	233(44.5)	133 (45.2)	366 (44.8)	
Black	55 (10.5)	26 (8.8)	81 (9.9)	
Asian	66 (12.6)	32 (10.9)	98 (12.0)	*0.28*
Other	34 (6.5)	31 (10.5)	65 (8.0)	
Missing	135 (25.8)	72 (24.5)	207 (25.3)	
Exposure to smoke				
No	326 (62.3)	165 (56.1)	491 (60.1)	
Yes	28 (5.4)	15 (5.1)	43 (5.3)	*0.17*
Missing	169 (32.3)	114 (38.8)	283 (34.6)	
Social Deprivation Index				
1	10(1.9)	3 (1.0)	13 (1.6)	
2	38 (7.3)	20 (6.8)	58 (7.1)	
3	40 (7.6)	29 (9.9)	69 (8.5)	*0.23*
4	129 (24.7)	70 (23.8)	199 (24.4)	
5	80 (15.3)	33 (11.2)	113 (13.8)	
Missing	226 (43.2)	139 (47.3)	365 (44.7)	
Physician Assessment of Asthma Severity				
Mild	335 (64.1)	194 (66.0)	529 (64.8)	
Moderate	149 (28.5)	80 (27.1)	229 (28.0)	*0.84*
Severe	39 (7.5)	20 (6.8)	59 (7.2)	
Reported Asthma Control				
Good	107 (20.5)	57 (19.4)	164 (20.1)	
Satisfactory	102 (19.5)	68 (23.1)	170 (20.8)	*0.66*
Poor	50 (9.6)	25 (8.5)	75 (9.2)	
Missing	264 (50.5)	144 (49.0)	408 (49.9)	
Comorbidities*				
Atopic No	366 (70.0)	193 (65.6)	559 (68.4)	*0.20*
Yes	157 (30.0)	101 (34.4)	258 (31.6)	
Upper Respiratory				
No	491 (93.9)	272 (92.5)	763 (93.4)	*0.45*
Yes	32 (6.1)	22 (7.5)	54 (6.6)	
Lower Respiratory				
No	501 (95.8)	286 (97.3)	787 (96.3)	*0.27*
Yes	22 (4.2)	8 (2.7)	30 (6.7)	
School Absenteeism in past year				
No	194 (37.1)	121 (41.2)	315 (38.5)	
Yes	66 (12.6)	54 (18.4)	120 (14.7)	*0.01*
Missing	263 (50.3)	119 (40.5)	382 (46.8)	
Reported ICS use in the past year				
No	385 (73.6)	212 (72.1)	597(73.1)	*0.64*
Yes	138 (26.4)	82 (27.9)	220 (26.9)	
Proper use of Device				
No	11 (2.1)	13 (4.4)	24 (2.9)	
Yes	273 (52.2)	164 (55.8)	437 (53.5)	*0.07*
Missing	239 (45.7)	117 (39.8)	356 (43.6)	

*The comorbidities include atopic conditions (food allergy, allergic rhinitis, eczema, conjunctivitis); upper-respiratory tract conditions (swallowing dysfunction, vocal cord dysfunction, recurrent sinusitis and recurrent otitis); and lower-respiratory tract conditions (bronchopulmonary aspergillosis, recurrent pneumonias, bronchitis and gastroesophageal reflux disease).

Table 4.3 provides the frequency of visits for the health services and OCS use with medical visits, hospital admissions, intensive care unit (ICU) admissions and OCS use in the year prior to the index visit reported by parents of the study participants reported by the study participants.

Table 4.3: Health Services and OCS Use

Table 4.3. Description of use health services (medical visits, hospital admission unit) and use of oral corticosteroids in the past year, reported at the index visit for the study participants.. The p-value represents the significance in differences between the weight group, α=0.05.

	N (%)			
	Normal Weight (N=523)	**Excess Weight (N=294)**	**Total (N=817)**	**p-value**
Medical Visits Reported				
No	193 (36.9)	103 (35.0)	296 (36.2)	
Yes	309 (59.1)	177 (60.2)	486 (59.5)	0.79
Missing	21 (4.0)	14 (4.8)	35 (4.3)	
Hospital Admission				
No	277 (53.0)	160 (54.4)	437 (53.5)	
Yes	210 (40.1)	117 (39.8)	237 (40.0)	0.81
Missing	36 (6.9)	17 (5.8)	53 (6.5)	
Previous ICU Admission				
No	427 (81.6)	244 (83.0)	671 (82.1)	
Yes	17 (3.2)	7 (2.4)	24 (2.9)	0.76
Missing	79 (15.1)	43 (14.6)	122 (14.9)	
Previous OCS use				
No	352 (67.3)	208 (70.7)	560 (68.6)	
Yes	113 (21.6)	54 (18.4)	167 (20.4)	0.52
Missing	58 (11.1)	32 (10.9)	90 (11.0)	

Primary Outcome: Effect of Excess Weight on use of β_2 -agonist

For each weight category, the number of doses per week during follow-up was calculated. The following figure illustrates the doses of β_2-agonist per weight category. The horizontal lines illustrate the dose limit separating controlled from uncontrolled asthma, where controlled asthma is defined as 2 or less doses of β_2-agonist per week by international standards, and less than 4 doses per week by the North American standards.

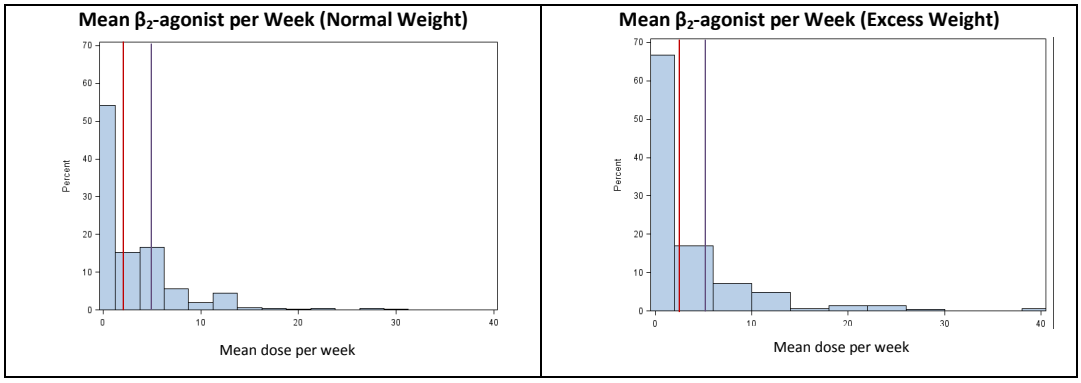


Figure 4.1: Distribution of Mean β_2-agonist Dose per Week. Sample distribution of the mean dose of β_2-agonists used per week, stratified by normal and excess weight. The vertical lines illustrates the threshold separating good and poor control based on the North American definition where 4 or more doses per week indicate poor control (blue) and the international definition where doses below 2 per week indicate good control (red).

The histograms illustrate the distribution of mean dose per week in our study population for each weight category. A similar pattern exists for those with normal weight and those with excess weight as they are both positively skewed (i.e. right-tailed) and the majority of patients used a small number of doses per week of β_2-agonist, categorizing them as having good control. In the histogram for children with excess weight, the mean doses per week exceeded that of 30 per week, with some participants filling as much as 40 doses per week. The numbers of participants that are categorized as having poor asthma control are summarized by weight category in Table 4.4.

Table 4.4: Asthma Control Stratified by Weight

Table 4.4. Asthma control cross-tabulated by weight groups (normal and excess) in study population (n=817). The p-value represents the significance in difference in proportions of asthma control between the weight groups

	N (%)			*p-value*
	Normal Weight (N= 523)	**Excess Weight (N=294)**	**Total (N=817)**	
Asthma Control by North American Standards				
Good Control	363 (69.4)	200 (68.0)	563 (68.9)	*0.68*
Poor Control	160 (30.6)	94 (32.0)	254 (31.1)	
Asthma Control by International Standards				
Good Control	283 (54.1)	153 (52.0)	436 (53.4)	*0.57*
Poor Control	240 (49.5)	141 (48.0)	381 (46.6)	

Figure 4.2 illustrates the patient profile for our study population of individuals that were classified as having poor asthma control by the North American and International standards. The figure uses only the proportion of those classified as having poor asthma control, with *n*=254 by the North American standards, and *n*=381 by the International standards. A linear relationship emerges between social deprivation and asthma control, with those experiencing poor asthma control being more likely to reside in areas that were the most disadvantaged (i.e. deprivation quintiles 4 and 5). A high proportion of Caucasian, previous medical visits, and reported hospital admission was observed in the study population.

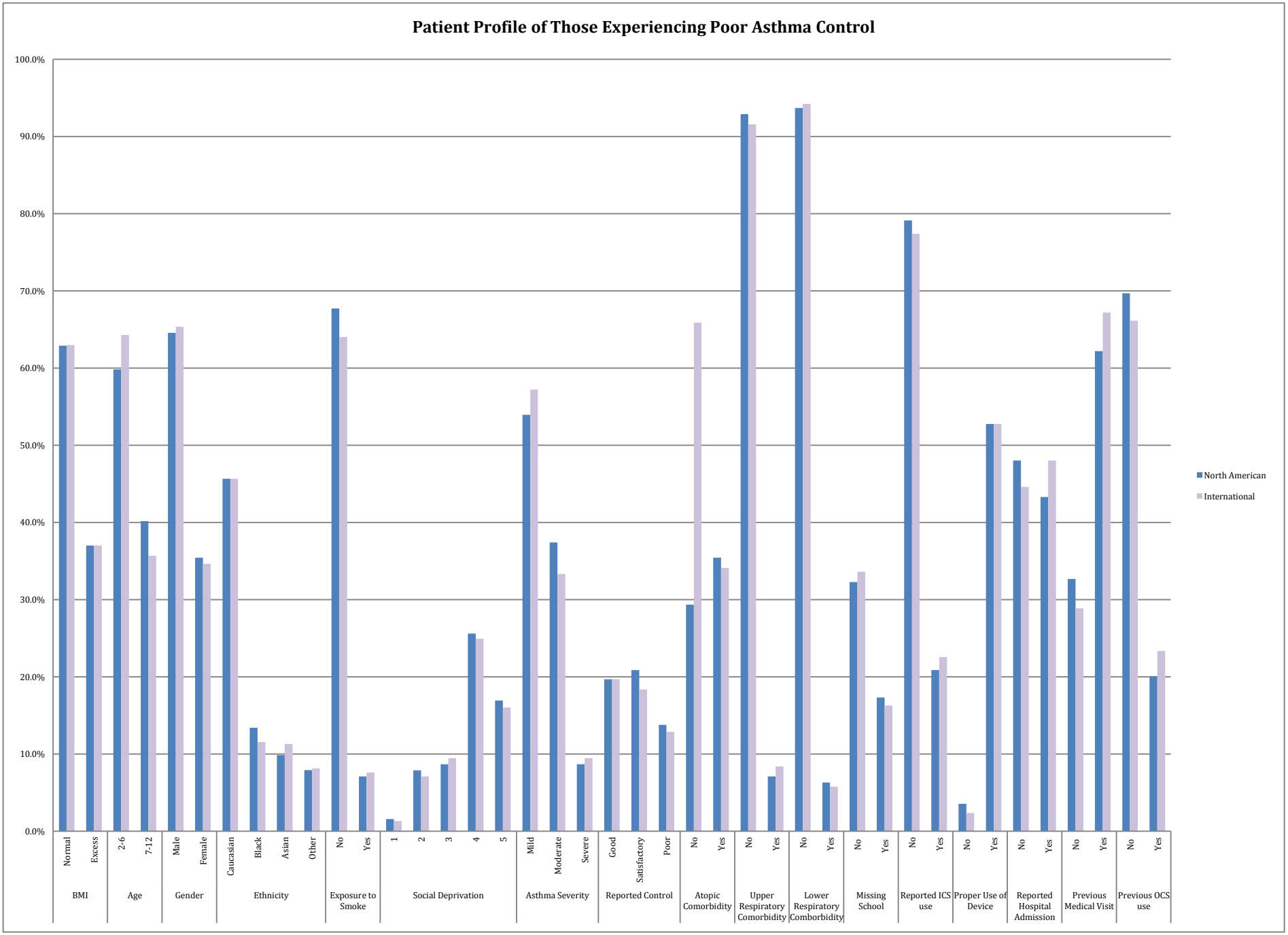


Figure 4.2: Patient profile of participants that were categorized as having "poor asthma control" during the follow up period. The denominator varies per group, by North American standards, 254 were identified as having poor asthma control, and by International standard, 381 were identified as having poor asthma control. *The comorbidities include atopic conditions (food allergy, allergic rhinitis, eczema, conjunctivitis); upper-respiratory tract conditions (swallowing dysfunction, vocal cord dysfunction, recurrent sinusitis and recurrent otitis); and lower-respiratory tract conditions (bronchopulmonary aspergillosis, recurrent pneumonias, bronchitis and gastroesophageal reflux disease)

Unadjusted odds ratios for the logistic regression analysis are summarized in Table 5 based on the North American and International standards of asthma control. Based on these unadjusted analyses, the only factors that significantly increased the likelihood of have poor asthma control were having self-reported moderately severe asthma and having a lower-respiratory comorbidity. The use of ICS was the only factor that lowered the likelihood of experiencing poor asthma control.

Table 4.5: Excess Weight and Poor Asthma Control: Summary of Crude Effects

Summary of unadjusted odds ratios (OR) and 95% Wald Confidence interval for asthma control for each candidate variable. The * denotes the reference category. ǂ represents statistical significance from the reference category where α=0.05

EXPLANATORY VARIABLE	CRUDE EFFECTS			
	North American Standards		International Standards	
	OR	95% Wald CI	OR	95% Wald CI
BMI Percentile Categories				
Excess Weight vs. Normal Weight*	1.07	(0.78-1.45)	1.09	(0.82-1.45)
Age Category (years)				
7-12 vs 2-6*	0.95	(0.70-1.29)	0.66	(0.50-0.88)
Sex, Male*				
Female	0.84	(0.62-1.14)	0.75	(0.56-0.99)
Ethnicity, Caucasian*				
Black	1.56	(0.95-2.55)	1.31	(0.81-2.12)
Asian	0.74	(0.45-1.22)	0.86	(0.55-1.35)
Other	0.96	(0.54-1.70)	1.01	(0.59-1.71)
Missing	0.86	(0.59-1.25)	0.83	(0.59-1.17)
Social deprivation Index, 1*				
2	1.18	(0.32-4.33)	1.39	(0.41-4.77)
3	1.05	(0.29-3.80)	1.75	(0.52-5.87)
4	1.09	(0.32-3.68)	1.46	(0.46-4.62)
5	1.38	(0.40-4.76)	1.88	(0.58-6.10)
Asthma Severity, Mild*				
Moderate	2.03	(1.46-2.81) ǂ	1.78	(1.30-2.43) ǂ
Severe	1.70	(0.97-2.99)	2.23	(1.29-3.87)
Reported Control, Good*				
Satisfactory	1.03	(0.65-1.64)	0.83	(0.54-1.28)
Poor	2.00	(1.14-3.50)	2.24	(1.27-3.94)
Comorbidities, None*				
Lower-Respiratory				
Yes vs. No*	2.64	(1.27-5.49) ǂ	3.28	(1.44-7.45) ǂ
Upper-Respiratory				
Yes vs. No*	1.12	(0.62-2.01)	1.73	(0.98-3.02)
Atopic				
Yes vs. No*	1.29	(0.94-1.77)	1.25	(0.93-1.68)
Exposure to Smoke				
Yes vs. No*	1.34	(0.71-2.52)	2.10	(1.08-4.06)
Missing vs. No*	0.54	(0.39-0.76)	0.63	(0.46-0.84) ǂ
ICS use				
Yes vs. No*	0.63	(0.44-0.89) ǂ	0.66	(0.48-0.90) ǂ
Proper Technique				
Yes vs. No*	0.74	(0.32-1.73)	1.42	(0.61-3.31)
Previous Medical Visits				
Yes vs. No*	1.24	(0.90-1.70)	1.88	(1.40-2.53)
Previous Hospital Admission				
Yes vs. No*	1.31	(0.96-1.79)	2.00	(1.49-2.67)
Previous OCS use				
Yes vs. No*	0.95	(0.65-1.38)	1.40	(0.99-1.97)
Previous ICU Admission				
Yes vs. No*	2.24	(0.99-5.07)	1.95	(0.84-4.52)
Missed School				
Yes vs. No*	1.65	(1.05-2.58)	1.56	(1.02-2.38)

For the multivariate logistic regression model, stepwise and backwards techniques were used wherein each covariate was added to the adjusted model based on significance (α=0.10). The p-value to stay in the model was based on α=0.15. Based on the North American standards, asthma severity, lower-respiratory tract comorbidities, and ICS use were entered in the model. Key variables were forced onto the model, irrespective of their p-value, based on previous literature establishing their association and potential confounding role with respect to asthma control, including: age, sex and ethnicity. The results of the adjusted model, including estimated odds ratio and 95% confidence intervals are summarized in Table 4.6.

Table 4.6: Excess Weight and Poor Asthma Control: Summary of Adjusted Effects of Final Model

Summary of adjusted odds ratios (OR) and 95% Wald Confidence interval on asthma control for each candidate variable. The reported point estimates control for other explanatory variables when predicting the outcome. The * denotes the reference category.

EXPLANATORY VARIABLE	ADJUSTED EFFECTS					
	North American Standards			International Standards		
	OR	(95% CI)	P-value	OR	(95% CI)	P-value
BMI Percentile Weight Categories						
Excess Weight vs. Normal*	1.146	(0.83-1.58)	0.40	1.243	(0.92-1.68)	0.16
Age category						
7-12 vs. 2-6*	0.95	(0.69-1.31)	0.77	0.63	(0.46-0.86)	<0.01
Sex						
Female vs. Male*	0.88	(0.64-1.21)	0.42	0.76	(0.56-1.02)	0.07
Ethnicity, Caucasian*						
Black	1.46	(0.88-2.44)	0.14	1.23	(0.74-2.04)	0.42
Asian	0.84	(0.50-1.41)	0.51	0.94	(0.59-1.51)	0.80
Other	1.03	(0.58-1.86)	0.90	1.04	(0.60-1.81)	0.88
Asthma Severity, Mild*						
Moderate	1.87	(1.34-2.63)	<0.001	1.54	(1.11-2.14)	<0.001
Severe	1.65	(0.92-2.98)	0.09	2.12	(1.19-3.79)	0.01
Comorbidities						
Lower-Respiratory						
Yes vs. No*	2.18	(1.01-4.7)	0.04	3.08	(1.30-7.33)	0.01
Exposure to Smoke						
Yes vs. No*	1.34	(0.70-2.57)	0.37	2.35	(1.19-4.68)	0.01
Missing vs. No*	0.58	(0.41-0.82)	0.01	2.12	(1.19-3.79)	0.03
ICS use						
Yes vs. No*	0.68	(0.47-0.99)	0.04	0.60	(0.42-0.87)	<0.001

To explore the role of asthma severity, analyses were stratified by severity. Figure 4.3 illustrates the distribution of the mean dose of β_2-agonist used per week stratified by severity.

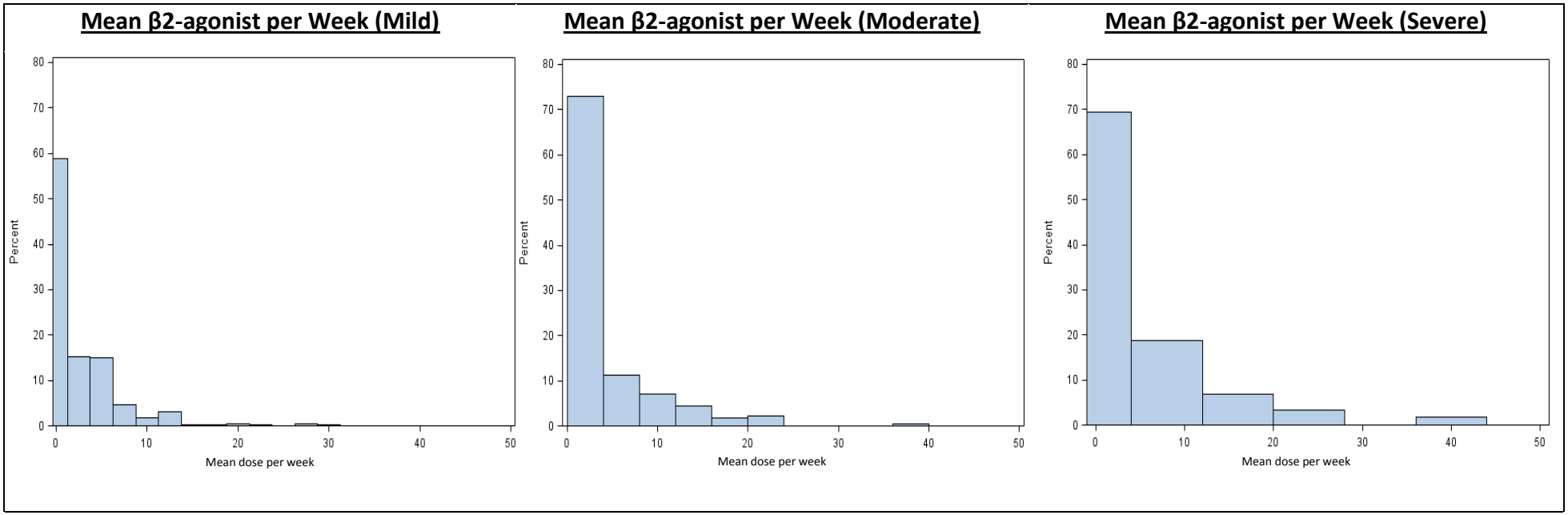


Figure 4.3: Distribution of Mean β_2-agonist Dose per Week. Sample distribution of the mean dose of β_2-agonists used per week, stratified by severity.

The histograms illustrate that as the severity becomes greater, there is a corresponding increase of study participants that use 30 or more doses of β_2-agonists per week. A multivariate regression analysis was performed with the stratified severity groups to observe whether stratifying severity had impact on our primary outcome, asthma control. Table 4.7 summarizes the adjusted effects of asthma control by the two severity strata (mild versus moderate and severe).

Table 4.7: Excess Weight and Poor Control: Adjusted Effects Stratified by Severity type

Summary of adjusted odds ratios (OR_{ADJ}) and 95% Wald Confidence interval for asthma control for each candidate variable stratified by severity (based on North American definition). In the adjusted model predicting poor asthma control, the reported point estimates control for all other explanatory variables that had a p-value below 0.05. BMI based Weight Categories, Age, Sex and Ethnicity were forced into the model. The * denotes the reference category.

EXPLANATORY VARIABLE	ADJUSTED EFFECTS					
	Mild			Moderate and Severe		
	OR	(95% CI)	P-value	OR	(95% CI)	P-value
BMI Percentile Categories						
Excess Weight vs. Normal*	1.05	(0.69-1.60)	0.81	1.34	(0.81-2.23)	0.25
Age category						
7-12 vs. 2-6*	0.93	(0.62-1.40)	0.74	0.97	(0.46-0.86)	0.92
Sex, Male*						
Female	0.81	(0.53-1.23)	0.33	0.91	(0.55-1.65)	0.71
Ethnicity, Caucasian*						
Black	1.49	(0.74-3.0)	0.26	1.53	(0.72-3.25)	0.27
Asian	0.90	(0.48-1.71)	0.76	0.66	(0.267-1.65)	0.37
Other	0.99	(0.46-2.16)	0.99	1.13	(0.44-2.95)	0.80
Comorbidities						
Lower-Respiratory						
Yes vs. No*	3.10	(1.03-9.35)	0.05	NI	NI	NI
Exposure to Smoke						
Yes vs. No*	1.00	(0.41-2.41)	0.99	2.02	(0.72-5.70)	0.18
Missing vs. No*	0.45	(0.29-0.72)	<0.001	0.81	(0.47-1.38)	0.43
ICS use						
Yes vs. No*	0.74	(0.46-1.21)	0.23	0.61	(0.33-1.12)	0.11

Lower respiratory was not found significant in the crude analysis and therefore not included (NI) in the adjusted model for the Moderate and Severe group.

Based on the summarized results, severity did not interact with the relation between weight status and asthma control, by the North American standards.

Secondary Outcome: Effect of Excess weight on Acute Care Visits, Hospital Admissions and OCS Use

Figure 4.4 illustrates the patient profile based on the frequency of health services and oral corticosteroid (OCS) used during follow-up.

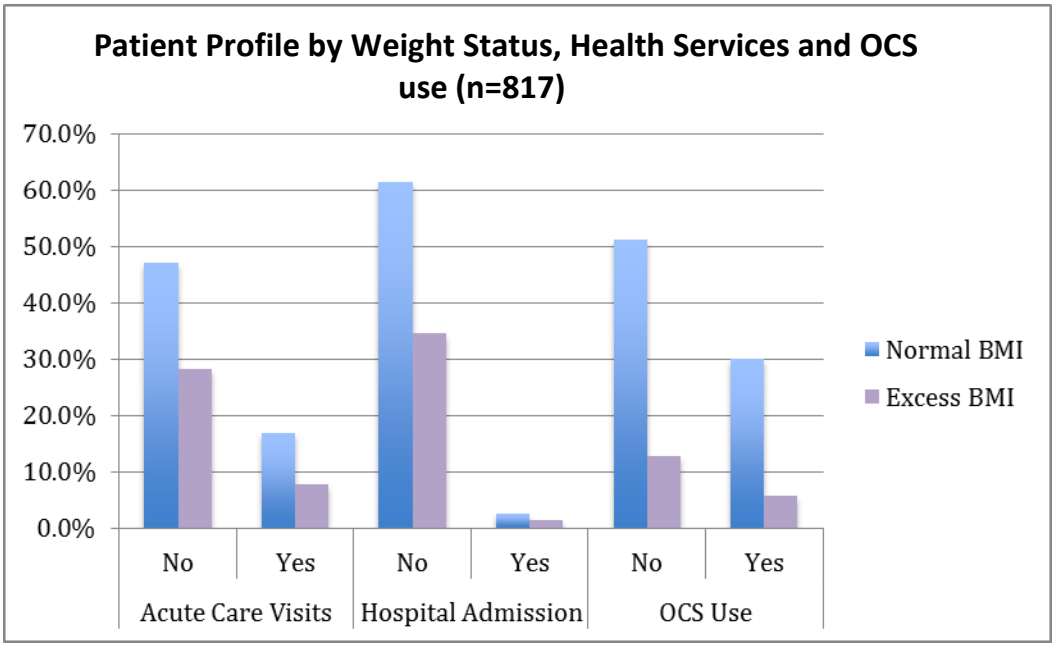


Figure 4.4: Patient Profile of Acute Care Visits, Hospital Admissions and OCS use per weight group. This information was collected from documented asthma related visits in the MED-ECHO database.

The use of health services was minimal in our sample. A total of 34 out of 817 (4.2%) participants were admitted to the hospital during the one-year follow-up period, less than half (n=12,35.3%) were individuals with excess weight. Only 201 out of 817 (24.0%) had acute care visits of which 63 (31.3%) had excess weight this represented 7.7% of the sample. Similarly, OCS was used by 152 out of 817, (18.6%) participants during follow-up, of which 48 (31.6%) were categorized as having excess weight representing 5.8% of the sample.

A crude regression was performed for acute care visits, hospital admission and OCS use as separate outcomes. Table 4.8 summarizes the results. Among those with excess weight, it appeared that participants were more likely to use OCS and have increased acute care visits or hospital admissions.

Table 4. 8: Excess Weight and OCS use, Acute Care visits, Hospital Admission: Summary of Crude Effects

Summary of crude odds ratios (OR_{CR}) and 95% Wald Confidence interval for asthma control (defined by OCS use, acute care visits, hospital admission) for each candidate variable. The * denotes the reference category. ǂ represents statistical significance from the reference category where α=0.05. [§]No OR and 95% CI were generated for hospital admissions due to the small sample resulting in unstable estimates.

EXPLANATORY VARIABLE	CRUDE EFFECTS					
	OCS Use		Acute Care Visits		Hospital Admission	
	OR	95% Wald CI	OR	95% Wald CI	OR	95% Wald CI
BMI Percentile Categories						
Excess Weight vs. Normal Weight*	0.79	(0.54-1.15)	0.76	(0.54-0.11)	0.97	(0.47-1.98)
Age Category						
7-12 vs. 2-6*	0.41	(0.28-0.62) ǂ	0.67	(0.48-0.93) ǂ	0.43	(0.19-0.96) ǂ
Sex, Male*						
Female	0.70	(0.48-1.01)	0.67	(0.48-0.94) ǂ	0.87	(0.43-1.8)
Ethnicity, Caucasian*						
Black	1.19	(0.67-2.11)	1.72	(1.03-2.89) ǂ	1.54	(0.54-4.36)
Asian	0.59	(0.31-1.12)	0.78	(0.44-1.36)	1.00	(0.32-3.07)
Other	0.79	(0.39-1.59)	1.06	(0.58-1.96)	0.74	(0.16-3.33)
Missing	0.76	(0.49-1.19)	1.09	(0.74-1.62)	0.94	(0.39-2.26)
Asthma Severity, Mild*						
Moderate	2.07	(1.40-3.05) ǂ	1.99	(1.40-2.84) ǂ	2.59	(1.19-5.6) ǂ
Severe	3.71	(2.07-6.65) ǂ	4.49	(2.58-7.83) ǂ	5.34	(2.04-14.0) ǂ
Reported Control, Good*						
Satisfactory	1.70	(0.92-3.15)	1.21	(0.70-2.09)	0.35	(0.09-1.34)
Poor	2.59	(1.28-5.25) ǂ	2.47	(1.33-4.60)	1.10	(0.32-3.77)
Comorbidities						
Lower-Respiratory						
Yes vs. No*	3.08	(1.45-6.54) ǂ	2.44	(1.16-5.11) ǂ	2.71	(0.78-9.42)
Upper-Respiratory						
Yes vs. No*	1.42	(0.74-2.73)	1.45	(0.79-2.63)	0.88	(0.21-3.77)
Atopic						
Yes vs. No*	1.34	(0.93-1.93)	1.15	(0.82-1.61)	1.04	(0.50-2.16)
Exposure to Smoke						
Yes vs. No*	1.04	(0.48-2.23)	1.09	(0.54-2.18)	1.86	(0.23-6.57)
Missing vs. No*	0.70	(0.47-1.04)	0.76	(0.53-1.07)	1.10	(0.53-2.30)
ICS use						
Yes vs. No*	0.71	(0.47-1.08)	0.84	(0.58-1.21)	1.14	(0.54-2.42)
Proper Technique						
Yes vs. No*	2.28	(0.53-9.9)	1.56	(0.52-4.67)	0.93	(0.12-7.30)
Previous Medical Visits						
Yes vs. No*	3.34	(2.14-5.21) ǂ	3.12	(2.12-4.59) ǂ	1.87	(0.83-4.22)
Previous Hospital Admission						
Yes vs. No*	4.26	(2.86-6.34) ǂ	3.56	(2.52-5.04) ǂ	2.19	(1.05-4.57)
Previous OCS use						
Yes vs. No*	3.07	(2.06-4.58) ǂ	2.67	(1.84-3.89) ǂ	4.77	(2.27-10.04) ǂ
Previous ICU Admission						
Yes vs. No*	3.00	(1.28-7.01) ǂ	1.36	(0.55-3.34)	4.22	(1.17-15.2)
Missed School						
Yes vs. No*	1.80	(1.01-3.21) ǂ	1.72	(1.04-2.83) ǂ	1.67	(0.53-5.21)
Social Deprivation, 1*[§]						
2	4.18	(0.50-35.0)	0.59	(0.15-2.24)	---	---
3	2.53	(0.30-21.3)	0.68	(0.18-2.50)	---	---
4	3.51	(0.44-27.68)	0.88	(0.26-2.98)	---	---
5 vs. 1	2.27	(0.28-18.58)	0.71	(0.20-2.48)	---	---

Table 4.9 summarizes the adjusted OR along with the 95% Wald Confidence interval for each explanatory variable.

Table 4.9: Excess Weight and Poor Asthma Control: Summary of Adjusted Effects of Final Model

Summary of adjusted odds ratios (OR_{ADJ}) and 95% Wald Confidence interval on asthma control for each outcome and candidate variable (based on North American definition). In the adjusted model predicting poor asthma control, the reported point estimates control for all other explanatory variables that had a p-value 0.05. BMI based weight categories, Age, Sex and Ethnicity were forced into the model The * denotes the reference category, ǂ represents statistical significance from the reference category where α=0.05

EXPLANATORY VARIABLE	ADJUSTED EFFECTS					
	OCS Use		Acute Care Visits		Hospital Admission	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
BMI Percentile Categories						
Excess weight vs. Normal*	0.93	(0.62-1.39)	0.84	(0.59-1.20)	1.08	(0.52-2.25)
Age category						
7-12 vs. 2-6*	0.43	(0.28-0.65) ǂ	0.84	(0.58-1.20)	0.49	(0.21-1.12)
Sex, Male*						
Female	0.65	(0.43-0.96) ǂ	0.65	(0.45-0.92) ǂ	0.87	(0.42-1.81)
Ethnicity, Caucasian*						
Black	1.05	(0.57-1.94)	1.74	(1.01-3.01) ǂ	1.63	(0.56-4.77)
Asian	0.67	(0.34-1.30)	0.87	(0.49-1.56)	1.11	(0.35-3.53)
Other	0.88	(0.42-1.84)	1.21	(0.63-2.32)	0.78	(0.17-3.62)
Missing	0.62	(0.38-1.01)	1.13	(0.74-1.73)	0.90	(0.36-2.25)
Asthma Severity, Mild*						
Moderate	1.75	(1.16-2.62) ǂ	1.77	(1.22-2.57) ǂ	2.48	(1.13-5.42)
Severe	3.06	(1.62-5.76) ǂ	3.96	(2.20-7.14) ǂ	4.78	(1.77-13.0)
Comorbidities						
Lower-Respiratory						
Yes vs. No*	2.46	(1.08-5.64) ǂ	2.02	(0.91-4.50)	NI	NI
Miss School						
Yes vs. No*	1.01	(1.0-1.01) ǂ	1.01	(1.0-1.01) ǂ	NI	NI
Previous Med Visit						
Yes vs. No*	0.98	(0.97-0.99) ǂ	NI	NI	NI	NI
Previous ICU admission						
Yes vs. No*	1.01	(1.0-1.01) ǂ	NI	NI	1.01	(1.0-1.02)
ICS use						
Yes vs. No*	0.52	(0.32-0.83) ǂ	0.64	(0.41-0.99) ǂ	NI	NI

(NI) represents variables that were found not significant in the crude and therefore not included in the adjusted model.

Based on the adjusted model, we did not find a statistically significant association between weight and the use of OCS, acute care visits and hospital admissions.

Sensitivity Analysis

A sensitivity analysis was performed to further investigate the effect of weight on asthma control, using a more flexible definition of the outcome. We created a composite outcome combining the primary outcome and secondary outcomes. We redefined poor asthma control as:

1. 4 or more doses of β_2 agonist
2. 1 or more hospitalizations
3. 1 or more OCS
4. 1 or more acute care visits

A patient profile was generated, showing the distribution of study participants that were identified as having poor asthma control according to the expanded definition (Figure 4.5).

Table 4.10 and 4.11 summarizes the odds ratios and 95% Wald confidence for the crude and adjusted model respectively.

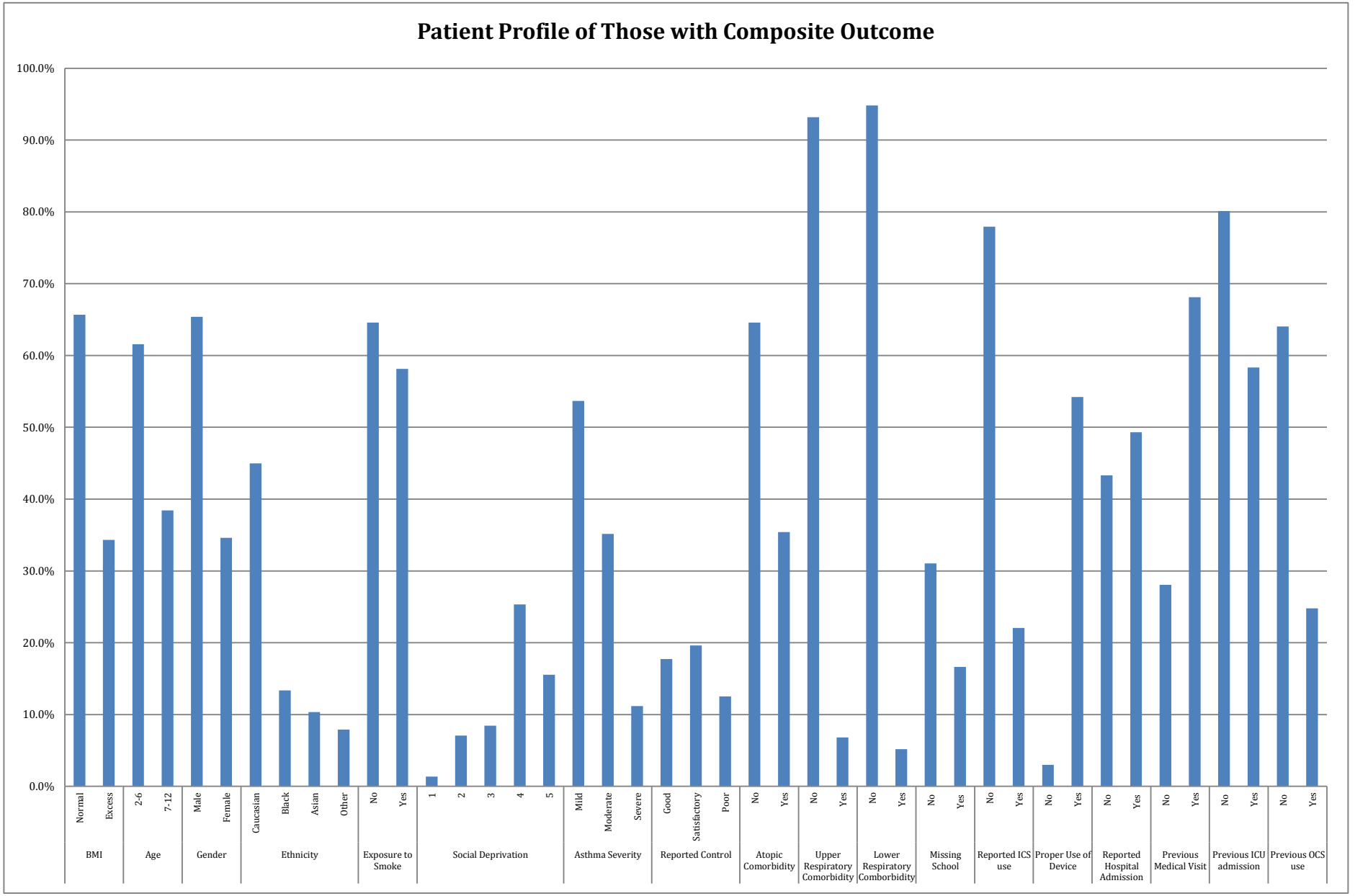


Figure 4.5: Patient profile of participants that were categorized as "poor control" based on the composite outcome combining the primary and secondary outcomes of the study during the follow up period. The denominator is the entire study population of 817. *The comorbidities include atopic conditions (food allergy, allergic rhinitis, eczema, conjunctivitis); upper-respiratory tract conditions (swallowing dysfunction, vocal cord dysfunction, recurrent sinusitis and recurrent otitis); and lower-respiratory tract conditions (bronchopulmonary aspergillosis, recurrent pneumonias, bronchitis and gastroesophageal reflux disease)

Table 4.10: Excess Weight and Composite Poor Control: Crude Effects of Composite Outcome

Summary of crude odds ratios (OR_{CR}) and 95% Wald Confidence interval for asthma control for each candidate variable (based on primary and secondary outcomes combined) for each candidate variable. The * denotes the reference category. ǂ represents statistical significance from the reference category where α=0.05. [§]No OR and 95% CI were generated for hospital admissions due to unstable estimates.

EXPLANATORY VARIABLE	UNADJUSTED EFFECTS	
	Composite Outcome	
	OR	95% Wald CI
BMI Percentile Categories		
Excess Weight vs. Normal Weight	0.88	(0.66-1.17)
Age Category		
7-12 vs. 2-6*	0.82	(0.62-1.09)
Sex, Male*		
Female	0.75	(0.57-1.00)
Ethnicity, Caucasian*		
Black	1.87	(1.14-3.05)
Asian	0.77	(0.49-1.22)
Other	0.98	(0.58-1.67)
Missing	0.87	(0.61-1.22)
Asthma Severity, Mild*		
Moderate	2.17	(1.59-2.98)
Severe	3.84	(2.15-6.87)
Reported Control, Good*		
Satisfactory	0.11	(0.72-1.73)
Poor	0.88	(1.38-4.23)
Comorbidities		
Lower-Respiratory		
Yes vs. No*	2.18	(1.02-4.64)
Upper-Respiratory		
Yes vs. No*	1.06	(0.61-1.85)
Atopic		
Yes vs. No*	1.38	(1.03-1.86)
Exposure to Smoke		
Yes vs. No*		
Missing vs. No*	1.49	(0.79-2.80)
ICS use		
Yes vs. No*	0.63	(0.46-0.87)
Proper Technique		
Yes vs. No*	0.99	(0.43-2.25)
Previous Medical Visits		
Yes vs. No*	1.98	(1.47-2.67)
Previous Hospital Admission		
Yes vs. No*	2.17	(1.62-2.90)
Previous OCS use		
Yes vs. No*	1.66	(1.17-2.35)
Previous ICU Admission		
Yes vs. No*	1.80	(0.79-4.10)
Missed School		
Yes vs. No*	1.82	(1.19-2.79)
Social Deprivation, 1*[§]		
2	1.30	(0.38-4.45)
3	1.31	(0.39-4.39)
4	1.40	(0.44-4.40)
5	1.63	(0.50-5.28)

Table 4.11: Excess Weight and Composite Poor Control: Adjusted Effects of Composite Outcome

Summary of adjusted odds ratios (OR_{ADJ}) and 95% Wald Confidence interval on asthma control for each candidate variable (based on primary and secondary outcomes combined). In the adjusted model predicting poor asthma control, the reported point estimates control for all other explanatory variables that had a p-value 0.05. BMI based weight categories, Age, Sex and Ethnicity were forced into the model. The * denotes the reference category".

EXPLANATORY VARIABLE	ADJUSTED EFFECTS		
	Composite Outcome		
	OR_{ADJ}	(95% CI)	p-value
BMI Percentile Categories			
Excess weight vs. Normal weight*	0.94	(0.69-1.27)	0.69
Age category			
7-12 vs. 2-6*	0.89	(0.66-1.20)	0.43
Sex, Male*			
Female	0.73	(0.54-0.98)	0.04
Ethnicity, Caucasian*			
Black	1.78	(1.07-2.96)	0.03
Asian	0.88	(0.54-1.40)	0.57
Other	1.08	(0.62-1.88)	0.79
Missing	0.87	(0.61-1.25)	0.45
Asthma Severity, Mild*			
Moderate	2.00	(1.44-2.76)	<0.0001
Severe	3.84	(2.10-7.01)	<0.0001
Missed School			
Yes vs. No*	1.00	(1.00-1.01)	0.007
Inhaled Corticosteroids (ICS) use			
Yes vs. No*	0.57	(0.40-0.80)	0.001

In both the crude and adjusted models weight is not associated with the composite measure of asthma control.

5.0 Discussion

The objective of this thesis was to determine whether excess weight had an effect on asthma control in children. This was measured primarily through the use of short acting β_2-agonists (SABA) and further explored through indicators of asthma control, mainly: use of oral corticosteroids, hospital admission and acute care visits. Contrary to the study hypothesis, there was no statistically significant association between excess weight and asthma control as defined by use of β_2-agonists (rescue medication) based on the North American and International thresholds among children diagnosed with asthma.

We hypothesized based on the literature that children with asthma who are also overweight or obese may face an additional challenge that can adversely impact asthma control [19]. In previous research, overweight children with asthma have been shown to be more resistant to available steroid treatments and require higher medication use [19, 39, 40]. The new asthma phenotype theory is strongly supported by longitudinal investigations that have found that overweight or obese children experience more asthma symptoms when compared with normal weight children [15, 16]This suggests that asthma in obese children may represent a unique phenotype that does not respond well to conventional therapy [180].

Our findings are different than what we hypothesized, these findings may be due to the design we chose in determining the effect of weight on asthma control. Previous studies have supported the relationship between excess weight and asthma control [39, 166, 17]. A retrospective study by Quinto et al reported that β_2-agonists were more likely to be dispensed to overweight (OR=1.15, 95% CI 1.02-1.27) and obese (OR=1.17, 95% CI 1.06-1.29) children [39] than to non-overweight children. The study used a similar methodology to that used in this thesis, by relying on prescription data. We found that the odds of exhibiting poor asthma control was not associated with weight status. The differences in our findings may be attributed to a few study design issues. Instead of using provincial prescription databases, the study by Quinto et al used individual medical records. They had a more detailed account for each patient's prescriptions, thus eliminating any assumptions we had to make in our

data. For example, to account for records that were incomplete, we imputed ß$_2$-agonists use per week for patients. In discussing the differences in outcomes between this thesis and the research by Quinto et al, it is important to consider the differences in the sample sizes between the two studies as well as in the definition of asthma control by β_2-agonist. The study by Quinto et al had a large number of children (*n*=32 321) and thus a much greater power. In addition, they had a larger proportion of overweight and obese individuals that accounted for approximately 50% of their sample, compared to the 36.0% in our sample. In defining asthma control Quinto et al also used a different definition; they defined poor control as having more than six β_2-agonist units dispensed per year [39]. Though similar methodologies were used between the two studies, differences in the definition of asthma control and sample may have attributed to contrasting results. Our results were not consistent with our initial hypothesis, however these findings are congruent with studies by Kwong et al and Giese et al that found no association between asthma control and excess weight [165, 167]. Overall, with the conflicting findings on the effect of weight on asthma control, there is no consensus on the association between excess weight and poor control measured by the use of SABA.

In considering our findings, it is important to take into account that we have selected children of persons with a public insurance plan. These are children whose parents or legal guardians fall under one of the following categories: (1) people who are not eligible for a private insurance plan (group insurance or employee benefit plan); (2) people who have reached retirement age of 65 years or over; and (3) people who are recipients of "last-resort financial assistance[15]" and/or are holders of a "claim slip.[16]" Most of the people who are parents of children will be in the first group as this will include people who are self-employed, unemployed, working part time or at positions where no company health insurance is provided i.e. lower earning positions. The selection criteria of public drug insurance coverage, therefore means that our study population will likely have a lower socio-economic status on average. In

[15] A program administered by the government of Quebec administering financial support to persons with limited resources (RAMQ,2014)

[16] Claim slip provided by the ministry of employment and solidarity to recipients of last-resort financial assistant programs and on occasion adults and families who do not have last-resort finanvcial assistance benefits. (RAMQ, 2014)

comparing the normal weight individuals versus excess weight individuals, we may consider that not finding a difference in asthma control by the use of SABA between the two groups may be explained by the health status implications attributed to lower socioeconomic status in "normal" weight children. Children of lower socioeconomic status experience more health problems [181, 182]. As it relates to asthma control, socioeconomic status has a negative impact on the management and severity of the disease [183, 184]. In our study, it could be that the lower SES of the normal weight and excess weight may have had a greater impact than weight, and thus both groups may not be different in respect to asthma control by the use of SABA and other asthma control indicators. In fact, a large proportion of our sample was found to have high social deprivation (see table 4.1). In our study population the most deprived quintiles (4 and 5) accounted for 57.3% of those with a known social deprivation quintile, and 31.6% of our overall sample population.

Although we did not find an association between weight and asthma control by use of SABA, we did find that several variables had an impact on the use of β_2-agonists. Age, sex, ethnicity and neighborhood factors may affect the relationship between excess weight and asthma control. Recent studies have shown the association between sex and asthma where asthma control was found to be better in girls than in boys prior to adolescence [164]. Our findings show that girls are 24.2% less likely to have poor control than boys (OR=0.63 (95% CI 0.46-0.86). In addition to age, sex, and ethnicity having an effect on weight status [185, 186, 187] these three factors have also been associated with asthma control [17, 188, 189]. We did not find an association between ethnicity and the use of SABA. However, from our analyses, we can conclude that age is associated with the use of β_2-agonists, and by extension, poor asthma control (OR= 0.63 (95% CI 0.46-0.86). Older children in the 7-12 years category were 37.2% less likely to have poor control than children aged 2-6 years. These findings are consistent with those reported by Holguin et al. who reported age differences in attaining good control. We speculate that older children may take a more active part in managing their asthma; by an older age they may take the necessary measures to decrease the risk of exacerbation [190]. In addition, older children may more easily differentiate asthma related symptoms from other

respiratory symptoms and in turn by using their β_2-agonists on an as needed basis, are less likely to treat non-asthma respiratory symptoms with rescue inhalers.

Individuals with lower-respiratory tract conditions were statistically more likely to use have poor asthma control (OR=2.17, 95% CI 0.70-4.7) by the North American definition and 3.09 (95% CI1.30-7.33) by the international definition of control. We suspected that respiratory related comorbidities might impact the use of β_2-agonists. In our study, we categorized gastroesophageal reflux (GERD) as a lower-respiratory tract condition. GERD has been associated with greater use of SABA [191]. In fact, there is a large amount of publication addressing GERD with asthma [192]. The association between the GERD and SABA can be described as a "loop of relief". McCallister et al explain that asthma patients often have lung hyperinflation that creates a pressure gradient between the abdomen and the chest due to the increased work of breathing. This pressure can cause the lower esophageal sphincter (LES) to herniate into the chest and in turn allow more reflux of gastric contents among children with asthma than non-asthmatic children. The relief loop occurs because SABA have been shown to reduce LES pressure, and thus individuals may seek symptom relief by using their SABA, however ß$_2$-agonists are one of several asthma medications that promote acid reflux. This creates "relief loop" where patients experience asthma symptoms from their GERD, and in an attempt to alleviate this they use SABA, which actually *promotes* more GERD [191]. This may translate into an increase use of SABA in patients with GERD due to misuse of β_2-agonist.

The physician assessment of severity was a significant determinant of asthma control in the univariate and multivariate analysis. For this reason, the sample was stratified by severity; this served a type of sensitivity analysis to assess whether the association between excess weight and asthma control within the adjusted model were potentially undetected due to the strong influence of severity. It is reasonable that high severity is associated with greater use of β_2-agonist. Earlier, we defined severity in two ways: 1. By the intensity of exacerbations, and 2, by the intensity of the therapy [8]. Using the definitions alone, we can expect severity to have a direct effect on the use of medication and thus we expected that it would impact our results. However, even by controlling for severity (via stratification), we did not observe

significant associations between asthma control and excess weight. This may be due to residual confounding. When comparing the crude and adjusted effects in the North American standards for example, we observed a difference in odds ratios of 2.03 vs. 1.87 in the moderate, and 1.70 vs. 1.66 in severe, suggesting the presence of confounding. However, when adjusting for this, due to the small size of the sample, we categories were collapsed the moderate and categories. Thus we speculate that residual confounding may have been introduced as small numbers did not allow us to analyze moderate and severe groups separately.

Secondary Outcomes (Acute Care Visits, OCS use, Hospitalization)

No association was found between excess weight and acute care visits, oral corticosteroid use or hospitalization. Similar findings in the relationship between excess weight and our secondary outcomes were obtained by Tantisra et al. The study, conducted in a pediatric population, found no relationship between BMI and the use of corticosteroids, emergency department visits and hospitalizations [193]. Our results are however conflicting with a study by Quinto et al. that reported an increased risk for oral corticosteroids dispensed (OR=1.21, 95% CI 1.13-1.29) using similar methodologies to those used in our research [39]. To our knowledge, pediatric studies assessing weight and asthma related hospitalizations have not been well studied, however, adult studies have reported increased risk of asthma related hospitalizations in obese individuals compared to non-obese individuals. We did not have a sufficient number of children who were obese to investigate this relationship and our use of excess weight may have diluted the strength of some of the associations.

While assessing the impact of excess weight on indicators of asthma control, we found associations between the indicators and other covariates. In our sample, girls were less likely to use OCS and visit acute care facilities for asthma related reasons, with OR of 0.65 (95% CI 0.43-0.96) and 0.65 (95% CI 0.45-0.92) respectively. We found that moderate severity was associated with the use of OCS and acute care, with OR of 1.75 and 1.77 in OCS use and acute care visits respectively when compared to mild severity. The OR are significantly higher where patients with severe asthma were three times more likely to use OCS, and almost 4 times more likely to have acute care visits (3.06, 95% CI 1.62-5.76; 4.0, 95% CI 2.20-7.14). We also found that having lower-respiratory tract comorbidity was associated with a higher use of OCS.

Our findings on sex differences and the use hospital admissions and acute care visits are consistent with the literature, suggesting that asthmatic boys are more likely to use health services than girls in this pre-pubescent age group [164, 39].

We expect children with lower-respiratory tract comorbidities in addition to their asthma to seek respiratory relief more often than children who do not. It is

possible that lower-respiratory tract conditions were confounded with OCS use, as illustrated in the differences between the crude and adjusted OR (3.08 vs. 2.47, respectively). Further exploration is necessary, by adjusting for lower-respiratory tract comorbidities, and analyzing its interaction with poor control and weight status to obtain a more accurate picture of the effect of weight status on asthma control.

Composite Outcome

We did not find an association between weight status and asthma control in our sensitivity analysis. A sensitivity analysis is broadly defined as "a series of analyses of a data set to assess whether altering any of the assumptions made leads to different final interpretations or conclusions" [194]. The sensitivity analyses are important in determining the consistency in the results and also to assess the robustness of our analysis and ensure the appropriate interpretation of results when other factors are taken into account. In this thesis there were several sensitivity analyses built into the analytical plan. We achieved this firstly by incorporating the two definitions of asthma control and secondly by creating a composite outcome. The key type of sensitivity analysis that we performed was by revisiting the definition of "poor asthma control". In doing so we redefined poor control as: 1) 4 or more doses of β_2 agonist, 2) 1 or more hospitalizations, 3) 1 or more OCS and 4) 1 or more acute care visits.

Our results did not correspond to the literature. A pediatric study has shown that overweight children who present to the emergency department with acute asthma exacerbations are significantly more likely to be admitted to the hospital than non-overweight children [40]. We can speculate that the differences between our findings and those found Caroll et al may be attributed to the fact that their study did not use BMI as a measure of excess weight using height and weight information but instead used weight-for-age percentiles. The methodological differences could contribute to the differences in our findings between Carroll et al and those presented in this study. BMI is an ideal measure as it provides an inexpensive, practical and universal means of assessing excess body fat. A great advantage of BMI percentile, unlike the weight for age percent used in the study is the fact that it is used widely within the literature and provides a figure that can be compared to other studies.

The use of ICS is protective against our composite outcome, meaning, children that use ICS reduce the likeliness of increased OCS use, SABA use, hospital admission and acute care visits. ICS has been demonstrated to be effective in controlling asthma and is prescribed as a controller medication. Interestingly, Boulet and Franssen, reported that obese asthmatics that are treated with inhaled corticosteroids were less likely to achieve good asthma control than normal weight

asthmatic patients [24]. The authors speculated that this was attributed to the impaired glucocorticoid sensitivity observed in obese individuals. In a previous study by Sutherland, there were no differences in therapeutic responses to leukotriene modifiers in the treatment of asthma amongst obese individuals suggesting a possible reduced effect of the inhaled corticosteroids controller medication [195]. Further explorations in medication resistance must be explored in pediatric populations. Sutherland reported in-vitro glucocorticoid[17] resistance in obese adult asthmatics, further suggesting that cellular glucocorticoid resistance may be in part explained by increased asthma attributable to obesity [195]. The glucocorticoid is an essential component of the feedback mechanism in the immune system that turns the immune activity of the body down. Extrinsic versions of the hormones are often used to treat asthma and other diseases that cause an overactive immune system. Our results indicate that ICS plays an important role in what we redefined as asthma control. Although we did not find this, previous research indicates that the response to asthma medications may be influenced by obesity. A randomized post hoc analysis that was pooled from four double blind, placebo controlled studies of 3 070 asthmatic adults by Peters-Golden et al based on BMI and asthma control demonstrated a decreased response to inhaled corticosteroids with increasing BMI [196]. Overweight and obese patients demonstrated significantly less improvement in exhaled nitric oxide[18] ($p=0.04$) and lung function ($p=0.04$) with the use of inhaled corticosteroids than normal weight patients. In reviewing this analysis, further studies can be done to evaluate the responsiveness of obese children to inhaled corticosteroids. Our studies confirm the association between the protective nature of ICS in exhibiting poor control. In analyzing the responsiveness of excess weight children to ICS, we would expect that ICS would be ineffective in excess weight individuals and subsequently there would be an increased risk for excess weight children to be associated with our composite outcome and by extension have poor control of their asthma.

[17] Glucocorticoids are corticosteroids that are involved in the metabolism of carbohydrates, proteins and fats and in anti-inflammatory response.

[18] Exhaled nitric oxide (NO)- Nitric oxide is a biological mediator produced by the lungs. It is produced to flight inflammation. High levels of nitric oxide is an indication of airway inflammation as NO is involved in the pathophysiology of lung disease.

Limitations of Research

Selection Bias. Our study population required the identification of patients with continuous medical coverage. The cohort of 2 141 represented patients with and without a public prescription drug insurance. Since medication records can only be obtained for children on the public prescription drug insurance administered by the *Régie de l'assurance maladie du Québec* (RAMQ), we removed those that had not been continuously covered during our follow-up period. Once those without prescription medical insurance were removed from the sample 817 participants remained. This represented approximately 40% of the sample. According to the annual report published by RAMQ in 2013, approximately 3.5 million individuals in Quebec receive the public drug insurance; this represents about 42.9% of the Quebec population [197]. Our cohort sample therefore had a proportion is consistent with what was expected given coverage. Based on the eligibility criteria in obtaining RAMQ coverage, our sample is inherently biased towards a low socioeconomic demographic thus not completely representative of the population of children with asthma. We know from the literature that socioeconomic status has a direct impact on health outcomes, and more specifically in experiencing asthma-related issues. It could be that normal weight individuals in our study population, due to lower socioeconomic status, may be experiencing poorer health outcomes than the population of normal weight children in Quebec, and thus our normal weight participants may not be detectably different from our excess weight group in achieving good control.

Unmeasured confounders. A number of confounders were identified in the beginning stages of the study based on published epidemiological studies. Based on these studies, we hypothesized that: age, sex and exposure to smoke would have confounding effects on our outcome, asthma control. We accounted for this by including these factors in our regression model. If we had a larger sample size, we could have adjusted for the confounders by matching excess weight individuals to normal weight individuals based on the forementioned characteristics. In our analysis, by comparing crude and adjusted OR, we can estimate that there may be confounding influence in: severity and comorbidities. However, computing stratum-specific effect

estimates for all covariates would have allowed us to identify confounders and effect modifiers more precisely.

Time-Dependent Exposure. We avoided patient reporting bias in the measure of height and weight. Since weight and height measures were obtained at the index visit by a health care professional, we did not have to make adjustments for the under-estimation of weight and overestimation of height. We did not however, account for the possibility that study participants may have lost or gained weight in the course of our one year follow-up in our analysis. This has allowed for the possibility of our exposure, BMI, to change. The stability in BMI classification over an extended follow-up time has mainly been studied in adults. Adults show stability in BMI over an extended period where their weight status does not fluctuate greatly. This is not the case in children, as they experience a greater fluctuation in weight over an extended time, and thus the stability in weight is exponentially smaller in children [198], heightening the possibility for a change in the weight categories over time. Because our weight categories were had a large range, where excess weight encompassed overweight (BMI 84th to 95th percentile) and obese individuals (BMI> 95th percentile), it is not likely that a child would change from normal weight to excess weight and vice versa in the course of a year. Nonetheless, to ensure that no change in weight categories has occurred, other measures of weight during follow-up should be considered, and analyzed for change. Individuals that do change weight categories should during follow-up be re-classified in the appropriate group.

Misclassification Bias. An advantage of this study is that we relied on physician diagnosis of asthma, and thereby avoided misclassification with self-reported asthma. Although it has been shown that there is an over diagnosis of asthma in overweight individuals, in adults, studies have shown that over diagnosis occur in the same rate in individuals who are not overweight [199]. Therefore, diagnosis of asthma by the physician would likely not bias our sample.

Sample size. We did not attain the maximum number of participants to detect an effect between BMI and asthma control and did not anticipate the missing data in our clinical database. The missing values consequently may have affected the resulting model predicting factors associated with asthma control. It is important to

note that we imputed the data for our primary measure, SABA doses per week and severity. To account for the missing data, imputations on variables such as: ethnicity and social deprivation for example would have minimized the impact of missing data. Despite the limited sample in some cases we were able to detect differences in asthma control, these differences were noted in age and asthma severity.

The lack of association between excess weight and asthma control appear to be consistent with published literature [193]. However, due to aforementioned methodological limitations, we cannot conclude that excess weight is not associated with the use of more than 4 SABA per week. The study however provides key analyses creating opportunities for further research.

Conclusion

The aim of this research was to *determine among children diagnosed with asthma, the extent to which having excess weight affects asthma control.* To accomplish this aim, two objectives were outlined:

1. To assess the extent to which excess weight has on the rate of SABA use per week
2. To assess the effect of excess weight on markers of asthma control, mainly health care visits, hospitalization and use of oral corticosteroids

We found our study results to be inconclusive and did not observe an association between excess weight and the use of SABA and by extension, asthma control. We speculate that with a larger sample size we would be able to make more accurate inferences in the extent to which excess weight affect the use of $ß_2$-agonists. We were also not able to make conclusive inferences on the effect of weight on the selected markers of asthma control. The occurrences of health care visits and hospitalizations were rare within our sample and made it difficult to make inferences on the association between excess weight and our secondary outcome.

This is important as it contributes to the literature in the effect of weight on asthma management. We found interesting associations but were unable to derive to conclusive results. This may be due to methodological limitations. Since researchers suggest addressing the potential association between weight and asthma control by adjusting medication dosage in obese children [39]. We believe that it is important that further analyses that address the methodological shortcomings addressed in the limitations be conducted.

Although we did not find a statistically significant association between excess weight and poor control, the study does provide insight into potential confounders of asthma control. The combination of the detailed clinical data combined with the pharmaco-epidemiological data derived from existing provincial databases provided a rich, unique data source to explore the objective of this study. In addition, what is unique to our study is incorporating the two definitions of asthma control by use of $ß_2$-agonists, this is especially interesting as it can encourage discussion around which definition, between the North American standard and the International standard, is

most true in defining poor control or whether there is a substantial difference between the two definitions in detecting individuals with poor control.

Possibilities for future research

This study can be replicated in a greater sample in order to provide results that with greater statistical power. In addition, based on the findings on this thesis there are opportunities for further research in the role of excess weight in asthma control. In our sensitivity analysis we noticed several interesting results: 1) ethnicity is associated with poor control, 2) ICS uses is protective against poor control. From the literature we explored the role of inhaled corticosteroids in the treatment of asthma and the pharmacokinetic differences the metabolism of ICS between obese and normal children. In our analyses, we established that ICS is protective in exhibiting markers of poor control. Taking the two concepts further, it would be interesting to analyze the responsiveness of obese children to ICS and subsequently evaluate whether their responsiveness has an impact on their ability to achieve good asthma control. Our sensitivity analysis also indicate that there is an association between our composite outcome for control and ethnicity, the concept of ethnicity and asthma prevalence has been studied before, but it would be interesting to see the association between asthma control across multiple ethnicities. And lastly, further studies can be done in investigating what is the best way to objectively assess control. In this thesis, two definitions were used: the North American and the International; however other studies have defined asthma control by a different volume of SABA dispensed or in some cases by the use of oral corticosteroids. It would be interesting to see which of these measures would provide the most sensitive objective measure of control across large sample sizes.

References

1. K. M. Conn, J. S. Halterman, K. Lynch and M. D. Cabana. The impact of parents' medication beliefs on asthma management. *Pediatrics* 2007; 120(3): e521-e526.
2. L. J. Akinbami and K. Schoendorf. Trends in childhood asthma: prevalence, health care utilization, and mortality. *Am Aca Pediatrics* 2002; 110(2): 315-322.
3. Public Health Canada. Life and Breath: Respiratory Disease in Canada. *Public Health Agency of Canada* 2007.
4. R. Garner and D. Kohen. Changes in prevalence of asthma among Canadian children. *Health Reports* 2008; 19(2): 45-50.
5. W. J. Miller and G. B. Hill. Childhood Asthma. *Health Reports* 1998; 10(3): 9-21.
6. H. K. Reddel, R. Taylor, E. D. Bateman, L.-P. Boulet, H. A. Boushey, W. W. Busse and T. B. Casale. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Journal of Respiratory and Critical Care Medicine* 2009; 180(1): 59-99.
7. A. Becker, D. Berube, Z. Chad, M. Dolovich, F. Ducharme, T. D'Urzo and P. Ernst. Canadian pediatric asthma consensus guidelines, 2003 (updated to December 2004). *Canadian medical Association Journal* 2005; 173(6): S12-S14.
8. W. M. Vollmer. Assessment of asthma control and severity. *Annals of Allergy, Asthma and Immunology* 2004; 93(5): 409-414.
9. W. M. Vollmer, L. E. Markson, E. O'Connor, L. L. Sanocki, L. Fitterman, M. Berger and S. Buist. Association of asthma control with health care utilization and quality of life. *American Journal of Respiratory and Critical Care Medicine* 1999; 160(5): 1647-1652.
10. C. Lemiere and M. FitzGerald. Canadian Thoracic Society 2012 guideline update: diagnosis and management of asthma in preschoolers, children and adults. *Can Respir J* 2012; 19(2): 127-164.
11. A. Leblanc, P. Robichaud, Y. Lacasse and L.-P. Boulet. Quantification of asthma control: validation of the Asthma Control Scoring System. Allergy 2007; 62(2): 120-125.
12. M. Masoli, D. Fabian, S. Holt and R. Beasley. The global burden of asthma: executive summary of the GINA Dissemination Committee. *Allergy* 2004; 59(5):469-478.
13. K. Roberts, M. Shields, M. de Groh, A. Aziz and J.-A. Gilbert. Overweight and obesity in children and adolescents: results from the 2009 to 2011 Canadian Health Measures Survey. *Health Reports* 2012; 23(3): 37-41.
14. C. Papoutsakis, K. N. Priftis, M. Drakouli, S. Prifti, E. Konstantaki, M. Chondronikola, G. Antonogeorgos and V. Matziou. Childhood overweight/obesity and asthma: is there a link? A systematic review of recent epidemiologic evidence. *Journal of the*

Academy of Nutrition and Dietetics 2013; 113(1): 77-105.

15. F. D. Gilliland, K. Berhane, T. Islam, R. McConnell, J. Gauderman, S. S. Gilliland, E. Avol and J. M. Peters. Obesity and the risk of newly diagnosed asthma in school-age children. *American Journal of Epidemiology* 2003; 158(5): 406-415.
16. S. Guerra, A. L. Wright, W. J. Morgan, D. L. Sherrill, C. J. Holberg and F. D. Martinez. Persistence of asthma symptoms during adolescence: role of obesity and age at the onset of puberty. *American Journal of Respiratory and Critical Care Medicine* 2004; 170(1): 78-85.
17. J. Castro-Rodriguez, C. Holberg, W. J. Morgan, A. L. Wright and F. D. Martinez. Increased incidence of asthmalike symptoms in girls who become overweight or obese during the school years. *American Journal of Respiratory and Critical Care Medicine* 2001; 163(6): 1344-1349.
18. D. R. Gold, A. Damokosh, D. W. Dockery and C. S. Berkey. Body mass index as a predictor of incident asthma in prospective cohort of children. *Pediatric Pulmonology* 2003; 36(6): 514-521.
19. D. A. Beuther. Recent insight into obesity and asthma. *Current Opinion in Pulmonary Medicine* 2010; 16(1): 64-70.
20. M. J. Akerman, C. C. M and M. K. Madsen. Relationship between asthma severity and obesity. *Journal of Asthma* 2004; 41(5): 521-526.
21. L. L. Barros, A. Souza-Machado, L. B. Correa, J. Santos, C. Cruz, M. Leite, L. Castro, A. C. Coelho, P. Almeida and A. A. Cruz. Obesity and poor asthma control in patients with severe asthma. *Journal of Asthma* 2011; 48(2): 171-176.
22. H. Bibi, D. Shoseyov, D. Feigenbaum, M. Genis, M. Friger, R. Peled and S. Sharff. The relationship between asthma and obesity in children: is it real or a case of over diagnosis. *Journal of Asthma* 2004; 41(4): 403-410.
23. V. Blandon, B. del Rio Navarro, E. B. A and J. J. L. Sienra Monge. Quality of life in pediatric patients with asthma with or without obesity: a pilot study. *Allergologia et Immunopathologia* 2004; 32(5): 259-264.
24. L.-P. Boulet and E. Franssen. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. *Respiratory Medicine* 2007; 101(11): 2240-2247.
25. N. Brisbon, J. Plumb, R. Brawer and D. Paxman. The asthma and obesity epidemics: the role played by the built environment—a public health perspective. *Journal of Allergy and Clinical Immunology* 2005; 115(5): 1024-1028.
26. D. F. Camilo, J. D. Ribeiro, A. D. C. Toro, E. C. E. Baracat and A. d. A. Barros Filho. "Obesity and asthma: association or coincidence?. *Journal de Pediatria* 2010; 86(1): 6-14.
27. S. Chinn. Obesity and asthma: evidence for and against a causal relation. *Journal of Asthma* 2003; 40(1): 1-16.
28. World Health Organization. Obesity: preventing and managing the global epidemic. *World Health Organization* 2000.
29. E. S. Ford. The epidemiology of obesity and asthma. *Journal of Allergy and Clinical Immunology* 2005; 115(5): 897-909.

30. S. Komakula, H. F, S. Khatri, J. Mermis, P. Shah and R. Ingram. Study to evaluate the impact of obesity on airway inflammation and mechanics in African American asthmatics. *Proceedings of the American Thoracic Society* 2005; 2: A771.
31. A. Lessard, H. Turcotte, Y. Cormier and L.-P. Boulet. Obesity and asthma: a specific phenotype?. *CHEST journal* 2008; 134(2): 317-323.
32. S. R. Lucas and T. A. Platts-Mills. Paediatric asthma and obesity. *Paediatric Respiratory Reviews* 2006; 7(4): 233-238.
33. P. Matricardi, C. Gruber, U. Wahn and S. Lau. The asthma-obesity link in childhood: open questions, complex evidence, a few answers only. *Clinical & Experimental Allergy* 2007; 37(4): 476-484.
34. T. M. Ball, J. A. Castro-Rodriguez, K. A. Griffith, C. J. Holberg, F. D. Martinez and A. L. Wright. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *New England Journal of Medicine* 2000; 343(8): 538-543.
35. T. A. Platts-Mills, G. Rakes and P. W. Heymann. The relevance of allergen exposure to the development of asthma in childhood. *Journal of Allergy and Clinical Immunology* 2000; 105(2): S503-S508.
36. R. A. Wood. Pediatric Asthma. *Jama* 2002; 288(6): 745-747.
37. R. Stelmach, R. C. Pinto, M. Reis, A. Halpern, A. Cukier and S. A. Dias-Júnior. Effects Of Weight Reduction In Obese People With Severe Asthma: Randomised Controlled Study. *Am J Respir Crit Care Med* 2011; 183: A4315.
38. H. A. Scott, P. G. Gibson, M. L. Garg and L. G. Wood. Airway inflammation is augmented by obesity and fatty acids in asthma. *European Respiratory Journal* 2011; 38(3): 594-602.
39. K. B. Quinto, B. L. Zuraw, K.-Y. T. Poon, W. Chen, M. Schatz and S. C. Christiansen, "The association of obesity and asthma severity and control in children. *Journal of Allergy and Clinical Immunology* 2011; 128(5): 964-969.
40. C. Carroll. Childhood Overweight Increases Hospital Admission Rates for Asthma. *Pediatrics* 2007; 120(4): 734-740.
41. J. A. Castro-Rodriguez and G. J. Rodrigo. β-Agonists through metered-dose inhaler with valved holding chamber versus nebulizer for acute exacerbation of wheezing or asthma in children under 5 years of age: a systematic review with meta-analysis. *The Journal of Pediatrics* 2004; 145(2): 172-177.
42. L. M. Schachter, J. K. Peat and C. M. Salome. Asthma and atopy in overweight children. *Thorax* 2003; 58(12): 1031-1035.
43. P. F. Belamarich, E. Luder, M. Kattan, H. Mitchell, S. Islam, H. Lynn and E. F. Crain. Do obese inner-city children with asthma have more symptoms than nonobese children with asthma?. *Pediatrics* 2000; 106(6): 1436-1441.
44. J. M. FitzGerald, L.-P. Boulet, R. A. McIvor, S. Zimmerman and K. R. Chapman. Asthma control in Canada remains suboptimal: the Reality of Asthma Control (TRAC) study. *Canadian Respiratory Journal: Journal of the Canadian Thoracic Society* 2006; 13(5): 253.
45. L.-P. Boulet, A. Becker, D. Bérubé, R. Beveridge and P. Ernst. Canadian asthma consensus report, 1999. *Canadian Medical Association Journal* 1999; 161(11)suppl

1: S1-S5.

46. L. P. Boulet, T. R. Bai, A. Becker, D. Berube, R. Beveridge, D. M. Bowie and S. Spier. What is new since the last (1999) Canadian Asthma Consensus Guidelines?. *Canadian Respiratory Journal: Journal of the Canadian Thoracic Society* 2000; 8: 5A-27A.
47. C. Lemiere, T. Bai, M. Balter, C. Bayliff, A. Becker, L.-P. Boulet and D. Bowie. Adult asthma consensus guidelines update 2003. *Can Respir J* 2004; 11: 9A-18A.
48. K. R. Chapman, P. Ernst, A. Grenville, P. Dewland and S. Zimmerman. Control of asthma in Canada: failure to achieve guideline targets. *Canadian Respiratory Journal: Journal of the Canadian Thoracic Society* 2000; 8: 35A-40A.
49. E. F. Juniper, K. Svensson, A.-C. Mork and E. Stahl. Measuring health-related quality of life in adults during an acute asthma exacerbation. *CHEST Journal* 2004*;*125(1): 93-97, 2004.
50. W. O. Spitzer, S. Suissa, P. Ernst, R. I. Horwitz, B. Habbick, D. Cockcroft, J.-F. Boivin, M. McNutt, A. S. Buist and A. S. Rebuck. The use of β-agonists and the risk of death and near death from asthma. *New England Journal of Medicine* 1992; 326: 501-506.
51. E. R. McFadden and E. L. Warren. Observations on asthma mortality. *Annals of Internal Medicine* 1997; 127(2): 142-147.
52. D. Cockroft and V. Swystun. Asthma Control versus Asthma Severity. *J Allergy Clin Immunol* 1996; 98: 1016-1018.
53. E. D. Bateman. Measuring asthma control. *Current Opinion in Alergy and Clinical Immunology* 2001; 1(3): 211-216.
54. E. D. Bateman, J. Bousquet and G. L. Braunstein. Is overall asthma control being achieved? A hypothesis-generating study. *European Respiratory Journal* 2001; 17(4): 589-595.
55. A. L. Fuhlbrigge. Asthma severity and asthma control: symptoms, pulmonary function, and inflammatory markers. *Current Opinion in Pulmonary* Medicine 2004; 10(1): 1-6.
56. National Asthma Education and Prevention Program (National Heart, Lung, and Blood Institute). *Second Expert Panel on the Management of Asthma* 1998.
57. Global Initiative for Asthma. Pocket Guide for Asthma Management and Prevention. [Online]. Available: http://www.ginasthma.org/local/uploads/files/GINA_Pocket_2014_Jun11.pdf. [Accessed 17 November 2014].
58. M. D. Lougheed, C. Lemiere, S. Dell, F. Ducharme, J. M. FitzGerald, R. Leigh and L. P. Boulet. Canadian Thoracic Society Asthma Committee commentary on long-acting beta-2 agonist use for asthma in Canada. *Canadian Respiratory Journal: Journal of the Canadian Thoracic Society* 2010; 17(2): 57.
59. P. M. Gustafsson, L. Watson, K. J. Davis and K. F. Rabe. Poor asthma control in children: evidence from epidemiological surveys and implications for clinical practice. *International Journal of Clinical Practice* 2006; 60(3): 321-334.
60. L. B. Bacharier, R. C. Strunk, D. Mauger, D. White, R. F. Lemanske Jr and C. A. Sorkness. Classifying asthma severity in children: mismatch between symptoms,

medication use, and lung function. *American Journal of Respiratory and Critical Care Medicine* 2006; 170(4): 426-432.

61. S. Godfrey. Problems peculiar to the diagnosis and management of asthma in children. *BTTA Rev* 1974; 4(1): 1-16.
62. R. S. Jones and M. H. W. M. J. Buston. The effect of exercise on ventilatory function in the child with asthma. *British Journal of Diseases of the Chest* 1962; 56(2): 78-86.
63. H. A. Kerstjens, P. L. Brand, P. M. de Jong, G. H. Koeter and D. S. Postma. Influence of treatment on peak expiratory flow and its relation to airway hyperresponsiveness and symptoms. *Thorax* 1994; 49(11): 1109-1115.
64. K. F. Rabe, P. A. Vermeire, J. B. Soriano and W. C. Maier. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. *European Respiratory Journal* 2000; 16(5): 802-807.
65. M. Adachi, A. Morikawa and K. Ishihara. Asthma insights & reality in Japan (AIRJ). *Arerugi* 2002; 51(5): 411-420.
66. P. Aurora, J. Stocks, C. Oliver, C. Saunders, R. Castle, G. Chaziparasidis and A. Bush. Quality control for spirometry in preschool children with and without lung disease. *American Journal of Respiratory and Critical Care Medicine* 2004; 169(10): 1152-1159.
67. W. Nystad, S. O. Samuelsen, P. Nafstad, E. Edvardsen, T. Stensrud and J. J. K. Jaakkola. Feasibility of measuring lung function in preschool children. *Thorax* 2002; 57(12): 1021-1027.
68. F. M. Ducharme, G. M. Davis and G. R. Ducharme. Pediatric reference values for respiratory resistance measured by forced oscillation. *CHEST Journal* 1998; 113(5): 1322-1328.
69. U. Frey, T. Brodbeck, A. Majumdar, D. R. Taylor, G. I. Town, M. Silverman and B. Suki. Risk of severe asthma episodes predicted from fluctuation analysis of airway function. *Nature* 2005; 438(7068): 667-670.
70. A. W. A. Kamps, R. J. Roorda and P. L. P. Brand. Peak flow diaries in childhood asthma are unreliable. *Thorax* 2001; 56(3): 180-182.
71. E. D. Bateman, H. A. Boushey, J. Bousquet, W. W. Busse, T. J. Clark, R. A. Pauwels and S. E. Pedersen. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. *American Journal of Respiratory and Critical Care Medicine* 2004; 170(8): 836-844.
72. F. M. Ducharme, G. M. Davis, F. Noya, H. Rich and P. Ernst. The Asthma Quiz for Kidz: a validated tool to appreciate the level of asthma control in children. *Canadian Respiratory Journal: Journal of the Canadian Thoracic* Society 2003; 11(8): 541-546.
73. K. R. Chapman, P. Ernst, A. Grenville, P. Dewland and S. Zimmerman. Control of asthma in Canada: failure to achieve guideline targets. *Canadian Respiratory Journal* 2000; 8: 35-40.
74. M. Lara, N. Duan, C. Sherbourne, M. Lewis, C. Landon, N. Halfon and R. Brook. Differences between child and parent reports of symptoms among latino children with asthma. *Pediatrics* 1998; 102: 68.
75. G. Guyatt, E. Juniper, L. Griffith, D. Feeny and F. P.J.Children and adult perceptions

of childhood asthma. *Pediatrics* 1997; 99: 165-168.

76. A. H. Liu, R. Zeiger, C. Sorkness, T. Mahr, N. Ostrom, S. Burgess and R. Manjunath. Development and cross-sectional validation of the Childhood Asthma Control Test. *Hournal of Allergy and Clinical Immunology* 2007; 119(4): 817-825.
77. G. Fritz and J. Overholser. Patterns of response to childhood asthma. *Psychosomatic Medicine* 1989; 51: 347-355.
78. M. Townsend, D. Feeny, G. Guyatt, W. Furlong, A. Seip and J. Dolovich. Evaluation of the burden of illness for pediatric asthmatic patients and their parents. *Annals of Allergy* 1991; 67:403-408.
79. E. A. Skinner, G. B. Diette, P. J. Algatt-Bergstrom, T. T. Nguyen, R. D. Clark, L. E. Markson and A. W. Wu. The asthma therapy assessment questionnaire (ATAQ) for children and adolescents. *Disease Management* 2004; 7(4): 305-313.
80. E. F. Juniper, G. H. Guyatt, P. J. Ferrie and D. R. King. Development and validation of a questionnaire to measure asthma control. *European Respiratory Journal* 1999; 14(4): 902-907.
81. E. F. Juniper, P. M. O'Byrne, P. J. Ferrie, D. R. King and J. N. Roberts. Measuring asthma control: clinic questionnaire or daily diary?. *American Journal of Respiratory and Critical Care Medicine* 2000; 162(4): 1330-1334.
82. R. A. Nathan, C. A. Sorkness, M. Kosinski, M. Schatz, J. T. Li, P. Marcus and T. B. Pendergraft. Development of the asthma control test: a survey for assessing asthma control. *Journal of Allergy and Clinical Immunology* 2004; 113(1): 59-65.
83. M. Schatz, M. Kosinski, C. Sorkness, J. Li, P. Marcus, J. Murray and P. Jhingran. Comparison of two patient-based measures of asthma control: ACT and ACQ. *Proceedings of American Thoracic Society* 2005; 2: A255.
84. A. H. Liu, R. Zeiger, C. Sorkness, T. Mahr, N. Ostrom, S. Burgess and R. Manjunath. Development and cross-sectional validation of the Childhood Asthma Control Test. *J Allergy Clin Immunol* 2007; 119(4): 817-825.
85. J. S. Halterman, K. M. McConnochie, K. M. Conn, H. L. Yoos, J. M. Kaczorowski, R. J. Holzhauer and P. G. Szilagyi. A potential pitfall in provider assessments of the quality of asthma control. *Ambul Pediatr* 2003; 3(2): 102-105.
86. Glaxosmithkline. Asthma in Canada 2000. [Online]. Available: http://asthmaeconomics.ca/pdf/GlaxoSmithKline.pdf. [Accessed November 2014].
87. L. P. Boulet, V. Boulet and J. Milot. How should we quantify asthma control? A proposal. *CHEST Journal* 2002; 122(6): 2217-2223.
88. C. E. Kuehni and U. Frey. Age-related differences in perceived asthma control in childhood: guidelines and reality. *European Respiratory Journal* 2002; 20(4): 880-889.
89. American Lung Association. Trends in asthma morbidity and mortality 2005. [Online]. Available: http://www.lungsusa.org/atf/cf/%7B7A8D42-C2-FCCA-4604-8ADE-7F5D5E762256%7D/ASTHMA1.pdf. [Accessed November 2014].
90. F. M. Ducharme, J. Morin, G. Michael Davis, J. Gingras and F. J. Noya. High physician adherence to phenotype-specific asthma guidelines, but large variability in phenotype assessment in children. *Current Medical Research & Opinion* 2012; 28(9):

1561-1570.

91. L. Brunton and B. Knollman, Goodman & Gilman's The Pharmacological Basis of Therapeutics 12 ed., United States: The McGraw-Hill Companies Inc, 2011.
92. M. Abramson, S. Kesten and J. Szalai. Adverse Effects of Beta-Agonists: Are They Clinically relevant?. *Am J Respir Med* 2003; 2(4): 287-297.
93. P. Lozano, J. Finkelstein, J. Hecht, R. Shulruff and K. Weiss. Asthma Medication Use of Disease Burden in Children in a Primary Care Population. *Arch Pediatr Adolesc Med* 2003; 157(1): 81-88.
94. P. J. Barnes and S. Pedersen. Efficacy and safety of inhaled corticosteroids in asthma. *American Review of Respiratory Disease* 1993; 148(4): S1-S26, 1993.
95. S. Szefler, S. Weiss, A. Tonascia, N. F. Adkinson, B. Bender, R. Cherniack and R. Zeiger. Long-term effects of budesonide or nedocromil in children with asthma. *Clinical Pediatrics* 2001; 343(15): 1054-1063.
96. L. Agertoft and S. Pedersen. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *New England Journal of Medicine* 2000; 343(15): 1064-1069.
97. C. Roux, S. Kolta, J. L. Desfougères, P. Minini and E. Bidat. Long-term safety of fluticasone propionate and nedocromil sodium on bone in children with asthma. *Pediatrics* 2003; 111(6): e706-e713.
98. E. Verona, D. Petrov, E. Cserhati, J. Hofman, N. Geppe, H. Medley and S. Hughes. Fluticasone propionate in asthma: a long term dose comparison study. *Archives of Disease in Childhood* 2003; 88(6): 503-509.
99. L. Zhang, S. O. Prietsch and F. Ducharme. Inhaled corticosteroids in children with persistent asthma: effects on growth. *Evidence-Based Child Health: A Cochrane Review Journal* 2014; 9(4): 829-930.
100. S. Pedersen. Do Inhaled Corticosteroids Inhibit Growth in Children?. *American Journal of Respiratory and Critical Care Medicine* 2001; 164(4): 521-535.
101. A. Pruteanu, B. Chauhan, L. Zhang, S. Prietsh and F. Ducharme. Inhaled Corticosteroids in Children with Persistent Asthma: Dose-Response Effects of Growth. *Evidence-Based Child Health: A Cochrane Review Journal* 2014; 9(4):931-1046.
102. G. Hawkins, A. D. McMahon, S. Twaddle, S. F. Wood, I. Ford and N. C. Thomson. Stepping down inhaled corticosteroids in asthma: randomised controlled trial. *BMJ* 2003; 326(7399): 1115.
103. M. Peters-Golden and W. R. Henderson Jr. Leukotrienes. *New England Journal of Medicine* 2007; 357(18): 1841-1854.
104. F. M. Ducharme. Inhaled glucocorticoids versus leukotriene receptor antagonists as single agent asthma treatment: systematic review of current evidence. *BMJ* 2003; 326(7390): 621.
105. M. Dorais, L. Blais, I. Chabot and J. LeLorier. Treatment persistence with leukotriene receptor antagonists and inhaled corticosteroids. *Journal of Asthma* 2005; 42(5): 385-393.
106. F. M. Ducharme and F. Di Salvio. Anti-leukotriene Agents Compared to Inhaled

Corticosteroids in the Management of Recurrent and/or Chronic Asthma in Adults and Children. *Cochrane Database Syst Rev* 2004; 1.

107. B. Rivington, J. Cote, H. Kreisman, D. Small, M. Alexander, A. Day, Z. Harsanyi and A. Darke. Efficacy of Slow-Release Theophylline, Inhaled Salbutamol and their Combination in Asthmatic Patients on High-Dose Inhaled Steroids. *Am J Respir Crit Care Med* 1995; 151: 325-332.

108. J. C. Kips and R. A. Pauwels. Long-acting inhaled β2-agonist therapy in asthma. *Am J Respir Crit Care Med* 2001; 164(6): 923-932.

109. F. M. Ducharme, M. Ni Chroinin, I. Greenstone and T. J. Lasserson. Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2010; 5(5).

110. F. M. Ducharme, M. Ni Chroinin, I. Greenstone and T. J. Lasserson. Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma. *The Cochrane Library* 2010; 4.

111. K. F. Rabe, T. Atienza, P. Magyar, P. Larsson, C. Jorup and U. G. Lalloo. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *The Lancet* 2006; 368(9537): 744-753.

112. M. N. Chroinin, I. Greenstone, T. J. Lasserson and F. M. Ducharme. Addition of long-acting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults and children. *The Cochrane Library* 2009; 4.

113. M. Gappa, W. Zachgo, A. von Berg, W. Kamin, C. Stern-Sträter and G. Steinkamp. Add-on salmeterol compared to double dose fluticasone in pediatric asthma: A double-blind, randomized trial (VIAPAED). *Pediatric Pulmonology* 2009; 44(11): 1132-1142.

114. J. Garrett, S. Williams, C. Wong and D. Holdaway, "Treatment of acute asthmatic exacerbations with an increased dose of inhaled steroid. *Archives of Disease in Childhood* 1998; 79(1): 12-17.

115. L. Hendeles and J. Sherman. Are Inhaled Corticosteroids Effective for Acute Exacerbations of Asthma in Children. *The Journal of Pediatrics* 2003; 142(2): S26-S33, 2003.

116. B. Chauhan, R. Ben Salah and F. Ducharme. Addition of Anti-Leukotriene Agents to Inhaled Corticosteroids in Children with Persistent Asthma. *The Cochrane Library* 2013.

117. J. S. Halterman, C. A. Aligne, P. Auinger, J. T. McBride and P. G. Szilagyi. Inadequate therapy for asthma among children in the United States. *Pediatrics* 2000; 105(Supp2): 272-276.

118. R. E. Dales, P. E. Kerr, I. Schweitzer, K. Reesor, L. Gougeon and G. Dickinson. Asthma management preceding an emergency department visit. *Archives of Internal Medicine* 1992; 152(10): 2041-2044.

119. K. Warman, E. Silver and R. Stein. Asthma Symptoms, Morbidity, and Anti-Inflammatory Use in Inner-City Children. *Pediatrics* 2001; 108(2): 277-282.

120. G. Wennergren, S. Kristjansson and I.-L. Strannergaard. Decrease in Hospitalisation for Treatment of Childhood Asthma with Increased use of Anti-Inflammatory Treatment, Despite an Increase in Prevalence of Asthma. *Journal of Allergy and Clnical Immunology* 1996; 87: 742-748.

121. P. A. Vermeire, K. F. Rabe, J. B. Soriano and W. C. Maier. Asthma control and differences in management practices across seven European countries. *Respiratory Medicine* 2002; 96(3): 142-149.

122. A. H. Anis, L. D. Lynd, X. H. Wang, G. King, J. J. Spinelli, M. Fitzgerald and P. Paré. Double trouble: impact of inappropriate use of asthma medication on the use of health care resources. *Canadian Medical Association Journal* 2001; 164(5):. 625-631.

123. V. Noble, N. R. Ruggins, M. L. Everard and A. D. Milner. Inhaled budesonide for chronic wheezing under 18 months of age. *Archives of Disease in Childhood* 1992; 67(3): 285-288.

124. H. Bisgaard, W. Petersen, S. L. Munck, J. P. Nielsen and S. V. Ohisson. Inhaled budesonide for treatment of recurrent wheezing in early childhood. *The Lancet* 1990; 336(8716): 649-651.

125. S. Pedersen, J. Warner, U. Wahn, D. Staab, M. Le Bourgeois, E. Van Essen-Zandvliet and S. J. Szefler. Growth, systemic safety, and efficacy during 1 year of asthma treatment with different beclomethasone dipropionate formulations: an open-label, randomized comparison of extrafine and conventional aerosols in children. *Pediatrics* 2002; 109(6): e92.

126. B. Salmon, N. M. Wilson and M. Silverman. How Much Aerosol Reaches the Lungs of Wheezy Infants and Toddlers?. *Archives of Disease in Childhood* 1990; 65(4): 401-403.

127. M. F. Beauchesne, A. Chartier, A. Fillion, C. Lemière, S. Lecompte and L. Blais, "Asthma control score based on filled medication prescriptions: A validation study. *Canadian Respiratory Journal: Journal of the Candian Thoracic Society* 2008; 15(8): 423.

128. A. Barbato, C. Panizzolo, L. Biserna, L. Cantarutti, C. Giaquinto, F. Frati and M. C. Sturkenboom. Asthma prevalence and drug prescription in asthmatic children. *European Annals of Allergy and Clinical Immunology* 2003; 35(2): 47-51.

129. W. Vollmer, L. Markson, E. O'Connor, L. Soncki, L. Fitterman, M. Berger and A. Sonia Buist. Association of asthma control with health care utilization and quality of life. *American Journal of Respiratory and Critical Care Medicine* 1999; 160(5): 1647-1652.

130. CBA Foundation Symposium. Evidence for the Increase in Asthma Worldwide. in *The Rising Trends in Asthma* 1997, Wiley Online Library.

131. H. Tunstall-Pedoe. Preventing Chronic Diseases. A Vital Investment: WHO Global Report. Geneva: World Health Organization. *International Journal of Epidemiology* 2006; 35(4): 1107.

132. J. Lang, H. Feng and J. Lima. Body Mass Index-Percentile and Diagnostic Accuracy of Childhood Asthma. *Journal of Asthma* 2009; 46(3): 291-299.

133. J. B. B. Holloway and S. Holgate. The Genetic Basis of Atopic Asthma. *Clinical and*

Experimental Allergy 1999; 29(8): 1023-1032.

134. E. Von Mutius. Relation of Body Mass Index to Asthma and Atopy in Children: The National Health and Nutrition Examination Study III. *Thorax* 2001; 56(11): 835-838.

135. D. Shawn. Overdiagnosis of Asthma in Obese and Non-Obese Adults. *Canadian Medical Association Journal* 2008; 179(11): 1121-1131.

136. S. Shore. Effect of Leptin on Allergic Airway Responses in Mice. *Journal of Allergyand Clinical Immunology* 2005; 121(5): 103-109.

137. S. Shore. Obesity and Asthma: Possible Mechanisms. *Journal of Allergy and Clinical Immunology* 2008; 121(5): 1087-1093.

138. F. Gurkan. Serum Leptin Levels in Asthmatic Children Treated with an Inhaled Corticosteroids. *Annals of Allergy, Asthma & Immunology* 2004; 93(3): 277-280.

139. X. Mai, M. Bottcher and I. Leijon. Leptin and Asthma in Overweight Children at 12 Years of Age. *Pediatric Allergy and Immunology* 2004; 15(6): 523-530.

140. A. Sood. Obesity-Asthma Association: Is it Explained by Systemic Oxidant Stress?. *CHEST Journal* 2009; 136(4): 1055-1062.

141. B. Xu. Body Build from Birth to Adulthood and Risk of Asthma. *European Journal of Public Health* 2002; 12(3): 166-170.

142. S. Huang, G. Shiao and P. Chou. Association between Body Mass Index and Allergy in Teenage Girls in Taiwan. *Clinical and Experimental Allergy* 1999; 29: 323-329.

143. B. Xu, M. Jarvelin and J. Pekkanen, "Body Build and Atopy. *J Allergy Clin Immunol* 2000; 105: 393-394.

144. G. Valdivia, S. Shaheen, J. Sterne and D. Jarvis, "Body Mass Index, Asthma Symptoms and IgE in Young Adults," vol. 14, p. 143, 1999.

145. D. Jarvis. Association of Body Mass Index with Respiratory Symptoms and AtopyL Results from the European Community Respiratory Health Survey. *Clin Exp Allergy* 2002; 32(6): 831-837.

146. A. Szczepankiewicz. Are Genes Associated with Energy Metabolism Important in Asthma and BMI. *Journal of Asthma* 2009; 46(1): 53-58.

147. A. Murphy. PRKCA: A Positional Candidate Gene for Body Mas Index and Asthma. *The American Journal of Human Genetics* 2009; 85(1): 87-96.

148. A. Neimark and R. Cherniack. Compliance of the Respiratory System and its Components in Health and Obesity. *Journal of Applied Physiology* 1960; 15(3): 377-382.

149. F. Adeniyi and T. Young. Weight Loss Interventions for Chronic Asthma. *The Cochrane Library* 2012; 7.

150. Z. Cordero-MacIntyre, S. Metghalchi, J. P. W. Rosen, T. Lohman and M. Fernandez. Impact of Weight Loss on Serum Leptin in Obese Postmenopausal Women. *Journal of Applied Research* 2004; 4(1): 60-67.

151. E. Luder, T. Melnik and M. DiMaio. Association of being Overweight with Great Asthma Symptoms in Inner City Black and Hispanic Children. *The Journal of Pediatrics* 1998; 132(4): 699-703.

152. P. Demoly. Prevalence of Asthma Control Among Adults in France, Germany, Italy, Spain and the UK. *European Respiratory Review* 2009; 18(112): 105-112.

153. L. Lafores. Influence of Patients' Characteristics and Disease Management on Asthma Control. *Journal of Allergy and Clinical Immunology* 2006; 117(6): 1404-1410.

154. K. Lavoie. Higher BMI is Associated with Worse Asthma Control and Quality of Life but Not Asthma Severity. *Respiratory Medicine* 2006; 100(4): 648-657.

155. D. Mosen. The Relationship Between Obesity and Asthma Severity and Control in Adults. *Journal of Allergy and Clinical Immunology* 2008; 122(3): 507-511.

156. P. Saint-Pierre. Are Overweight Asthmatics More Difficult to Control?. *Allergy* 2006; 61(1): 79-84.

157. J. Peters. Impact of Obesity in Asthma: Evidence from a Large Prospective Disease Management Study. *Annals of Allergy , Asthma & Immunology* 2011; 106(1): 30-35.

158. B. Taylor. Body Mass Index and Asthma Severity in the National Asthma Survey. *Thorax* 2008; 63(1): 14-20.

159. A. Youkou. Influence of Obesity on Control in Asthmatic Japanese Patients Defined by the Japanese Definition of Obesity. *Internal Medicine* 2011; 50(18): 1911-1916.

160. T. Haselkorn. Effect of Weight Change on Asthma-Related Health Outcomes in Patients with Sever or Difficult-to-Treat Asthma. *Respiratory Medicine* 2009; 103(2): 274-283, 2009.

161. J. Sastre. Increased Body Mass Index Does Not Lead to a Worsening of Asthma Control in Large Adult Asthmatic Population in Spain. *Journal of Investigational Allergology & Clinical Immunology* 2010; 20(7): 551.

162. E. Clerisme-Beaty. Does Higher Body Mass Index Contribute to Worse Asthma Control in an Urban Population?. *Journal of Allergy and Clinical Immunology* 2009; 124(2): 207-212.

163. T. Leung. The Relation Between Obesity and Asthmatic Airway Inflammation. *Pediatric Allergy and Immunology* 2004; 15(4): 344-350.

164. L. Borrell, E. Nguyen, L. Roth, O. S.S, H. Tcheurekdjian and S. Sen. Childhood obesity and asthma control in the GALA II and SAGE II studies. *American Journal of Respiratory and Critcal Care Medicine* 2013; 187(7): 697-702.

165. K. Kwong, I. Rhandhawa, J. Saxena, T. Morphew and C. A. Jones.Ability to control persistent asthma in obese versus non-obese children enrolled in an asthma-specific disease management program (breathmobile). *Journal of Asthma* 2006; 43(9): 661-666.

166. M. Kattan. Asthma Control, Adiposity, and Adipokines Among Inner City Adolescents. *Journal of Allergy and Clinical Immunology* 2010; 125(3): 584-592.

167. J. K. Giese. Pediatric obesity and its effect on asthma control. *Journal of the American Association of Nurse Practitioners* 2014; 26(2): 102-109.

168. Regie de L'Assurance Maladie, "Prescription Drug Insurance," [Online]. Available: http://www.ramq.gouv.qc.ca/en/citizens/prescription-drug-

insurance/Pages/eligibility.aspx. [Accessed 10 October 2014].

169. R. Tamblyn, G. Lavoie, L. Petrella and J. Monette. The use of Prescription Claims Databases in Pharmacoepidemiological Research: the Accuracy and Comprehensiveness of the Prescription Claims Database in Quebec. *Journal of Clinical Epidemiology* 1995; 48(8): 999-1009.

170. R. Delfino, M. Becklake and J. Hanley. Reliability of Hospital Data for Population-Based Studies of Air Population. *Archives of Environmental Health: An International Journal* 1993; 48(3): 140-146.

171. A. Mondared and J. LeLorie. Accuracy and Validity of using Medical Claims Data to Identify Episodes of Hospitalizations in Patients with COPD. *Pharmacoepidemiology and Drug Safety* 2006; 15(1): 19-29,.

172. L. Blais, P. Ernst and J. Boivin. Inhaled Corticosteroids and the Prevention of Readmission to Hospital for Asthma. *American Journal of Respiratory and Critical Care Medicine* 1998; 158 (1).

173. D. W. Cockcroft and V. A. Swystun, "Asthma control versus asthma severity," vol. 98, no. 6, pp. 1016-1018.

174. C. Blais and C. B. D. Lemiere. Validation of Asthma Diagnostic Codes in the Administrative Health Databases of Quebec, Canada. *Pharmacoepidemiology and Drug Safety* 2004.

175. L. Blais, S. Suissa and J. Boivin, "First Treatment with Inhale Corticosteroids and the Prevention of Admissions to Hospital for Asthma. *Thorax* 1998; 53: 1025-1029

176. I. Wahedna, C. Wong, A. Wisniewski, I. Pavord and A. Tattersfield. Asthma Control During and After Cessation of Regular Beta2-Agonist Treatment. *American Review of Respiratory Disease* 1993; 148: 707-712.

177. World Health Organization. The WHO Child Growth Standards [Online]. Available: http://www.who.int/childgrowth/standards/en/. [Accessed March 2014].

178. R. Pampalon, D. Hamel, P. Gamache, M. D. Philibert, G. Raymond and A. Simpson. An area-based material and social deprivation index for public health in Quebec and Canada," *Canadian Journal of Public Health* 2012; 103(8): S16-S22.

179. E. De Groot, E. Duiverman and P. Brand, "Comorbidities of asthma during childhood possibly important, yet poorly studied. *Eur Respir J* 2010; 36: 671-678.

180. A. Dixon. Adipokines and Asthma. *CHEST Journal* 2009; 135(2): 255-256.

181. J. Currie. Healthy, wealthy, and wise: socioeconomic status, poor health in childhood, and human capital development. *Journal of Economic Literature* 2009; 47(1): 87-122.

182. R. H. Bradley and R. F. Corwyn. Socioeconomic status and child development. *Annual Review of Psychology* 2002*;* 53: 371-399.

183. A. Mielck, P. Reitmeri and M. Wjst. Severity of childhood asthma by socioeconomic status. *The International Journal of Epidemiology* 1996*;* 25(2): 388-393.

184. E. Chen, E. Fisher, L. Bacharier and R. Strunk. Socioeconomic status, stress, and immune markers in adolescents with asthma. *Journal of Behavioral Medicine* 2003*;* 65(6): 984-992.

185. C. L. Ogden, M. D. Carroll, B. K. Kit and K. M. Flegal. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. *JAMA* 2012; 307(5): 483-490.

186. M. S. Tremblay and J. D. Willms. Secular trends in the body mass index of Canadian children. *Canadian Medical Association Journal* 2000; 163(11): 1429-1433.

187. A. Kukaswadia, W. Pickett and I. Janssen. Influence of country of birth and ethnicity on body mass index among Canadian youth: a national survey. *Canadian Medical Association Open Access Journal* 2014; 2(3): E145-E152.

188. P. Vo, K. Makker, E. Matta-Arroyo, C. B. Hall, R. Arens and D. Rastogi. The Association of Overweight and Obesity with Spirometric Values in Minority Children Referred for Asthma Evaluation. *Journal of Asthma* 2013; 50(1): 56-63.

189. T. Hampton. Studies Probe Links Between Childhood Asthma and Obesity. *JAMA* 2014; 311(17): 1718-1719.

190. F. Holguin and A. Fitzpatrick. Obesity, asthma, and oxidative stress. *Journal of Applied Physiology* 2010; 108(3): 754-759.

191. J. W. McCallister, J. P. Parsons and J. G. Mastronarde.The relationship between gastroesophageal reflux and asthma: an update. *Therapeutic Advances in Respiratory Disease* 2010.

192. K. Thakkar, R. O. Boatright, M. A. Gilger and H. B. El-Serag. Gastroesophageal reflux and asthma in children: A systematic review. *Pediatrics* 2010*;* 125(4): 925-980.

193. G. Tantisira and S. T. Weiss. Complex interactions in complext traits: obesity and asthma. *Thorax* 2001*;* 56: 64-74.

194. L. Thabane, L. Mbuagba, S. Zhang, Z. Samaan, M. Marcucci, C. Ye and M. Thabane. A tutorial on sensitivity analyses in clinical trials: the what, why, when and how. *BMC medical research methodology* 2013*;* 13(1): 92.

195. E. Sutherland. Body Mass and Glucocorticoid Response in Asthma. *American Journal of Respiratory and Critical Care Medicine* 2008; 178(7): 682-687.

196. M. A. Peters-Golden, S. S. Swern, C. M. Bird, C. M. Hustad, E. Grant and J. M. Edelman. Influence of body mass index on the response to asthma controller agents. *European Respiratory Journal* 2006*;* 27(3): 495-503.

197. Regie de l'assurance maladie Quebec, "Rapport annuel de gestion 2013-2014," [Online]. Available: http://www.ramq.gouv.qc.ca/fr/regie/salle-presse/actualites/2014/Pages/rapport-annuel-2013-2014.aspx. [Accessed December 2015].

198. L. H. Epstein, A. M. Valoski, M. A. Kalarchian and J. McCurley. Do children lose and maintain weight easier than adults: a comparison of child and parent weight changes from six months to ten years. *Obesity Research* 1995*;* 3(5): 411-417.

199. S. D. Aaron, K. L. Vandemhee, L.-P. Boulet, A. McIvor, M. FitzGerald, P. Hernandez and C. Lemiere. Overdiagnosis of asthma in obese and nonobese adults. *Canadian Medical Association Journal* 2008*,* 179(11): 1121-1131.

Appendix I

Code (based on ICD9)	Condition	ICD 10 Code
Asthma		
4930	Extrinsic asthma	J4520
4931	Intrinsic asthma	J4520; J4522; J4521
4939	Asthma unspecified	J45909; J45998; J45902; J45901
Respiratory Conditions		
4659	Acute upper respiratory infections	J069
4660	Acute bronchitis	J209
4661	Acute bronchiolitis	J210; J218
4787	Other diseases of larynx	J387; J386; J385
4789	Respiratory tract diseases	J398; J399
4800	Adenovirus pneumonia	J120
4801	Pneumonia due to respiratory syncytial virus	J121
4809	Pneumonia virus	J129
4819	Pneumococcal pneumonia	---
4820	Klebsiella pneumonia	J150
4829	Bacterial pneumonia	J159
4839	Pneumonia due to micro-organisms specified	---
4840	Pneumonia in measles	---
4859	Bronchopneumonia, organism specified	---
4869	Pneumonia, organisms unspecified	---
4870	Flu with pneumonia	J1100; J129
4871	Flu with other respiratory manifestation	J111
4909	Bronchitis not specified as acute or chronic	---
4910	Simple chronic bronchitis	J410
4918	Other chronic bronchitis	J418
4919	Unspecified chronic bronchitis	J42
4949	Bronchiectasis	---
5070	Pneumonia due to inhalation of food	J690
5180	Pulmonary collapse	J9811; J9819
5188	Other diseases of lung	J984
5191	Other diseases of trachea and bronchi	J398; J9809
5198	Other diseases of the respiratory system	J988
5199	Other diseases of the respiratory system	J989
7707	Chronic respiratory disease arising in the prenatal period	P270; P271; P278
7860	Dyspnea and respiratory abnormalities	R069
7861	Stridor	R061
7862	Cough	R05
7865	Chest pain	R079 (unspecified)

		R072; R071; R0781; R0782; R0789
7869	Other symptoms of respiratory/chest	R0689
9973	Respiratory complications not elsewhere classified	J9588; J9589

Appendix II

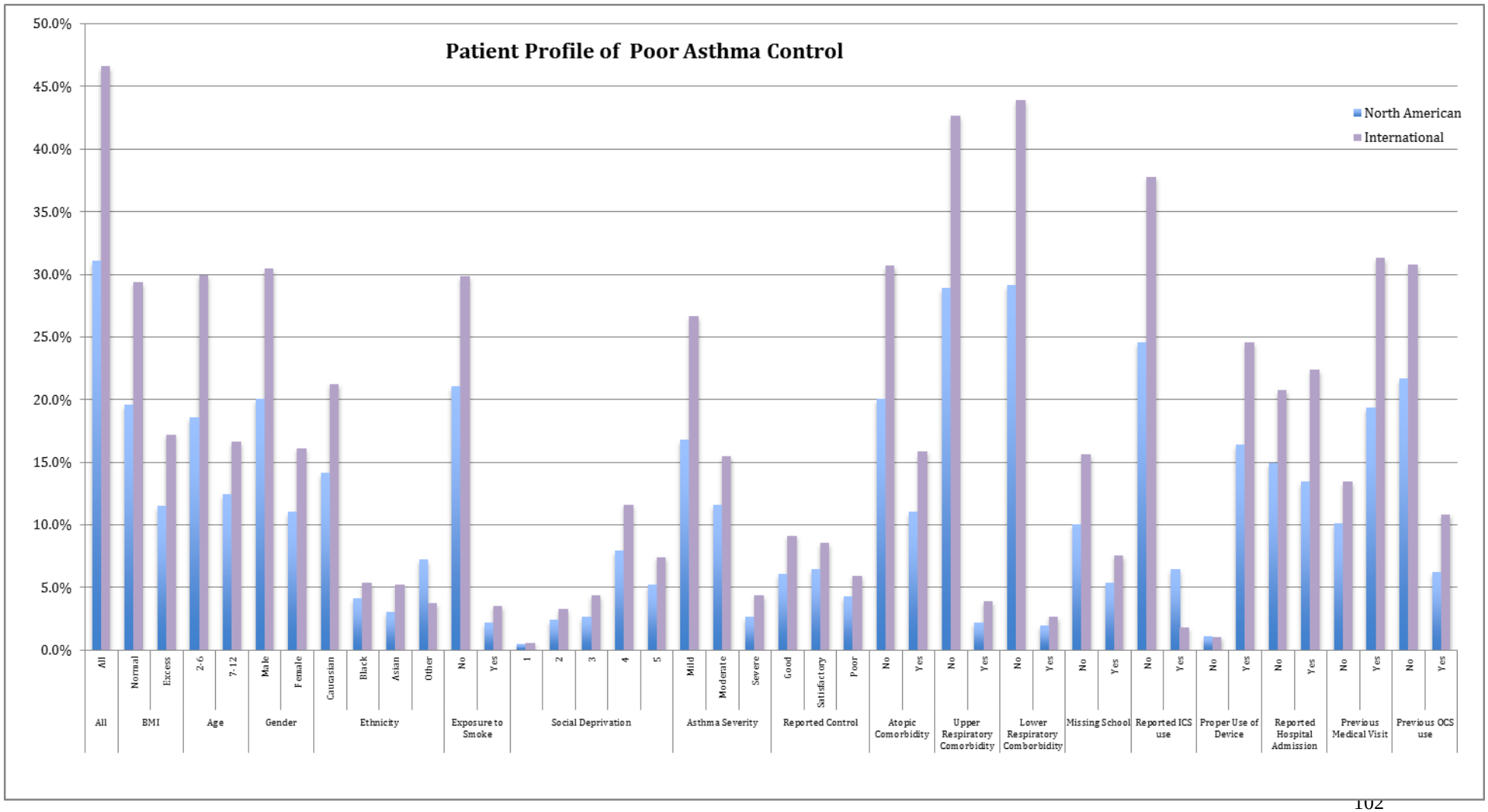
B-2-Agonist by Code in the RAMQ List of Medications:

Medication	Code	Brand Name
Salbutamol	02232570	Airomir
	02245669	Apo-Salvent
	02326450	Novo-Salbutamol HFA
	02241497	Ventolin HFA
Salbutamol Sulfate	02146843	Apo-Salvent
	02146851	Apo-Salvent
	02208245	pms-Salbutamol Polynebs
	02239365	Ratio-Salbutamol
	02213400	Ventolin Nebules P.F
	02208229	Pms-Salbutamol Polynbes
	01986864	Ratio-Salbutamol
	01926934	Teva-Salbutamol Sterinebs P.F
	02213419	Ventolin Nebules P.F
	02208237	Pms-Salutamol Polynebs
	02239366	Ratio-Salbutamol
	02228297	Salmol
	02173360	Teva-Salbutamol Sterinebs P.F
	02213427	Ventolin Nebules P.F
	02069571	Pms-Salbutamol
	00860808	Rati-Salbutamol
	02154412	Sandoz Salbutamol
	02213486	Ventolin
Terbutalin Sulfate	00786616	Bricanyl Turbuhaler

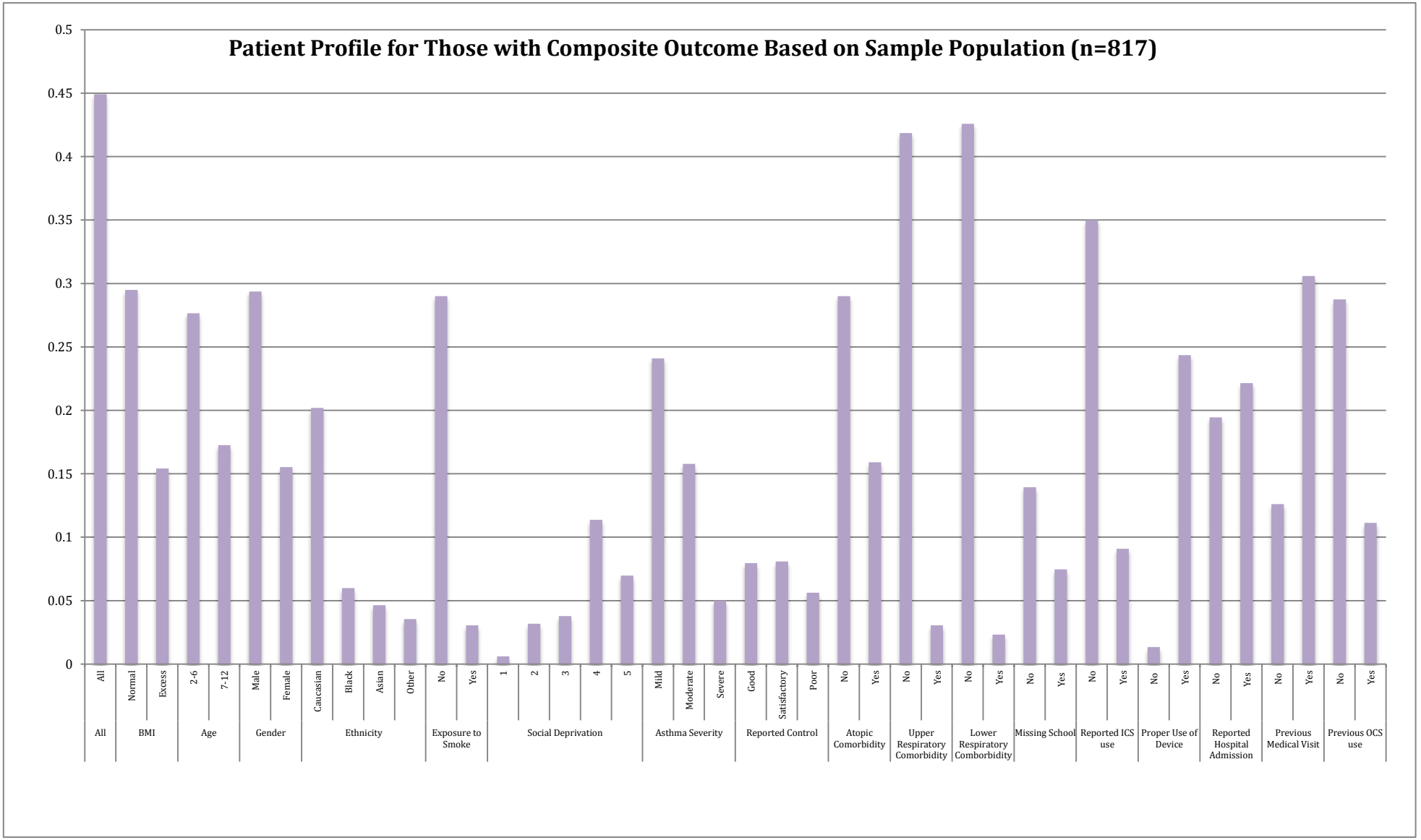
Medication	DIN	Brand Name
Methylprednisolone	00030988	Medrol
	00036129	Medrol
Prednisolone	02230619	Pediapred
	02245532	Pms-prednisolone
Prednisone	00598194	Apo-prednisone
	00271373	Winpred
	00312770	Apo-prednisone
	00021695	Novo-prednisone

	00156876	Prednisone-5
	00232378	Novo-prednisone
	00607517	Prednisone-50
Dexamethasone	02261081	Apo-Dexamethasone
	02237044	Phl-Dexamethason
	01964976	Pms-Dexamethasone
	02240684	Ratio-Dexamethasone
	01964968	Pms-Dexamethasone
	02279363	Pms-Dexamethasone
	02250055	Apo-Dexamethasone
	00489158	Dexasone
	02237046	Phl-Dexamethasone
	01964070	Pms-Dexamethasone
	02311267	Pro-Dexamethasone-4
	02240687	Ratio-Dexamethasone
	01946897	Pms-Dexamethasone
Hydrocortisone	00030910	Cortef
	00030929	Cortef

Appendix III



Appendix IV


Patient Profile for Those with Composite Outcome Based on Sample Population (n=817)
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
All
Normal
Excess
2-6
7-12
Male
Female
Caucasian
Black
Asian
Other
No
Yes
1
2
3
4
5
Mild
Moderate
Severe
Good
Satisfactory
Poor
No
Yes
No
Yes
No
Yes
No
Yes
No
Yes
No
Yes
No
Yes
No
Yes
All
BMI
Age
Gender
Ethnicity
Exposure to Smoke
Social Deprivation
Asthma Severity
Reported Control
Atopic Comorbidity
Upper Respiratory Comorbidity
Lower Respiratory Comorbidity
Missing School
Reported ICS use
Proper Use of Device
Reported Hospital Admission
Previous Medical Visit
Previous OCS use

Appendix V

The sample size calculation is derived from the need for the estimates of the effect of weight on asthma control to be obtained by testing relationships using binary logistic regression. The selected samples are assumed to be independent. For the purpose of this calculation the overweight and normal weight categories will be considered since it is most difficult to detect the difference in asthma control versus detecting differences between obese and normal weight. For this reason overweight and obese sample will be combined. From Canadian statistics it was found that that the ratio of overweight to normal weight children and adolescents in Canada is 0.459. This is a measure considered since analysis on the proportion of normal and overweight group within the sample has not been determined and can only be assumed by figures in the population. The sample size calculation assumes that the proportion of poor asthma control occurring in the population has a range of 10-70% with an 80% power and type I error (α) of 0.05 for a two sided hypothesis. Based on the following calculation equation:

$$n = [(z^2 * p * q) + ME^2] / (ME^2)$$

where ME represents the Margin of Error, z is the standard z score (1-alpha/2 in two tailed hypothesis test), p is the proportion and q is 1-p.

The minimum sample size to detect a 5% difference in the proportion is between 432-787 in the normal weight group and between 940-2103 in the overweight group.