Université de Montréal

Impact of asthma education and/or specialized asthma care on subsequent morbidity in asthmatic children

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Ce mémoire intitulé

Impact of asthma education and/or specialized asthma care on subsequent morbidity in asthmatic children

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Résumé

Introduction: Des essais cliniques randomisés ont démontré que l'éducation sur l'asthme, sans ou avec un suivi médical, réduit le risque de visites à l'urgence subséquentes. Toutefois, l'éducation sur l'asthme et le suivi médical spécialisé sont souvent offerts dans des contextes différents, ce qui rend difficile l'implémentation en pratique clinique.

Objectifs: Chez les enfants référés au Centre d'enseignement sur l'asthme (CEA) suite à une visite à l'urgence pour asthme, l'objectif principal est d'évaluer l'impact réel individuel et combiné d'une visite au CEA et d'un suivi médical spécialisé (SMS) sur une visite à l'urgence subséquente pour l'asthme au cours de l'année suivante.

Méthodes: Étude de cohorte rétrospective d'enfants référés au CEA dans l'année suivant une visite à l'urgence pour l'asthme. Le délai jusqu'à la visite subséquente à l'urgence pour asthme a été analysé par un modèle à risques proportionnels de Cox avec les variables d'exposition (CEA et SMS) variant dans le temps.

Résultats: Comparativement aux enfants qui n'ont reçu aucune exposition, ceux qui ont effectué une visite au CEA seulement [Hazard Ratio (HR) =0.68, IC 95% 0.53-0.86] ou avec un SMS (HR=0.43, IC 95% 0.34-0.53) ont eu un risque instantané moins élevé d'une visite à l'urgence subséquente. Une visite au SMS seule n'a pas d'effet statistiquement significatif.

Conclusion: Dans une cohorte d'enfants référés au CEA suite à une visite à l'urgence pour l'asthme, le fait de recevoir l'éducation sur l'asthme avec ou sans suivi spécialisé est associé à une protection contre une visite subséquente à l'urgence.

Mots-clés : asthme, enfants, enseignement, suivi médical spécialisé, spécialiste

Abstract

Background: Randomized controlled trials have shown that asthma education alone or in combination with medical review reduces the risk of subsequent emergency department (ED) visits. Nevertheless, asthma education and specialized care often provided in different settings, which increases the implementation burden in clinical practice.

Objectives: In children referred to the Asthma Education Centre (AEC) following an ED visit for asthma, the primary objective was to evaluate the real-life individual and combined impact of an AEC visit and specialized asthma care (SAC) visit on a subsequent ED visit for asthma over the following year.

Methods: Retrospective cohort study of children referred to the AEC in the year following an ED visit for asthma. The time to subsequent ED visit for asthma was analyzed by a Cox proportional hazards model with time-varying exposures (AEC and SAC).

Results: Compared to the children who did not receive any of the exposures, those who had exposure to AEC alone [Hazard Ratio (HR) =0.68, CI 95% 0.53-0.86] or with SAC (HR=0.43, CI 95% 0.34-0.53) had a decreased risk of an earlier subsequent ED visit. Exposure to SAC alone did not have a statistically significant effect on a subsequent asthma visit for asthma

Conclusion: In a cohort of children referred to the AEC following an ED visit for asthma, receiving asthma education with or without specialized care was associated with protection against a subsequent ED visit for asthma.

Keywords: asthma, children, education, specialized care, specialist

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List of acronyms

AC : Asthma Centre

ACV: acute care visit

AEC : Asthma Education Centre

CI : Confidence interval

CSSS : Health and Social Services Centres

DIN : Drug identification number

ED: Emergency department

FEV_1: Forced expiratory volume in the first second

GINA: Global Initiative for Asthma

HR : Hazard ratio

ICD-9/ICD-10: International Classification of Diseases 9^{th} and 10^{th} revisions of diagnostic codes

ISAAC: International Study of Asthma and Allergies in Childhood

LABA: Long acting beta-2 agonist

LTRA: Leukotriene receptor agonist

MCH: Montreal Children's Hospital

MDI: Metered dose inhaler

MED-ECHO: Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière

OCS: Oral corticosteroid

OR: Odds ratio

PCP: Primary care physician

PCR: Polymerase chain reaction

PDC: Proportion of days covered

PEF: Peak expiratory flow

PPACI: Pharmacoepidemiologic Pediatric Asthma Control Index

RAMQ : Régie de l'assurance maladie du Québec

RCT: Randomized controlled trial

RQAM: Réseau québécois de l'asthme et de la maladie pulmonaire obstructive chronique

RQESR : Réseau québécois d'éducation en santé respiratoire

RR: Rate ratio

SABA: Short-acting beta-agonists

SAC : Specialized asthma care

Para mi familia, por su apoyo incondicional

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Introduction

Asthma is a major public health problem. In Canada, it affected 3.8 million individuals in 2011-2012.[1] Moreover, it is the most common pediatric chronic disease, affecting 15% of Canadian children (0-19 years) in 2013-2014.[2] Asthmatic children experience greater morbidity than adults in terms of emergency department visits and hospital admissions. Indeed, the rates of ED visits are 3.5 times higher in children than in adults[3] and asthma is the main cause of hospitalizations in children.[4] Of note, preschoolers (children of age 0 to 4 years) experience the highest rates of ED visits and the larger peak in ED visits in the month of September among children.[5] A greater difficulty or hesitation to establish an objective asthma diagnosis and thus to initiate long-term therapy in this age group may contribute to these statistics.[6]

Asthma is associated with an important economic burden both at the healthcare system and the patient levels; it causes impairment in the quality of life of children and their family, limitation of physical activity, and can even cause death.[7] The direct and indirect costs for the Canadian healthcare system were $2.2 billion in 2010 and are estimated to increase to $4.2 billion by 2030.[8] A large part of these costs are due to emergency department visits for asthma, which signal poor asthma control and could be prevented with an appropriate management of the disease. Nevertheless, physicians, particularly in the emergency department, are often reluctant to make a diagnosis of asthma for 'asthma-like symptoms' and to initiate long-term therapy, which can delay adequate asthma management.

National and international asthma guidelines recommend guided self-management for all affected patients.[6,9,10] Guided self-management includes asthma education, a written action plan, self-monitoring and regular medical follow-up.[10] Asthma education serves to explain the disease, the role of medications and environmental control, and to teach the required self-management skills. Medical follow-up serves to accurately make a diagnosis, assess asthma control and co-morbidities in the patient, provide a personalized written action plan including an appropriate asthma controller prescription, when indicated. A 2009 Cochrane review of pediatric randomized controlled trials showed that asthma education alone (or with medical follow-up and other self-management components) decreased the risk of subsequent ED visits

in children presenting to the ED for asthma.[11] Moreover, previous studies have shown that asthma specialists are more likely to adhere to guidelines' recommendations than generalists.[12,13]

There is a systematic referral program of hospitalized asthmatic children to the Asthma Education Centre (AEC) in Quebec since 1994. However no standardized referral criteria to AEC and specialized asthma care exist for children presenting to the ED with an asthma/asthma-like diagnosis. Moreover, in real-life, asthma education and specialized care are often provided in different settings, at different times and by different providers, increasing the implementation burden and potentially interfering with uptake and challenging their effectiveness.

Therefore, the objective of this thesis was to examine the individual and combined real-life impact of a visit to the Asthma Education Centre (AEC) and a visit to specialized asthma care (SAC) on a subsequent ED visit for asthma in children referred to the AEC following an ED visit. Moreover, we aimed to evaluate the individual and combined impact of AEC and SAC on subsequent asthma control, short-acting beta-agonist use and oral corticosteroid use. Since the benefits of AEC and SAC are likely mediated by improvements in controller medication use, we also explore the individual and combined impact of these services on subsequent adherence to inhaled corticosteroids.

Chapter 1: Literature review

1.1 Asthma definition

Asthma is a chronic inflammatory disease of the respiratory airways, characterised by signs of airway obstruction, reversibility of these signs, and a history of recurrent symptoms varying in intensity and frequency, including cough, dyspnea, chest tightness, breathlessness, wheezing, and sputum production.[9,10] Asthma symptoms respond to bronchodilator anti-inflammatory therapy and can be triggered or exacerbated by exercise, respiratory infections, allergens, irritants, and change of weather.[10]

Asthma usually starts in early childhood, arising from the interplay of genetics (genetic predisposition, epigenetic modulation),[14] environmental pollution, family history of atopy, and early-life viral respiratory infections.[15,16] Recent studies also suggest that imbalances of gut microbiota composition increase the risk of asthma incidence by interfering with immune mechanisms.[15,17]

Moreover, different phenotypes based on clinical, genetic, and molecular factors have been proposed to describe the variability of the disease, with the hope of developing more targeted treatments for the affected patients.[18]

1.1.1 Asthma diagnosis in the clinical setting

Since asthma symptoms can also be present in other respiratory diseases, asthma diagnosis should be confirmed by objective methods. Standard pulmonary function tests, namely spirometry, can be performed in individuals of 6 years old and older to document airway obstruction and reversibility.[9] Indeed, the 2012 Asthma Canadian guidelines recommend pre- and post-bronchodilator spirometry showing reversible airway obstruction as the preferred diagnostic method; peak expiratory flow (PEF) variability may be used as an alternative method.[9] The definitive approach is a provocation test using methacholine or other techniques such as exercise, cold air, hypertonic saline or a suspected offending agent.[9]

Establishing an asthma diagnosis in preschoolers is challenging primarily because of the inability of young children to perform the forced expiratory manœuvre required for spirometry. Alternative lung function tests are available but their diagnostic ability has not been sufficiently demonstrated to be recommended;[19] in addition, the testing equipment and expertise is available only in a few selected pediatric academic settings in Canada and abroad, thus limiting their access. Moreover, bronchiolitis also presents with similar signs and symptoms, usually in children less than 1 year of life. Indeed, more than 40% of infants experience wheezing in their first year of life.[20,21]

One third of children aged 1-5 years suffer from asthma-like symptoms.[22] However, the condition resolves by the age of 6 years in 60% of preschool wheezers.[23] The spontaneous resolution has led to the popular notion that 'preschool wheeze' may be a separate entity from asthma and bronchiolitis. Consequently, physicians (particularly emergency physicians) hesitate to make a diagnosis of asthma in this age group,[24] and instead, commonly use alternative diagnosis such as wheezy bronchitis, happy wheezer , recurrent bronchiolitis, bronchospasm or reactive airway disease.[6]

Delay in asthma diagnosis leads to inappropriate and/or delayed disease management, which puts children at greater risk of exacerbations. Indeed, in a Denmark qualitative study of children aged 2-15 years, most had experienced asthma symptoms since their first year of life.[25] Yet, 30% of the participants had a delayed asthma diagnosis and 30% experienced more than five hospital admissions for respiratory conditions before confirmation of asthma diagnosis,[25] reflecting substantial morbidity that could be prevented with a timely management.

Of importance, irreversible airway remodelling (permanent changes in airway wall structure) contributes to impaired lung function and a decline in lung growth. It has been documented within 2 years of the onset of symptoms in preschoolers.[26,27] Although controversial, airway remodelling is commonly attributed to an underlying chronic inflammatory process.[28] Impaired lung function at 6 years of age has been documented in a substantial proportion of preschool wheezers in multiple birth cohort studies,[29,30] with the impairment being tracked until early and middle adulthood.[31] This is not trivial as a statistically significant association has been described between lung function decline and

severe exacerbations in children and adults with persistent asthma, with inhaled corticosteroids attenuating the decline.[32] Moreover, children with lower lung function trajectories than their normal counterparts are at increased likelihood of exhibiting chronic obstructive pulmonary disease (COPD) in adulthood.[33] Whereas 40% of the lung function observed at 7 years appears determined at birth, 60% occurs between birth and 6 years, raising the possible window of opportunity to intervene in this age group.[34] Perhaps, a timely diagnosis and appropriate therapy could prevent airway remodelling and impaired lung growth, both being conditions that do not respond to standard medication.[35]

In view of the unclear definition of asthma diagnosis in this age group,[36] the Canadian Thoracic Society and the Canadian Pediatric Society released a position paper in 2015 where they offered a pragmatic asthma diagnosis algorithm for children aged 1-5 years old.[6] Briefly, asthma diagnosis is based on documented signs of airflow obstruction, documented reversibility of these signs in a child with recurrent (>= 2) asthma-like symptoms or exacerbations, and no suspicion of an alternative diagnosis.[6] In the absence of documentation by a health care professional, children with convincingly-reported signs of obstruction must undergo a therapeutic 3-month trial with a moderate dose of ICS to confirm reversibility.[6] In the absence of a clear improvement after therapy, the referral to an asthma specialist is recommended.[6] The position paper specifically recommended that asthma-like diagnoses commonly used to depict asthma, such as wheezy bronchitis, happy wheezer, recurrent bronchiolitis, bronchospasm or reactive airway disease must be abandoned in favour of ‘confirmed asthma’, ‘suspected asthma’ or an alternative diagnosis (bronchiolitis, upper respiratory tract infections, etc.).[6]

1.1.2 Operational definitions of asthma diagnosis developed for epidemiological studies

Population-based epidemiological studies are based on the combination of rich information contained in administrative databases of medical services and pharmacy claims. However, they lack subject-level information about patients, symptoms, and lung function tests. In order to address this need, several validated algorithms for the diagnosis of asthma based on health services and medication usage have been developed. Using a database from

primary care physician (PCP) practices, an asthma case definition consisting of one hospital admission for asthma and/or two asthma physician visits occurring at least 14 days apart within 2 consecutive years was developed for surveillance and research purposes in Ontario.[37,38] Compared with a chart review by an expert panel, this asthma case definition has 89% sensitivity and 72% specificity in children aged 0-17 years[38] and a 84% sensitivity and 77% specificity in the adult population.[37] The same definition was validated in a sample of children aged 9-12 years in Toronto schools, with a sensitivity of 88% and a specificity of 64% compared with a clinical diagnosis of asthma, as per physician assessment (pediatric respirologist or pediatric allergist), spirometry, methacholine challenge, exhaled nitric oxide and allergy skin testing.[39] In a Manitoba birth cohort study, multiple algorithms were developed for asthma diagnosis using medication usage in addition to health services. For example, a definition based on one asthma hospital admission or two physician visits for asthma or any two asthma prescription medications was found to be 67% sensitive and 92% specific, as compared to a pediatric allergist diagnosis asthma in the following year.[40] The latter algorithms were not validated in another sample or in another population. Differences in the validity scores of the case definitions of Ontario and Manitoba could be reflective of the different sources of databases, gold standards used as a reference, and the context in which the studies took place. Since sensitivity is more important than specificity in studies looking to identify all asthmatic patients,[41,42] the case definition developed in Ontario is more suitable for studies requiring a validated asthma definition for cohort selection. Therefore, this is the definition that will be used in the present study.

1.2 Epidemiology

In 2002-2003, a cross-sectional survey of 70 countries by the World Health Organization reported that 301 million individuals aged 18-45 years had a doctor-diagnosed asthma, with prevalence rates ranging from 0.2% in China to 21% in Australia.[43] In the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three of 98 countries (2000-2003), 100,967 children aged 13-14 years and 36,474 children of 6-7 years reported having been diagnosed with asthma ever, with the highest prevalence in Oceania.[44]

Demographic patient characteristics, such as gender, age, ethnicity, and socioeconomic status, also affect asthma prevalence and morbidity. Asthma prevalence is higher in boys than in girls (18% vs. 13%, respectively) and the trend is reversed in adults (11% in women vs. 8% in men),[45] whereas asthma hospital admissions are also common in women.[46] These observations are likely explained by hormonal changes, gender-specific genetics, and environmental factors.[47,48] In children, asthma is the most common chronic disease and among the ten leading causes of years lived with disability.[49] Furthermore, children experience higher asthma-related morbidity than adults. Children have higher asthma-related hospital admission rates (1.4 times)[50] and higher ED visit rates (3.5 times), compared to adults.[3] Among children, those aged 0-4 years old are the group with the highest risk of asthma-related ED visits, followed by children 5-9 years old.[3] Moreover ethnic minorities, such as Puerto Ricans and African Americans, exhibit the highest asthma prevalence and morbidity in the United States; which has been associated to genetic risk factors, exposure to smoke, lower income, and psychological factors.[51,52] Furthermore, the protective effects of living above the poverty line may be greater in white than in black children, reflecting higher societal and structural barriers experienced by black families.[53] Of note, the prevalence of wheezing is higher in Inuit children aged 0 to 4 years old than in those from Southern Quebec of the same age,[54] which is possibly related to housing and environmental factors that increase the risk of respiratory disease (overcrowding, inadequate ventilation and high smoke exposure).[55]

The most frequent triggers of asthma in children include respiratory tract infections (e.g., cold, bronchitis, otitis, pneumonia),[56,57] allergens (e.g., pollen, animals, pets, dust),[58] and irritants (e.g., cigarette smoke[59] and air pollution,[60] molds[61]). Of note, 17% of prevalent asthma in children aged 6 months to 12 years old in Montreal have been attributed to exposure to excessive humidity and molds, which are also risk factors (attributable risk=13%) for current uncontrolled asthma and current severe asthma.[61] Asthmatic children exposed to allergens, including cockroach, pollen and dust mite, are more likely to experience asthma admissions than those not exposed.[62] Yet, polymerase chain reaction (PCR)-based studies report that respiratory viruses are present in more than 50% of pediatric asthma-related exacerbations.[63]

There are also seasonal patterns of asthma exacerbations, with the highest peak in the early fall in children and in the winter in adults.[64] In children, the September peak timing coincides with the return to school in the Northern Hemisphere and is closely associated with upper respiratory tract infections, which present in 62% of asthma-related emergency visits.[65] The September epidemic has been described in preschoolers and children aged 5-9 years old, who experience the highest peaks in ED visits in September than all other months, with rates of 18.35/1000 and 8.11/1000, respectively, followed by those aged 10-14 years with rates of 3.34/1000.[5]

Asthma is an important cause of school absenteeism, affecting 59% of asthmatic children[66] and accounting for 14.4 million missed school days annually in the United States.[67] Moreover, parents of school-age children with poorly controlled asthma miss 1.2 to 1.8 times more work days than parents of school-age children without asthma.[68] The impact of uncontrolled asthma in childhood is thus seizable.

1.3 Asthma control

Asthma control has been frequently linked to medication non-use or non-adherence; however, there are difficult-to-control patients who experience ongoing bothersome symptoms interfering with their daily activities despite adequate controller therapy.[69] These daily activities include feeding, sleep, sports, and play.[10] Moreover, asthma control can be improved spontaneously, or by changes in the environment and avoidance of triggers.

1.3.1 Clinical definition

Global Initiative for Asthma (GINA) guidelines define asthma control as the degree to which asthma manifestations are observed, comprising two domains that should be evaluated separately: symptom control and risk of future adverse events.[10] GINA guidelines also provide a tool for the assessment of asthma symptom control and the risk of poor asthma outcomes. Asthma symptoms assessed in the four previous weeks include daytime symptoms more than twice per week, night waking, reliever needed for symptoms more than twice per week and activity limitation. Patients well controlled with respect to symptoms do not have this frequency of symptoms. Risk factors for adverse events (e.g., asthma exacerbations) include

high short-acting β2-agonists (SABA) use, inadequate inhaled corticosteroids (ICS) use, low forced expiratory volume in the first second (FEV_1), allergen or smoke exposure, comorbidities, sputum or blood eosinophilia, higher bronchodilator reversibility, and significant psychological or socioeconomic issues. Patients having at least one of these risk factors are considered uncontrolled in this domain.[10]

According to the 2012 Canadian Asthma guidelines, children and adults are considered to have an appropriate asthma control if they experience diurnal symptoms less than 4 days per week, nocturnal symptoms less than one night per week, no interference in physical activity, no school/work absences, less than 4 doses per week of short-acting beta-agonists, FEV_1 or peak expiratory flow (PEF) 90% or higher of personal best and up to 15% PEF diurnal variation) and infrequent or no exacerbations (no asthma-related emergency visits nor hospital admissions).[9]

Previous studies have shown that good asthma control is associated with a reduction in asthma-related unscheduled health care utilization,[70] and reductions in the patient's perception of asthma burden and improvement in the quality of life,[71] both of which attest to the importance of achieving and maintaining an appropriate asthma control. On the other hand, parents of poorly controlled asthmatic children tend to overestimate their child's asthma control[72] and to express higher concern about asthma medication side effects.[73] These observations suggest that there is still work to do concerning asthma education to empower patients to effectively manage their disease.

1.3.2 Pharmacoepidemiologic measures of asthma control

Multiple instruments based on symptoms, reliever medication use, and exacerbations have been developed to facilitate the assessment of asthma control in the clinical setting, including Asthma Control Questionnaire, Asthma Control Test and Childhood Asthma Control Test.[10] However, health administrative databases used for population-level studies usually lack clinical information about symptoms.

To address this issue, pharmacoepidemiologic indexes based on health care utilization and rescue medication usage have been developed and validated to monitor asthma control in adults[74] and children.[75] Of interest, the Pharmacoepidemiologic Pediatric Asthma Control

Index (PPACI), which is based on criteria from the 2012 Canadian asthma guidelines, is the only pediatric asthma control index solely based on information obtained from healthcare databases.[75]

1.3.3 Epidemiology of asthma control

Poor asthma control remains a problem worldwide. Despite the dissemination of asthma guidelines and advances in asthma care, no improvement in asthma control has been observed in the last 20 years. Among Canadians living with asthma, 53% to 59% of adults[70,76] and 69 to 75% of children[77,78] exhibit poor asthma control. In a 2014 survey of 11 European countries, 45% of adults 18-50 years old had uncontrolled asthma[79] and in the 2006-2010 Asthma Call-back Survey in the United States, inappropriate asthma control was reported in 50% of adults and 38% of children.[80] The discrepancy in the prevalence of patients with poor asthma control reported in these studies possibly reflects the distinct methodologies used (e.g. asthma control criteria to classify control) and differences in the access to healthcare services in the countries.

1.3.4 An asthma emergency department visit as a marker of poor asthma control

Since asthma control is a large concept, many studies focus on markers of asthma control. An asthma exacerbation requiring an emergency visit generally reflects poor asthma control and is an important risk factor for a subsequent asthma emergency visit in the subsequent year.[81] Thus, children who experience asthma emergency visits should be targeted for optimal management. In the 2016-2017 fiscal year, there were approximately 62,180 emergency visits with an asthma diagnosis in Canada and 77.7% of these visits had a triage level of urgent, emergent or resuscitation,[82] which attests to the severity of asthma-related exacerbations. Recurrent emergency visits are often related to lack of continuity of care,[83,84] which results in fragmented care and conflicting care plans.[85] Indeed, a 10% increase in access to a primary care provider is associated with a 32% decrease in the likelihood of emergency admissions for asthma.[86] Nevertheless, only 57% of children report having a routine medical visit prior to an asthma-related emergency visit,[87] highlighting the importance of ensuring

continuity of care, particularly following an acute care visit, to ensure the appropriate management of the disease of high-risk children.

1.4 Asthma management

Due to the chronic nature of asthma, the goal of asthma management is to help patients attain and maintain an appropriate asthma control, thereby reducing the risk of future exacerbations.[9,10]

Since 1996, the Canadian Asthma Consensus publishes clinical practice guidelines for the diagnosis and management of asthma, with the purpose of providing health care professionals with evidence-based recommendations for the best standards of asthma care. The most recent general version of the Canadian Asthma guidelines for patients 6 years of age and older was published in 2012.[9] Moreover, Canadian guidelines for the diagnosis and management of asthma in preschoolers[6] and for severe asthma[88] were published in 2015 and 2017, respectively. At the international level, the Global Initiative on Asthma (GINA) publishes asthma guidelines annually since 1993.

1.4.1 Components of guided self-management

Canadian and GINA asthma guidelines highlight the importance of guided self-management, which refers to empowering patients by teaching them how to effectively and actively manage their disease. Optimal guided asthma self-management comprises asthma education, written action plan, self-monitoring and regular medical review.[9,10]

The purpose of asthma education is to enable patients to better recognize the signs and symptoms of the disease, learn how to self-monitor, and understand the management of their disease and exacerbations. Self-monitoring involves regular self-assessment by the patient. A written action plan contains personalized instructions to maintain asthma control, when and how to adjust reliever and controller therapy in response to acute loss of asthma control, and when to seek urgent medical care. Regular medical review is necessary to periodically evaluate asthma control and adjust therapy, if necessary.

Monitoring asthma control at each medical follow-up visit is a key recommendation of the Canadian Asthma Guidelines and should guide physicians to make appropriate management decisions to maintain or achieve control.[9] Indeed, regular physician assessment of asthma control and medications is associated with improvements in asthma control.[89]

Moreover, patients are encouraged to take an active role in asthma control assessment by documenting changes to the frequency and severity of their symptoms[6] or by using a written asthma action plan.[90] Optimal asthma control is more likely to be achieved by having physicians working together with patients.

1.4.2 Pharmacotherapy

1.4.2.1 Types of asthma medications

Canadian and GINA asthma guidelines recommend a stepwise approach to asthma therapy. Controller medications are the maintenance treatment, they target airway inflammation[9] and have been shown to prevent exacerbations and lung function decline in school-age children.[91] Controller medications include ICS, leukotriene receptor agonists (LTRA), ICS in combination with long acting beta-2 agonist (ICS/LABA) and ICS-LTRA.[9]

Reliever medications are used for quick-relief of asthma symptoms during exacerbations. Reliever medications include short-acting $beta_2$-agonists (SABA)[9] and oral corticosteroids (OCS), which are used in the emergency department for severe exacerbations. Additionally, children 12 years and older using ICS-LABA as a controller, may use this medication as a reliever if the LABA is formoterol.

1.4.2.2 Pharmacological management for children of 6 years old and older[9]

Long-term monotherapy is the first step for patients with persistent symptoms or episodic exacerbations; usually ICS or as second line, LTRA. For the next steps, the recommendations are specific to the age groups. In children 6-11 years old, the next phase is increasing the ICS dose to moderate dose and if control is not achieved, it is recommended to adjunct therapy to ICS, either with LABA or LTRA. For all patients that escalate to medium dose of ICS to improve asthma control, the dose should be reduced to the lowest effective

dose once adequate asthma control is reached.[9] In children aged 12 years and older, the second step is adding LABA as adjunct therapy to ICS and the third step is including LTRA as adjunct therapy to ICS.

1.4.2.3 Pharmacological management for children of 5 years old and younger

The following treatment recommendations are based on symptom severity in asthmatic children aged 1 to 5 years (Table 1).

Table 1. Treatment recommendations for preschoolers with asthma[6]

Control classification	Definition	Treatment
Mild intermittent symptoms or exacerbations	-Symptoms occurring < 8 days/month -Mild exacerbations lasting hours to days, that don't require rescue oral corticosteroids or hospital admission	SABA as-needed
Persistent symptoms or moderate to severe exacerbations	-Symptoms occurring > 8 days/month, requiring use of SABA, with ≥ 1 night awakening due to symptoms/month, any exercise limitation/month or any interference with usual activities - Exacerbations requiring rescue oral corticosteroids or hospital admission	-Daily low dose ICS with as-needed SABA -If asthma remains uncontrolled, medium dose ICS and if unsatisfactory response, referral to an asthma specialist are recommended

Adapted from Ducharme FM, Dell SD, Radhakrishnan D, Grad RM, Watson WT, Yang CL, Zelman M. Diagnosis and management of asthma in preschoolers: A Canadian Thoracic Society and Canadian Pediatric Society position paper. Canadian Respiratory Journal 2015; 22(3): 135-143

1.4.2.4 Determinants of adherence to asthma controller medication

To account for the multifaceted nature of medication adherence, the WHO recommended the following taxonomy of interrelated determinants of adherence: social and economic factors, condition-related factors, health care team/health care system-related factors, therapy-related factors, and patient-related factors.[92] Previous studies have shown that

children from socio-economically disadvantaged families (poor income[93,94] and less-educated parents[95]) have lower controller medication adherence than those from families with more favorable socio-economic backgrounds. In a comprehensive taxonomy, our team identified three main domains of barriers and facilitators that modulated adherence to asthma control medication, namely those related to the: patient (cognition, motivation, attitudes and preferences, practical implementation, and parental support); the patient-physician interaction (communication and patient-physician relationship); and the health care system (resources and services).[96] We further established that patient's perception of the disease and the treatment goals influenced asthma self-management behaviors related to environmental control, lifestyle habits, and medication intake.[97]

For example, patient-reported barriers to adherence include the fear of medication side effects[98,99] and the belief that asthma has resolved in the absence of symptoms.[100] Another barrier is low parental health literacy, which is associated with lower knowledge about appropriate medication and inhaler use,[101,102] and lower self-efficacy to manage their children's asthma.[103] Of note, a previous randomized controlled trial showed that using a shared decision-making electronic portal was associated with improvements in medication adherence and parental communication with providers.[104] Barriers related to healthcare access include long waiting times to access medical care,[105] and issues related to medications access include cost and lack of insurance.[106] On the other hand, continuity of care and tailored asthma education are facilitators of effective asthma management.[105]

Given the importance of a patient-centered approach with shared decision-making[96,107] and the fact that many factors are related to patients' misconceptions about appropriate asthma management,[105] asthma education and regular follow-up are two strategies that could contribute to enhance medication adherence.

1.4.3 Asthma education

1.4.3.1 Definition

Asthma education allows patients to effectively manage their disease, by providing them with a better understanding of the disease and the skills required to control their symptoms and reduce the risk of future asthma exacerbations.[10] Table 2 summarizes the key topics commonly covered in asthma education sessions. Asthma education has traditionally been provided in person, but in recent years the web, mobile apps and games are increasingly being used to this end. Although technology based educational methods can address the access barrier, they have not resulted in substantial improvements in clinical outcomes when used alone,[108,109] which suggests that they may be more beneficial when used to reinforce asthma education provided in person. Asthma education has been associated with improvements in medication adherence and reduction in subsequent exacerbations.[11,110]

Table 2. Components of asthma education

Topic	Subtopics
Asthma definition	-Understand that asthma is a chronic disease that can be controlled[111] -Self-monitoring of symptoms and if needed, peak flows[112] -Identification, avoidance and management of triggers[112] -Set goals for asthma management[113]
Asthma control	-Understand what constitutes good asthma control[114] -Self-assessment of asthma control[110,115]
Medications	-Understand the appropriate use of controller and reliever medications[116] -Appropriate technique of inhaler, chamber and spacer[114]
Regular medical review	-Medical review is important, especially after an exacerbation[112,114,117] -During medical review, the physician can assess asthma control and determine the most appropriate treatment at the present moment[9]

Written Action Plan	- Individual recommendations to determine how to adjust treatment when asthma control is inappropriate and when to seek doctor's help[118]

1.4.3.2 Context of the Asthma Education Centre (AEC) in Quebec

The *Réseau québécois d'éducation en santé respiratoire* (RQESR), previously named the *Réseau québécois de l'asthme et de la maladie pulmonaire obstructive chronique* (RQAM), was born in 1994 by the joint effort of the Quebec Lung Association, the Quebec Ministry of Health and Social Services, partners from the pharmaceutical sector and Quebec associations of asthmatics.[119,120] Since then, the RQESR has established 117 Asthma Education Centres (AEC) within hospitals and CSSS (Health and Social Services Centres) across the province of Quebec. Following a referral by a health professional, patients can benefit from a free standardized asthma self-management education session offered by a specialized asthma educator (a nurse or a respiratory therapist) at the AEC.[121] Since 1994, there is a systematic referral program to the AEC only for all children hospitalized for asthma in Quebec.

1.4.4 Medical follow-up

Regular follow-up is a key recommendation of the asthma guidelines. Moreover, a follow- up visit with the primary care physician is recommended in the 4 weeks following an asthma exacerbation requiring an emergency visit, which signals a management failure.[122] The quality of the medical visit and continuity in care are two important aspects to reduce the risk of subsequent asthma exacerbations. An effective follow-up visit should include the clinical assessment of asthma control, asthma education, prescription of asthma controller medication as per asthma guidelines and provision or review of a written action plan.[10,117] Moreover, care coordination strategies in the ED have been associated with improvements in follow-up in the primary care setting.[123]

In an comprehensive qualitative study to understand the physicians' perspective regarding the factors that influence the prescription of long-term asthma controller and the

provision of written self-management plans for asthmatic patients, ten categories of barriers and facilitators addressing three physician needs were identified: support physicians in delivering optimal care (5 categories); assist patients with following recommendations (3 categories); and offer efficient services (2 categories).[124]

Factors that influence the quality of medical care provided include the physician's knowledge of, agreement with, and self-efficacy to implement asthma guidelines' recommendations.[125] Organizational factors that could contribute to physicians' adherence to guidelines recommendations are facilitated referrals to the AEC and specialized care and easier access to spirometry.[126]

Importantly, patients followed by asthma specialist are more likely to receive guideline-based care,[127,128] reporting better use of asthma medication[129] and less morbidity,[117] compared to children who do not receive such care. Indeed, decreased access to pediatric asthma specialists is associated with hospital admissions.[130]

1.4.5 Context of the Asthma Education Centre (AEC) and the Asthma Centre (AC) at the Montreal Children's Hospital (MCH)

The Asthma Education Centre (AEC) of the MCH is part of the Quebec Respiratory Health Education Network and is located inside the Asthma Centre (AC). At the AC, asthmatic children with a referral can benefit from specialist care provided by pediatricians, allergists and pediatric respirologists. During the medical visit, physicians confirm the asthma diagnosis, assesses asthma control, establish a treatment plan and provide a written action plan. They can also request allergy and pulmonary function testing (offered on site) or refer them to the AEC.

1.5 Care gap between optimal asthma management and actual practice

Despite the dissemination of asthma guidelines and the advances in asthma care, efforts remain to be made to improve asthma control and address asthma care gaps. In Canada, 53% to 59% of asthmatic adults[70,76] and 69% to 75% of asthma children[77,78] exhibit poorly

controlled asthma. Successful implementation of asthma management guidelines' recommendations faces barriers at the physician and patient levels.[131,132] Asthma care gaps related to physicians include omission to provide personalized written action plan,[126,133] underprescribing of asthma controller medication,[134] low referral rate to asthma education[126,135] and infrequent asthma control assessment, which is related to insufficient knowledge about asthma control criteria or lack of time.[131,136] Asthma care gaps related to patients include insufficient knowledge about appropriate asthma management, underuse of written action plan, low adherence to medication and non-pharmaceutical recommendations, low attendance to asthma education and medical follow-up.[137,138]

Asthma education is recommended for all affected patients by national[6,9] and GINA guidelines,[10] but less than 30% of children who visit the emergency department report having receiving prior asthma education.[87,90] Unfortunately, even if physicians recognize the importance of asthma education, most report barriers for integrating it into their practice, such as lack of time,[139] organizational constraints,[110,140] and insufficient training.[105] Patients can also be unwilling to visit the AEC due to access constraints (i.e., limited hours of operation of the AEC[141] or long waiting times to get an appointment[142]) or the belief that they do not require an educational intervention.[110] Moreover, asthma education providers should adapt the asthma education content to the patients' literacy levels since poor parental healthy literacy is associated with lower asthma education knowledge,[101] and a two-fold higher likelihood of uncontrolled asthma (OR: 2.66, 95% CI 1.55-4.56).[143]

Although GINA guidelines highlight the importance of prompt medical follow-up after an asthma exacerbation, only one third of asthmatic children have a follow-up visit within one month of an emergency visit for asthma.[144,145] This could be due to problems related to healthcare access (i.e., difficulty in obtaining a doctor's appointment, lack of access to specialist care, patients' perceptions that ED quality of care is better than primary care or sufficient) and misconceptions about the need for treatment.[105] Moreover, only 36%[146] to 59%[147] of children have visited an asthma specialist in the year following an asthma-related hospital admission, an exacerbation that signals poor asthma control.

Furthermore, ICS adherence remains suboptimal, with rates ranging from 20%[148] to 30%[149] in cohort studies of asthmatic children with a public drug plan. Even if they agree that

ICS can prevent future exacerbations, less than 25% emergency physicians initiate a long-term maintenance treatment for patients that they cannot follow-up, instead relying on primary care physicians to prescribe controller medications.[150,151] Nevertheless, prescribing patterns can also be inadequate in primary care, with one third of asthmatic children inappropriately using ICS only at the onset of symptoms as per their physician's advice rather than daily as recommended by guidelines.[152] Furthermore, infrequent inhaler technique review at follow-up medical visits,[126] and barriers related to health literacy[101,102] result in up to 40% of children not using their inhaler correctly.[153]

The quality of care also remains to be improved, as less than 30% of asthmatic children receive a written action plan[131] and 35% of primary care physicians report being unaware or forgetting to assess asthma control by using the Canadian and GINA guidelines.[126] Clearly, asthma specialists are more likely to adhere to guidelines' recommendations, being twice as likely to provide a written action plan[12] and 20%[12] to 30%[13] more likely to prescribe long term controller medications as compared with general practitioners. Moreover, in children with an asthma exacerbation treated with oral corticosteroids, those receiving primary care have higher rates of ED visits compared to those followed in allergy/immunology/pulmonary clinics within 30 days of the initial exacerbation.[154]

As a consequence of delayed or inappropriate management after an asthma-related emergency visit, patients experience ongoing symptoms affecting their quality of life and resulting in school and work absenteeism, more exacerbations requiring emergency visits and hospital admissions, and even death.[155] Repeated emergency visits reflect poor asthma control and should be prevented because they are associated with irreversible impaired lung function.[156] Furthermore, asthma-related urgent healthcare use (hospital admissions, unscheduled medical visits, emergency department visits, rescue drug treatment, and ambulance rides) results in $162 million annual costs in Canada.[157]

1.6 Characteristics of patients at high risk of a subsequent emergency department visit

Even if all asthmatic patients could benefit from specialized follow-up and asthma education, in the context of limited health resources, we should prioritize for referral those who are at high risk of recurrent emergency visits since this signals poor asthma control.

An Ontario population-based birth cohort study reported that, among children who were diagnosed with asthma before 6 years old, 18.4% of patients with persistent asthma had emergency visits or hospital admissions in a 6-year follow-up period.[158] Other studies have reported 15% of children with persistent asthma experience a subsequent ED visit in the 6 months[62] and among those hospitalized at the index ED visit, a third experience an ED/hospital admission relapse in the subsequent year.[81,159]

Risk factors associated with a subsequent ED visit in asthmatic children can be related to the patient, to the index ED visit, or to medication. Table 3 includes a summary of 13 retrospective and prospective cohort studies on this topic published between 2003 and 2017, most based on pediatric populations and two mixed-age studies that were stratified for children.

1.6.1 Patient-related factors associated with a subsequent asthma emergency department visit

For children presenting to the ED for asthma, previous asthma morbidity is the most important predictor of a subsequent asthma emergency visit. Indeed, children who experience at least one asthma emergency visit prior to the index ED visit are 6.27 times more likely to have an asthma ED return visit in the subsequent six months,[87] and two to three times more likely to return to the ED in the 12 subsequent months.[81,144,160] Furthermore, hospital admissions prior to an index ED visit can increase the risk of a subsequent asthma ED visit by 1.5[161] times within 72 hours and by 3 times within 28 days.[162] Two studies used composite measures of asthma exacerbation as outcome.[163,164] In the first study, prior asthma exacerbations were associated with twice the risk of a severe asthma exacerbation (hospital admissions or an ED visit or a prescription of systemic corticosteroid for asthma) in the

subsequent year.[163] In the second study, asthma-related acute care visits (ACVs) were defined as either an ED visit, an urgent care centre visit or a hospital admission for asthma.[164] Of note, this latter study reported that compared to no previous ACVs, the likelihood of a subsequent exacerbation within the next 12 months increases with each previous ACV (adjusted OR=3.60, 95% CI 3.14-4.12 for 1 previous ACV; adjusted OR=7.14, 95% CI 5.81-8.77 for 2 previous ACVs; and adjusted OR=11.89, 95% CI 8.95-15.80 for 3 previous ACVs).[164]

Multiple retrospective and prospective cohort studies considered the effect of age, all showing that young children were the group at the highest risk of a subsequent asthma ED visit.[81,144,161,165,166] Tolomeo et al. (2009) reported that, among children of age 2-15 years, there was a 10% increase in risk of a subsequent ED visit for each year increase in age.[81] Most studies evaluated children from 2 years old, probably due to the difficulty in establishing a firm asthma diagnosis in infants. Compared to children aged 8 to 12 years, those of age between 2 and 7 years are 1.3 times more likely to have a subsequent ED visit within 72 hours of the index ED visit.[161] Other cohort studies showed that, compared to older children, preschoolers were more likely to have an earlier ED return visit[144] and 2.1 times as likely to have a subsequent ED visit in the following year.[165] A prospective cohort study reported among children diagnosed with asthma or wheezing, those younger than 2 years old where twice as likely to have an asthma ED relapse within 7 days of the index asthma ED visit compared to those aged 2-18 years.[166]

Furthermore, very poor asthma symptom control,[167] low income,[165] lower reading levels,[168] obesity[169] and races other than white[170] are also associated with an increased risk of a subsequent asthma exacerbation. Children whose parents have low literacy report higher rates of asthma-related emergency visits (IRR=1.40, 95% CI 0.97-2.00), even after adjusting for child age, household income, parental race, asthma knowledge, parental smoking, and asthma severity.[101] Of note, psychosocial stress at the individual, parental and community level is associated to increased asthma morbidity.[171-173] Environmental factors such as residential proximity to traffic (OR=3.27, 95% CI 1.08- 9.89)[174] and secondhand smoke exposure (OR=1.66, 95% CI 1.02-2.69)[175] are associated with increased likelihood of asthma emergency department visits and contribute to asthma disparities.[176]

1.6.2 Index emergency department visit factors associated with a subsequent asthma emergency department visit

Two studies reported that triage levels 1-2 (resuscitation, emergent) in the index emergency department visit were associated with a subsequent asthma emergency department visit [adjusted HR 1.67, 95% CI 1.54-1.80 when compared to triage level 4-5 (less urgent, non urgent) and unadjusted OR 1.15 95% CI 1.01-1.31 when compared to triage level 3], respectively.[144,161] The season of the index ED visit is also important, since children with an index asthma hospital admission during spring, summer or fall had an increased risk of having a earlier subsequent asthma hospital admission than those who came in winter.[177]

In addition, with poor asthma controller medication adherence (controller-to-total asthma medication ratio <0.5), the risk of a subsequent asthma emergency visit increases by 21% and the risk of a future hospital admission increases by 70%, as compared to a controller-to-total asthma medication ratio > 0.5.[170] In order to address the barrier to medication access, a study tested the effect of systematic provision of a beta-agonist metered dose inhaler (MDI) to asthmatic patients at ED discharge at no cost. This strategy was associated with a lower risk of subsequent ED visits (adjusted OR=0.37, 95% CI 0.14-0.95), compared to the usual care group.[162]

Although the previous studies allowed a better understanding of the risk factors of asthma ED recurrence in the pediatric population, there are still questions that remain to be answered. Clearly, there would be a need to develop and validate a comprehensive tool to identify children at high risk of recurrence in real-life clinical practice, which should guide further management. The present study is not addressing such tool but is setting the basis for further investigation in this area.

Table 3. Summary of studies about factors associated with a subsequent ED visit in asthmatic children

Authors	Asthma diagnosis definition	Outcome definition	Study design and population	Results
Section: Patient characteristics (previous morbidity, gender, age, socioeconomic level and asthma control)				
To T, Wang C, Dell S, Fleming-Carroll B, Parkin P, Scolnik D, et al. (2008)[87]	Asthma diagnosis was determined by the ED physician	Self-reported asthma ED visits at 6-month follow-up	Prospective cohort study of children with acute asthma aged 2 to 17 years old visiting the ED of a pediatric tertiary hospital in Ontario (Canada)	**Subtopic: Previous morbidity** Having ED visits in the 12 months prior to baseline was highly associated with having repeat ED visits at 6 months post-ED discharge (adjusted OR: 6.27; 95% CI, 1.54–7.12)
Guttmann A, Zagorski B, Austin PC, Schull M, Razzaq A, To T, et al. (2007)[161]	An ED visit with asthma or status asthmaticus as a primary diagnosis (ICD 10 J45 and J46) or as a secondary diagnosis with a primary diagnosis of wheeze, dyspnea, cough, or respiratory failure	Unplanned asthma return visits to any ED within 72 hours of the initial visit	Retrospective cohort study of children 2- to 17-years old who were seen for asthma in an ED in Ontario (Canada)	**Subtopic: Previous morbidity** A history of asthma admission is associated with an increased risk of asthma ED return visits (adjusted OR: 1.45 95% CI 1.21-1.72) **Subtopic: Gender** Boys had a slightly reduced risk of returning to the ED for asthma (adjusted OR: 0.83; 95% CI 0.75–0.91) **Subtopic: Age** Compared with children 8 to 12, children of 2 to 7 were more likely to return to the ED for asthma (adjusted OR: 1.28; 95% CI 1.13–1.46)
Li P, To T, Guttmann, A. (2012)[144]	1 hospitalization or 2 ED visits for asthma within 2 years	Asthma ED return visit in the 28 days following the index ED visit (ICD 10 J45)	Retrospective cohort study of children aged 2-17 years with prevalent asthma who visited the ED of Ontario (Canada) hospitals for asthma	**Subtopic: Previous morbidity** -Asthma admissions in the 2 years prior to the index ED visit (adjusted HR: 1.45, 95% CI 1.35-1.55) -Asthma ED visits in the 2 years prior to the index ED visit (adjusted HR: 2.03, 95% CI 1.91-2.14) **Subtopic: Age** Compared to children 2-5 years old: -Those 6-9 years old had adjusted HR=0.83 95% CI 0.78-0.89 -Those 10-13 years old had adjusted HR=0.76 95% CI 0.71-0.82 -Those 14-17 years old had adjusted HR=0.80 9% CI 0.74-0.87 **Subtopic: socioeconomic level** Using 2006 Canada Census Neighbourhood income quintile 5 (highest) as reference: -Quintile 1 (adjusted HR= 1.23, 95% CI 1.13-1.33)

				-Quintile 2 adjusted HR=1.15, 95% CI 1.06-1.25 -Quintile 3 has adjusted HR=1.11, 95% CI 1.02-1.21 -Quintile 4 has adjusted HR=1.04, 95% CI 0.96-1.14
Hall AB, Novotny A, Bhisitkul DM, Melton J, Regan T, Leckie M. (2017)[162]	An index ED visit with an asthma dx (ICD-9: 493)	Rate of asthma ED visits /hospital admissions within 28 days of the index ED visit	Retrospective cohort study of children 0-17 years old (United States)	**Subtopic: Previous morbidity** Hospital admissions for asthma within the past 12 months is associated with increased risk of asthma related subsequent ED visits (OR=3.10, 95% CI 1.72-5.62)
Engelkes M, Janssens HM, de Ridder MA, Sturkenboom MC, de Jongste JC, Verhamme KM. (2016)[163]	Asthma cases were retrieved by an automated search on both International Classification of Primary Care asthma codes (ICPC code, R96) and free text that was relevant to asthma	A severe asthma exacerbation in the year following the index ED: hospitalization, ED visit, or prescription of systemic corticosteroids for at least 3 days, all because of asthma.	Retrospective cohort study of children 5-18 years old (Netherlands)	**Subtopic: Previous morbidity** Prior asthma exacerbations were associated with twice the risk of having a severe asthma exacerbation (RR=2.17 IC 1.30-3.60)
Hanson JR, Lee BR, Williams DD, Murphy H, Kennedy K, DeLurgio Sr SA, et al. (2016)[164]	A visit to an outpatient primary care, allergy-asthma-immunology or pulmonology clinic with an asthma diagnosis (ICD-9: 493)	Asthma-related acute care visits (ACV): ED, urgent care centre or inpatient admission with a primary diagnosis of asthma (ICD-9 493).	Cohort study, but not specified if retrospective or prospective. Population consisted of children 3-17 years old (United States). Analysis is based on visits, rather than patients	**Subtopic: Previous morbidity** The higher the number of previous ACV, the greater the likelihood of a future ACV. -1 ACV (adjusted OR=3.60, 95% CI 3.14-4.12) -2 ACV (adjusted OR=7.14, 95% CI 5.81-8.77) -3 ACV (adjusted OR=11.89, 95% CI 8.95-15.80)
To T, Cicutto L, Degani N, McLimont S, Beyene J. (2008)[160]	Physician-diagnosed mild to moderate asthma	Self-reported asthma related ED visits	Prospective cohort study stratified for children (2-17 years) and adults from primary practices of Ontario (Canada)	**Subtopic: Previous morbidity** In children, asthma ED visits in the last 6 months are a predictor of asthma ED visit at 12-month follow-up in children (adjusted OR=3.23, 95% CI 1.45–7.15)
Tolomeo C, Savrin C, Heinzer M, Bazzy-Asaad A. (2009)[81]	Hospital admission with a primary diagnosis of asthma	Asthma related ED visit	Retrospective cohort study of children aged 2-15 years (United States)	**Subtopic: Previous morbidity** Subjects with a previous asthma-related emergency department visit were more likely to experience a subsequent asthma-related emergency department visit (adjusted OR=3.32, 95% CI = 1.39–7.96).

				Subtopic: Age For each year increase in age, the risk of a subsequent asthma-related emergency department visit increased. Adjusted RR=1.1, 95% CI = 0.998–1.170
Johnson LH, Beck AF, Kahn RS, Huang B, Ryan PH, Olano KK, et al. (2017)[165]	A hospitalization for asthma (diagnosis established by physician) with provision of oral steroids and b-agonists	ED visit with ICD-9 code for asthma (493.XX) or wheeze (786.07) within a year, with albuterol or systemic Corticosteroids administration/prescription at discharge	Prospective cohort study of children 2-16 years old admitted for asthma (United States)	**Subtopic: Age** Compared to children ≥ 12 years old: -Those of age 2-3 years old had unadjusted OR=2.07, 95% CI 1.17-3.64 -Those 4-11 years old had unadjusted OR=1.97, 95% CI 1.16-3.34 **Subtopic: Socioeconomic level** Annual household income with <14999$ as reference: 15000-29000$ non stat sig difference 30000-44999$ non stat sig difference 45000-59999$ non stat sig difference 60000-89999$ unadjusted OR=0.55, 95% CI 0.31-0.98 ≥ 90000$ unadjusted OR=0.16, 95% CI 0.67-0.39
Walsh-Kelly CM, Kelly KJ, Drendel AL, Grabowski L, Kuhn EM. (2008)[166]	Physician diagnosed asthma	ED visits for acute asthma within 7 days of a prior visit	-Prospective cohort of children with asthma and wheezing (United States)	**Subtopic: Age** Compared to 2-18 years old: -Those younger than 2 years old had adjusted OR=2.00 95% 1.39-2.88
Rust G, Zhang S, Reynolds J. (2013)[170]	An asthma (ICD-9 code: 493) hospital admission or 2 outpatient visits	ED visits and hospital admissions (ICD-9: 493) within 90 days after ICS initiation	Retrospective cohort study of children aged 5–12 years in 14 southern states using Medicaid claims data (United States)	**Subtopic: Race** Compared to white, -Black has adjusted OR: 1.12 (1.05-1.19) -Hispanic has adjusted OR: 0.71 (0.65-0.78) -Other race has adjusted OR: 1.21 (1.10-1.33)
Haselkorn T, Fish JE, Zeiger RS, Szefler SJ, Miller DP, Chipps BE, et al. (2009)[167]	Physician diagnosed asthma	Self-reported composite exacerbation measure (a hospitalization, ED visit, or corticosteroid burst)	Prospective cohort study of children and adults followed by an asthma specialist (United States)	**Subtopic: Asthma symptom control** Children who were consistently classified as having VPC (very poorly controlled) asthma had more than a 6-fold increased risk of an exacerbation (a hospitalization, ED visit, or corticosteroid burst) (adjusted OR, 6.4; 95% CI, 1.18-34.5) compared with children who improved from VPC asthma.
Section: Characteristics of the index ED visit				
Guttmann A, Zagorski B,	An ED visit with asthma or status asthmaticus as a	Unplanned asthma return visits to any	Retrospective cohort study of children 2 to 17-years who	**Subtopic: triage level** Compared with patients with initial ED visit with triage

Austin PC, Schull M, Razzaq A, To T, et al. (2007)[161]	primary diagnosis (ICD 10 J45 and J46) or as a secondary diagnosis with a primary diagnosis of wheeze, dyspnea, cough, or respiratory failure	ED within 72 hours of the initial visit	visited the ED of Ontario (Canada) hospitals for asthma	level 3, -Triage level 1-2 (unadjusted OR: 1.15, 95% CI1 1.01-1.31) - Triage level 4-5 (unadjusted OR: 0.75 95% CI 0.68-0.83)
Li P, To T, Guttmann A. (2012)[144]	1 hospitalization or 2 ED visits for asthma within 2 years	Asthma ED return visit in the 28 days following the index ED visit (ICD 10 J45)	Retrospective cohort study of children aged 2-17 years with prevalent asthma who visited the ED of Ontario (Canada) for asthma	**Subtopic: triage level** Compared with triage level 4-5 (less urgent, non urgent), -Triage level 1-2 (resuscitation, emergent), adjusted HR: 1.67, 95% CI 1.54-1.80 -Triage level 3 (urgent), adjusted HR: 1.28, 95% CI 1.19-1.37
Liu SY, Pearlman DN. (2009)[177]	An asthma hospital admission	Time to next asthma hospital admission	Prospective cohort study of children 0-18 years (United States)	**Subtopic: season** Season of index asthma hospital admission predicts time to subsequent hospital readmission Winter (reference) Spring: HR=1.23 (0.94, 1.61) Summer: HR=1.83 (1.31, 2.54) Fall: HR= 1.39 (1.07, 1.81)
Section: Medications				
Hall AB, Novotny A, Bhisitkul DM, Melton J, Regan T, Leckie M. (2017)[162]	An index ED visit with an asthma dx (ICD-9: 493)	Rate of asthma ED visits/hospital admissions within 28 days of the index ED visit	Retrospective cohort study of children 0-17 years old (United States)	**Subtopic: Beta-agonist metered dose inhaler (MDI)** **Beta**-agonist metered dose inhaler (MDI) dispensed in ED is associated with decreased risk of asthma related subsequent ED visits (adjusted OR=0.37, 95% CI 0.14-0.95)
Rust G, Zhang S, Reynolds J. (2013)[170]	An asthma (ICD-9 code: 493) hospital admission or 2 outpatient visits	ED visits and hospital admissions (ICD-9: 493) within 90 days after ICS initiation	Retrospective cohort study of children aged 5–12 years in 14 southern states using Medicaid claims data (United States)	**Subtopic: ICS** Compared to controller-to-total asthma medication ratio of >=0.5, controller-to-total asthma medication ratio of < 0.5 (adjusted OR: 1.21, 95% CI 1.14-1.27)

1.7 Emergency department-based interventions to prevent subsequent emergency department visits

GINA asthma guidelines recommend prompt medical appointment following ED discharge and addressing strategies to improve asthma management, including medications, inhalation skills and a written action plan.[10] Following an ED visit, the 2010 Canadian Asthma Guidelines for 6 year old and older also recommend prompt review of maintenance therapy and addressing the factors that resulted in poor asthma control.[178] Whereas patients should be recommended a medical follow-up at least with their general practitioners for education and management, it is still not clear who should be referred to the AEC, a specialized clinic or both. Indeed, specific criteria for referral to asthma education and/or specialist care following an ED visit are inconsistently mentioned, let alone harmonized, across guidelines. GINA guidelines recommend targeting patients discharged from the emergency department or a hospital admission to an asthma education program,[10] while Canadian guidelines, although they recommend asthma education for all affected patients, do not include any criteria for referral to the AEC for preschoolers[6] or for children aged 6 years and older.[9,178] GINA[10] and Canadian guidelines (for preschoolers[6] and children aged 6 years and older[9,178]) recommend referral to specialist care when there is failure to achieve proper control (i.e., asthma exacerbations) despite good adherence to controller medications. Additionally, Canadian guidelines have issued specific recommendation for when preschoolers should to be oriented towards specialist care. Indeed, the 2015 Canadian guidelines for preschoolers recommend that in children aged less than 6 years, an specialist referral should be considered if there is diagnostic uncertainty, repeated (≥2) exacerbations requiring rescue oral corticosteroids or hospitalization or frequent symptoms (≥8 days/month) despite moderate (200 µg to 250 µg) daily doses of inhaled corticosteroids, a life-threatening event (e.g., an admission to the intensive care unit), need for allergy testing or other considerations.[6] Otherwise, in pediatrics, referral to AEC, SAC or both services are based on the perception of needs of the emergency physician or on the institution-specific clinical protocols.

In an effort to facilitate the management of the patients following an ED visit, several ED interventions were tested in randomized controlled trials. Since a follow-up to a family

physician is most frequently indicated, several randomized controlled trials have centered on ED coordination strategies to ensure a prompt follow-up with the primary care provider. Previous pediatric studies analyzed the impact of scheduling a primary care follow-up visit for the patient,[179] combining an educational video in ED with mailed reminders to schedule a follow-up[180] and asthma coaching combined with a monetary incentive.[181] The first of these strategies increased the likelihood of medical follow-up by 1.4 times[179] while the others had no impact of follow-up rates. None of the strategies was successful in reducing the number of subsequent ED visits. Therefore, globally, these strategies had not been efficient to improve follow-up rates nor subsequent health care outcomes.

Some RCT have focused on providing asthma education in the emergency department, thus addressing the access barrier and taking advantage of the "teachable moment" where patients may be more receptive.[182-184] These studies found no statistically significant effect of ED-based asthma education compared to usual care on the risk of subsequent ED visits,[182-184] although an exploratory stratified analysis of one study reported a beneficial effect of ED-based asthma education for the subgroup of patients with intermittent asthma symptoms compared to usual care (OR=0.32, 95% CI 0.12-0.88).[183] A RCT showed that children exposed to ED-based asthma education had improvements on controller medication dispensing,[182] attesting to the efficacy of the intervention on process outcomes. In accordance to this, we decided to also explore the impact of the interventions on adherence to controller medication in our study.

1.8 Impact of asthma education and/or specialized care following an asthma ED visit

Table 4 includes a summary of a meta-analysis of asthma education provided in different settings and timings and studies on interventions provided outside the ED (asthma education alone, specialized care alone and both asthma education and specialized care).

1.8.1 Impact of asthma education alone or as part of a comprehensive management

Boyd et al.'s (2009) meta-analysis was based on 38 randomized controlled trials of children 0-18 years old. It analyzed the impact of asthma education alone or in combination with other self-management components (written action plan, self-monitoring of symptoms, assessment of pharmacological treatment and of environmental triggers), initiated in the ED or not, individual or in group, in different settings (hospital, clinic, community education centre, home or school) and at different timings (early or delayed) following the index ED visit on subsequent health care use.[11] The baseline characteristics of patients varied among the RCTs, with participants' age ranging from 0 to 18 years old, with at least one emergency visit with or without hospital admission within 12 months of study entry.[11] There were beneficial effects of asthma education on the risk of subsequent emergency visits (RR=0.73, 95% CI 0.65-0.81), hospital admissions (RR=0.79, 95% CI 0.69-0.92) and unscheduled medical visits (RR=0.68, 95% CI 0.57-0.81).[11] The authors also performed subgroup analyses to determine if the timing of the intervention and the education content could influence the outcomes. Both early and delayed educational interventions were associated with statistically significant reductions in the risk of subsequent emergency visits (RR=0.76, 95% CI 0.67-0.86 and RR=0.60, 95% 0.45-0.79, respectively). Moreover, comprehensive interventions (information, self monitoring and action plan) were associated with RR=0.60, 95% CI 0.47-0.77, while interventions based on information only were associated with no statistically significant effect. However, these results should be interpreted with caution, because, due to the substantial heterogeneity remaining within the subgroups, the authors could not make any conclusions from the subgroup analyses regarding timing of intervention and education content.

After Boyd et al.'s (2009) meta-analysis of trials, 4 other RCTs[185-188] examining the impact of asthma education alone following an asthma ED visit were reviewed. Among them, two studies reported that multiple sessions of asthma education (lasting from one month to two months) were associated with reductions ranging from 38% in children aged 3 to 16 years recruited from the ED[186] to 48% in students from grade 9th and 10th with moderate to severe persistent asthma recruited in schools[188] in the risk of subsequent asthma ED visits in the subsequent year. [185,186,188] Otsuki et al. (2009) reported a reduction in the risk of subsequent

asthma ED visits only when asthma education was offered in conjunction with controller medication adherence feedback from the physician.[186] Although Indinnimeo et al. (2009) reported no effects of two sessions of asthma education on subsequent emergency visits in children 6-14 years with newly diagnosed intermittent or mild persistent asthma, the intervention had beneficial effects on subsequent asthma attacks (1.65 $\pm$ 1.21 in the intervention group vs. 2.34 $\pm$ 1.73 in the control group, $p<0.05$).[187] Indinnimeo et al. (2009) concluded that asthma education might be more beneficial for patients with moderate to severe asthma and in studies where patients were not followed by specialists.[187] Collectively, these efficacy studies showed that long-term asthma education is associated with a reduction in the risk of subsequent asthma ED visits as detailed in Table 4.

The retrospective cohort study of Gaudreau et al. (2014) explored the real-life impact of the intensity of asthma education at the AEC on subsequent primary care and emergency visits in patients not recruited from the ED in Prince Edward Island, Canada.[189] The authors of this study did not specify whether asthma education was offered to the children alone, the parents alone or both. In the year following AEC contact, children who received 2 AEC sessions (adjusted RR=1.80, 95% CI 1.39-2.34) experienced greater reductions in subsequent ED visits than those receiving 1 AEC session (adjusted RR=1.95, 95% CI 1.28-2.99) compared to the children not referred to the AEC after adjustment for age, urban-rural residence, year and season of contact with the AEC.[189] Surprisingly, the children who received asthma education remained at a higher risk of an ED visit than those not referred to the AEC during the 3-year follow-up period,[189] which may be due to a higher baseline morbidity of patients referred to the AEC compared to those not referred to the AEC. Although it is likely that there are subgroups of patients who would benefit more from the AEC intervention, no subgroup analyses were performed in this study. This highlights the importance of selecting a group of patients who have similar morbidity at baseline, which will be done in the present study. Gaudreau et al. (2014) also highlighted the importance of developing standardized criteria of referral to the AEC to encourage physicians to refer patients to this service.[189]

1.8.2 Impact of specialized asthma care

To our knowledge, only four published pediatric cohort studies focused on examining the impact of specialist care alone following an asthma ED visit (mostly with hospital admission) on subsequent asthma ED visits in children aged 2 to 18 years old;[146,147,154,165] no RCT was identified, reflecting that further research is required in this topic. Two of the studies reported a protective effect of specialist asthma care alone on the risk of a subsequent asthma emergency visit over the next 12 months.[147,154] Aragona et al. (2014) reported that among moderate-severe asthmatic children with one or more prior ED visits, those not seeing an specialist within 3 months of the index admission were 6 times more likely to experience an ED relapse compared to those receiving such care.[147] In the study of McNamara et al. (2016), children who received specialist care had lower rates of ED visits within 30 days of the index asthma exacerbation than those who received primary care.[154] Collectively, these studies suggest that asthma specialist care is associated with a reduced risk of subsequent ED visits only in patients at high risk of exacerbations.

1.8.3 Impact of asthma education in combination with specialized asthma care

In the controlled trial of Kelly et al. (2000) involving 2-16 year old children with two ED visits or one admission for asthma in the previous year, usual care was associated with a 40% increase in the risk of a subsequent ED visit over the 12 subsequent months compared to a comprehensive asthma program (asthma education, a written action plan and allergist care) in the first visit to the allergy clinic, with reinforcement at 1 and 6 months.[190] The RCT of Teach et al. (2006) reported that, in children recruited from the ED, an intervention combining asthma education, specialist care and care coordination was associated with a 46% reduced risk of a future ED visit in the next 6 months compared to receiving only an asthma educational booklet at the index ED visit.[191] Moreover, Snyder et al.'s (2017) cohort study of patients recruited from a primary care network for at-risk, largely (95%) Medicaid children reported that the beneficial effects of a comprehensive intervention composed of follow-up by a pediatrician in combination with asthma education were sustained for 3 years after the intervention, decreasing in the intervention group while increasing during the same period in

the usual care group ($p<0.001$).[192] Overall, these studies suggested that interventions comprising asthma education and specialist care could provide protective effects against a subsequent ED visit in children at high risk of relapse.

Table 4. Summary of studies of the individual and combined effect of asthma education and specialized asthma care on subsequent ED visits

Authors	Inclusion criteria and asthma diagnosis definition	Outcome definition	Study design, population and intervention	Results
Intervention: asthma education alone or in combination with other self-management components				
Boyd M, Lasserson TJ, McKean MC, Gibson PG, Ducharme FM, Haby M. (2009)[11]	-Children aged 0 to 18 years -ED attendance for asthma in the past 12 months -Diagnosis of asthma: variable across studies (physician diagnosis or objective criteria for asthma symptoms and severity) s and necessarily new asthma diagnosis	Risk of subsequent asthma emergency visits, hospital admissions and unscheduled medical visits	-Meta-analysis of 38 RCT -**Intervention** was education given at different settings (ED, hospital, home or in community), providers (nurse/ pharmacist, educator or health or medical practitioner) and formats -**Control group** could be usual care, waiting list or lower intensity education	-There was a significantly reduced risk of subsequent emergency department visits (RR 0.73, 95% CI 0.65 to 0.81, N = 3008) and hospital admissions (RR 0.79, 95% CI 0.69 to 0.92, N = 4019) compared with control group over the next 12 months* *Most studies had a follow-up period of 12 months
Intervention: asthma education alone				
Watson WT, Gillespie C, Thomas N, Filuk SE, McColm J, Piwniuk MP, et al. (2009)[185]	-Children aged 3 to 16 years -Participants were recruited in the ED -Physician diagnosed asthma.	Asthma-related ED visits	-RCT (United States) -**Intervention**: 4 weekly group meetings of 1.5 hours, including interactive group education program, along with personalized information and facilitated by nurse and a respiratory therapist. Patients also received personalized mailings that reinforced the key educational messages at 2,4,6 and 12 months following the index ED visit -**Control group**: care by primary care MD and booklet with basic information on asthma	- The level of attendance to the education program varied among age groups (65% in the preschoolers, 80% in the school-aged children and 79% in adolescents) -Crude analysis: intervention group had a lower likelihood of requiring emergency care. (RR 0.62, 95% CI 0.48–0.81) in the subsequent year -Adjusted analysis: not reported

Otsuki M, Eakin MN, Rand CS, Butz AM, Zuckerman IH, Ogborn J, et al. (2009)[186]	-Children aged 2-12 years - Recruited in the ED -Had 2 ED visits or 1 hospitalization for asthma in the preceding year -Were prescribed an asthma controller medication -Physician diagnosed asthma.	Asthma ED visits	-RCT of inner city children (United States) **-AMF intervention:** five 30- to 45-minute home visits by trained asthma educators (AEs) 1, 2, 3, 4, and 8 weeks after randomization combined with medication adherence feedback **-ABC intervention:** Same components as Intervention 1, but excluding medication adherence feedback **-Control group:** usual care	-Of the participants assigned to AMF intervention or ABC intervention, 67% completed all five visits. The average number of visits completed for both groups was four -Crude analyses: not reported -Adjusted analyses (adjusted for insurance type and baseline level of ED visits): In the 18 months following study entry, ED visits decreased faster for the AMF group than for the control group (IRR=0.85, 95% CI 0.74-0.97). No statistically significant difference in subsequent ED visits was found between the ABC and the control group (IRR=0.92, 95% CI 0.81-1.06), nor between the AMF and the ABC groups (IRR= 0.92, 95% CI 0.81-1.05)
Indinnimeo L, Bonci E, Capra L, La Grutta S, Monaco F, Paravati F, et al. (2009)[187]	-Children aged 6 to 14 years -Recruited from six specialist pediatric clinics -Newly physician diagnosed intermittent or mild persistent asthma	Asthma ED visits	-RCT (Italy) -Participants had an average of 1.75 emergency visits in the past year **-Intervention:** specialist care in pediatric clinic and a one hour asthma self-management education program given by resident physicians and nurses at baseline and 2 months later **-Control group:** specialist care in pediatric clinic	-Participation rates in the education program were not reported -Crude analysis: No significant difference in number of emergency visits between the intervention and the control group in the subsequent year. However there were fewer asthma attacks in patients who received the intervention (1.65 $\pm$ 1.21 and 2.34 $\pm$ 1.73; respectively, $p<0.05$) compared to the control group in the subsequent year -Adjusted analysis: not reported
Bruzzese JM, Sheares BJ, Vincent EJ, Du Y, Sadeghi H, Levison MJ, et al. (2011)[188]	-Children of 9th and 10th grade with moderate to severe persistent asthma -Recruited from five high schools (enrolment took place between 2001 and 2004) -Physician diagnosed asthma	Asthma ED visits and hospital admissions	-RCT (United States) - Children with mean age of 15 years, from high schools with high proportions of Latino and African American -The intervention and the control group reported an average of 1.80 and 1.92 asthma ED visits in the previous year, respectively **-Intervention**: During 8 weeks, students received three school-based 45- to 60- minute group sessions, and individual coaching sessions at least once	-Most participants (90%) attended all three group sessions and 78% met four to six times individually with a health educator; -Crude analysis: not reported -Adjusted analysis (adjusted for age, sex, race, asthma severity and presence/absence of medical provider at baseline): the intervention group had a reduced risk of ED visits (adjusted RR=0.52, 95% CI 0.40-0.68 compared to the control group in the subsequent year

			per week for 5 weeks provided by a health educator. The intervention also included academic detailing for their medical providers. **-Control group**: usual care	
Intervention: specialized asthma care				
Drewek R, Mirea L, Rao A, Touresian P, Adelson PD. (2016)[146]	-Children aged 5-18 years -Presentation to the ED with or without admission for asthma (ICD10: J45.901) between January 2014 and December 2016 -Duration of follow-up period was not mentioned	Asthma (ICD10: J45.901) readmission	-Retrospective cohort study (United States) **-Intervention:** pulmonology follow-up consultation **-Control group:** no pulmonology follow-up consultation	-Only 36% of the patients referred to pulmonology attended their pulmonology follow-up -Crude analysis: There were no differences in readmission rates between patients who did and those who did not have a pulmonology follow-up (p=1.0) -Adjusted analysis: not reported
Aragona E, Wang J, Scheckelhoff T, Hyacinthe A, Nino G, Pillai KG. (2014)[147] (abstract)	-Children older than 2 years old -Cohort entry was during an admission for an asthma exacerbation to an inner-city tertiary children's hospital -Children were followed for 12 months following the index admission for asthma -Physician diagnosed asthma	Asthma-related ED visit	-*Incomplete study design description. Preliminary results.* -Retrospective cohort study (United States) -Mean age was 8.4 years -Patients with moderate-severe asthma and ≥ 1 ED visit prior to admission **-Intervention:** follow-up in a specialist clinic (ED based asthma clinic, pulmonary clinic or allergy clinic) **-Control group:** no follow-up in a specialist clinic	-Overall, 75% of patients were referred to specialist care and 44% saw an asthma specialist within 12 months of discharge. One third of patients saw an asthma specialist within 3 months of discharge -Crude analysis: not reported -Adjusted analysis: Not seeing a specialist within 3 months of hospital discharge was associated with an increased risk of having an asthma related ED visit (RR=6.2; p=0.017) in the 12 subsequent months compared to seeing a specialist -*To this date, this study remains unpublished*
McNamara K, Stukus DR. (2016)[154] (abstract)	-Children aged 6-21 years -Participants were recruited from a tertiary care pediatric hospital system database -Cohort entry was an asthma exacerbation with a prescription of oral corticosteroids between January 1 and December 31,	Rates of asthma ED visits	-*Incomplete study design description. Preliminary results.* -Retrospective cohort study (United States) -Mean age was 6.9 years in the control group and 7.2 years in the intervention group **Intervention:** follow-up in	-Crude analysis: Rates of ED visits within 30 days of the index asthma exacerbation were lower in the intervention group (4.58 visits/100 patients) compared with those of the control group (7.18 visits/100 patients); p <0.01 -Adjusted analysis: not reported -*To this date, this study remains unpublished*

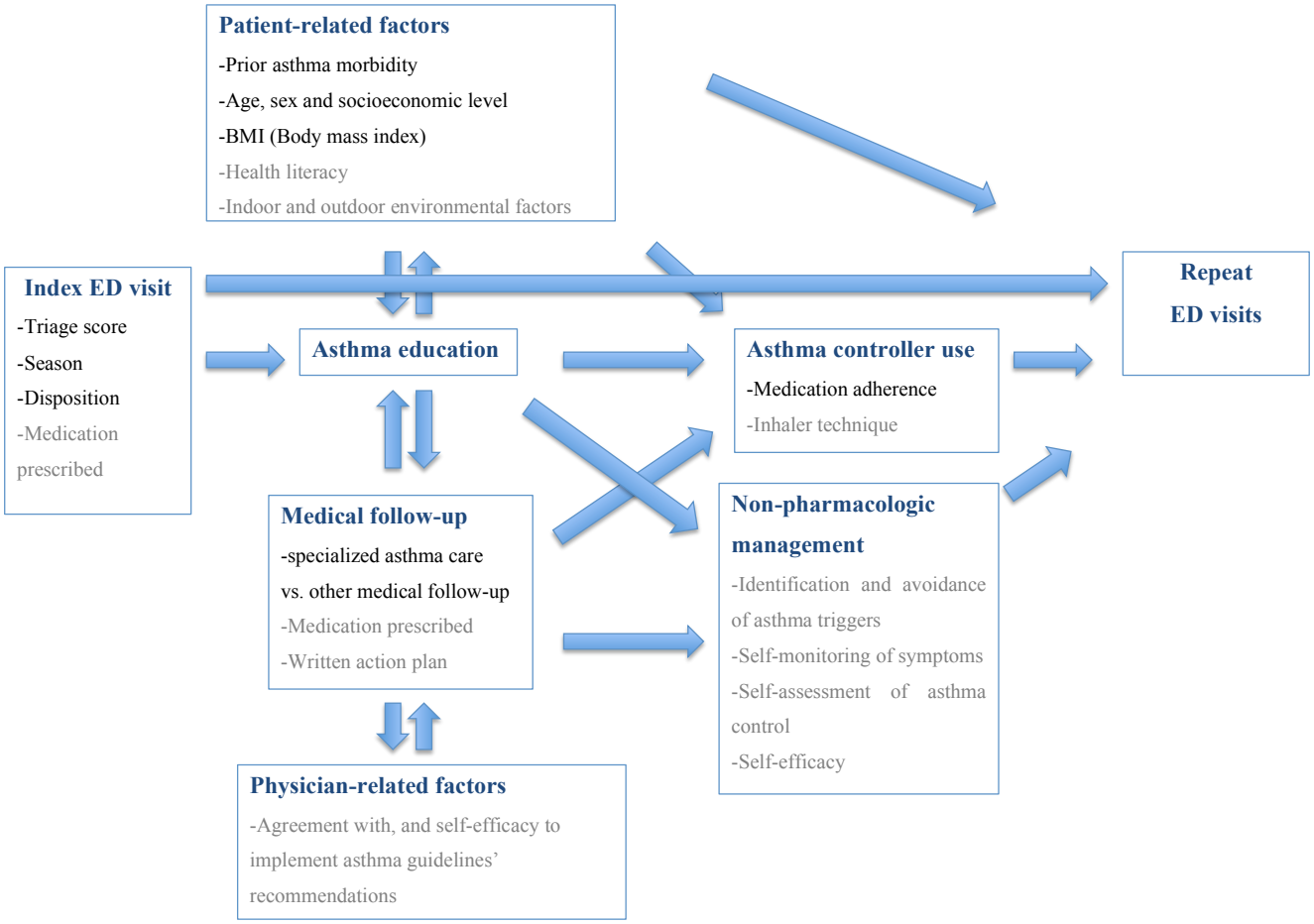
	2014 - Asthma diagnosis (ICD-9 493) -Participants were followed for 30 days following the index asthma exacerbation		allergy/immunology/pulmonary outpatient clinics **Control group**: follow-up in primary care	
Johnson LH, Beck AF, Kahn RS, Huang B, Ryan PH, Olano KK, et al. (2017)[165]	-Children 2-16 years old -Cohort entry was during a hospitalization for asthma, with provision of oral steroids and beta-agonists between August 2010 and October 2011 -Children were followed for 12 months following the index admission for asthma -Physician diagnosed asthma	Asthma (ICD-9: 493) ED visit where albuterol or systemic corticosteroids were administered or prescribed at discharge	-Prospective population-based cohort study (United States) **-Intervention:** asthma specialist as usual care **-Control group:** primary care as usual care	Overall as their source of usual care, 4.2% of children reported having an asthma specialist, 44.5% had primary care and 51.2% went to the ED -Crude analysis: There was no difference in the likelihood of a subsequent ED visit in the 12 subsequent months among the children followed in primary care and those followed by an asthma specialist (OR=0.77, 95% CI 0.32-1.85) -Adjusted analysis: not reported
Intervention: Combined asthma education and specialized asthma care				
Kelly CS, Morrow AL, Shults J, Nakas N, Strope GL, Adelman RD. (2000)[190]	-Children aged 2 to 16 years -Two emergency visits or one hospital admission with an asthma diagnosis (as per hospital records) in the previous year -Medicaid insurance coverage -Participants received primary care in the hospital's outpatient clinic -Children were enrolled in the intervention group in their initial visit to the allergy clinic -Children were followed for 12 months	ED visits for asthma	-Controlled clinical trial with alternate assignment of participants to the exposure groups (United States) **-Intervention:** individual asthma education by physician and nurse during the initial allergy clinic visit (including a written action plan), with follow-up visits at the allergy clinic at 1 and 6 months where asthma education was reinforced **-Control group:** usual care	-Two children in the intervention group were lost to follow-up, none in the control group -Crude analysis: not reported -Adjusted analysis (adjusted for ED visits, hospitalizations and hospital days for asthma in the previous year): The control group had a higher risk of a subsequent ED visit compared to the intervention group (RR=1.4, 95% CI 1.02-1.9).
Teach SJ, Crain EF, Quint DM, Hylan ML, Joseph JG. (2006)[191]	-Children aged 1-17 years -Patients were recruited from the ED from April 2002 and January 2004 -Prior physician diagnosed asthma -Had ≥1 unscheduled l asthma	Unscheduled visits for asthma (ED and other sources of urgent care)	-RCT (United States) -Most children (60%) were preschoolers (1 to 5 years old) -92% of patients had at least 1 ED visit for asthma in the 12 previous months) **-Intervention:** One visit to an	-Overall, 71% of patients assigned to the intervention group, attended their education session -The intervention group had a lower risk of subsequent ED visits (RR=0.54, 95% CI 0.40-0.72) than the control group in the 6 months following the index ED visit

	visit (to the ED or other health care source) in the 6 previous months and/or ≥ 1 hospital admission in the previous year -Three or more doses of nebulized albuterol in the ED at time of enrolment -Patients were followed for 6 months		ED-based asthma clinic, consisting 60 to 90 minutes education session with action plan, specialist care and care coordination **-Control group:** asthma educational booklet only	
Snyder DA, Thomas OW, Gleeson SP, Stukus DR, Jones LM, Regan C, et al. (2017)[192]	-Children aged 2-18 years old -Recruitment started in December 2011 -Physician diagnosis of asthma in the 24 previous months -Patients from a primary care office --Data was analyzed from 2012 to 2015	Rates of ED visits with a primary diagnosis of asthma (493/J45) / 100 000 patients	-Prospective cohort study (United States, 2012-2015) -High risk population -95% of patients was Medicaid enrolled **-Intervention**: specialist care by pediatrician and asthma education embedded in a primary care office. Follow-up appointments were recommended at the following intervals: well-controlled intermittent asthma (at 6 months), well-controller persistent asthma (at 3 months) and poorly controlled asthma (at 4 weeks) **-Control group:** primary care	In 2012, asthma ED visits by intervention and control groups were similar (p=0.43). After the intervention implementation, asthma ED visit rates were significantly lower for the patients who received the intervention versus those who received primary care (p < 0.001), declining in the intervention population by 26.2%, 25.2%, and 31.8% in 2013, 2014, and 2015, respectively, from 2012 baseline, versus increases of 3.8%, 16.2%, and 9.5% in the usual care population

1.9 Summary of the literature review

The conceptual framework that will guide the present study was developed from the literature review findings (Figure 1).

Figure 1. Conceptual framework of factors associated with pediatric asthma-related emergency visits



*The factors in gray cannot be obtained from hospital and healthcare administrative databases

Collectively, randomized controlled trials confirm that ED-based interventions to encourage primary care follow-up don't have a significant impact on subsequent ED visits. Generally, asthma education has beneficial effects when provided at the index ED visit or within 12 months of an index ED visit to reduce subsequent ED visits and to improve the use of controller medication. Cohort studies suggest that, compared to usual care, specialist care is associated with a reduction in the risk of subsequent ED visit but only in selected patients with a high morbidity, including those with moderate-severe asthma and those with an asthma exacerbation requiring oral corticosteroids. Moreover, follow-up by an asthma specialist appears to be associated with more beneficial health care outcomes than follow-up in primary care for patients at high-risk of exacerbations. That is, those with persistent and uncontrolled asthma or two or more previous ED or 1 previous hospital admission. Overall, comprehensive care consisting of asthma education, specialist care and other self-management components (i.e., written action plan or care coordination) was associated with a decrease in the risk of a subsequent ED visit.

Since there are barriers to providing self-management interventions in the ED, most ED physicians currently make referral to the service they deemed suitable for the child and that will happen after the index ED visit. Yet, attendance rate is suboptimal in real-life, with only 12%[193] to 33%[144] of children having a primary care follow-up visit within one to two months of the index ED visit. Of note, at the Montreal Children's Hospital, once referral was sent to the AEC, the educator contacted the parents who had not made an appointment promptly to try to organize one. This was perceived important as only two thirds of children referred to the AEC following an ED visit tend to schedule an appointment,[142] and 34%[146] to 60%[147] of children referred to specialist care following a hospital admission receive such care in the subsequent year.

However, dissociating the impact of asthma education from that of regular review by a general practitioner or a specialist is difficult, as patients enrolled in the above-mentioned studies may have received medical care from different sources during the follow-up period. To our knowledge, no previous study has explored both the real-life individual and the combined impact of asthma education and specialist care on subsequent morbidity in the pediatric population.

1.9.1 Efficacy vs. effectiveness studies

Efficacy randomized controlled trials allow the evaluation of the impact of interventions under ideal experimental conditions, while effectiveness trials explore the real-life impact of interventions. Efficacy trials can overestimate the effect of an intervention in clinical practice.[194] Indeed, the external validity of efficacy trials is limited by the strict eligibility criteria used. Effectiveness trials or observational studies may have lower internal validity than efficacy RCTs,[195] but offer the advantage of selecting a group of patients more representative of the heterogeneous real-life population[196] and allowing the pragmatic evaluation of interventions that take place at different time intervals from study entry, just as they take place in real-life. Randomized controlled trials are the gold standard, but can be complemented by population-level observational studies[197] of patients who would benefit from the intervention under study.

The proposed natural experiment study of patients identified as needing asthma education following an ED visit (as per referral to the AEC), with or without attendance to AEC appointment, would provide a unique opportunity to evaluate the individual and combined real-life impact of asthma education at the AEC and specialized follow-up at the AC on the occurrence of subsequent asthma emergency visits. Furthermore, the individual and combined impact of the exposures of interest on other markers of poor asthma control and medication adherence will also be analyzed. If the interventions are shown to be effective, the next priority will be to operationalize referral criteria to AEC and/or SAC in children presenting to the ED for asthma for standardization purposes and to develop strategies to increase the attendance rates at these services. If the interventions are not effective in reducing the risk of a subsequent ED visit in real-life conditions, the next priority will to identify better referral criteria to AEC and SAC, and most importantly, to explore the reasons behind the ineffectiveness of the interventions. Possible explanations could include not receiving the interventions at the same time, suboptimal adherence of physicians to the guidelines' recommendations (i.e., not an effective medical visit), variable asthma education, mixed messages received, suboptimal patient adherence, etc. An ideal scenario would be providing asthma education and specialist care on the same visit with similar messages to reinforce the physician's recommendations by the asthma educator.

1.10 Analytical approach in observational longitudinal studies

1.10.1 Time-varying exposures

Unlike randomized controlled trials where patients assigned to the intervention group receive the exposure of interest within a period of time chosen by the researchers, patients can receive the interventions at different points in time in real-life. Therefore, it is important to correctly assign patients to the exposure groups during the follow-up period to avoid reporting biased estimates. Indeed, estimates are subject to immortal time bias when the time-varying nature of exposure variables is not taken into account in the statistical analysis.[198] Different methods that take into account the time-dependent nature of variables are currently used, ranging from using time-varying covariates to more complex approaches such as marginal structure models and structural nested failure time models.[199]

Time-varying covariates are most commonly used because of their simplicity of implementation in Poisson regression models and in Cox proportional hazard models.[198] Furthermore, two approaches can be taken when using time-varying exposures: they can be created for the entire follow-up period or only for interventions taking place during a critical period. The latter approach implies investigating the impact of receiving the intervention during time increments and determining the time period during which the intervention has the most beneficial effects for the patients ("the critical period"). For example, the impact of interventions received in 30-day increment periods (e.g., 30 days, 60 days, 90 days, etc.) can be analyzed. In this thesis, the first approach will be explored, since it provides an overall picture of the impact of the interventions that take place at any point during the follow-up period.

1.10.2 Possibility of confounding by indication

Confounding by indication is likely to take place because severity and poor asthma control are probably highly associated with a referral to asthma education and specialized asthma care, prescription of, and adherence to, asthma controller medications. Admitted patients (who are at high risk of returning to the hospital) are also be more likely to receive asthma education than patients discharged from the ED due to Quebec's systematic referral

program for hospitalized patients in application in the Montreal Children's Hospital at the time of the cohort accrual. The relationship between hospital admission and referral to asthma education can thus result in unexpected and/or spurious results. Three approaches that are commonly used to prevent confounding by indication are stratification, selection, and adjustment. To address this concern, the latter two approaches were selected. Statistical analyses of this thesis will be adjusted for prior morbidity indicators (number of asthma/asthma emergency visits, asthma/asthma-like hospital admissions and in a subcohort, asthma control in the preceding 6 to 12 months), and a cohort of at-risk patients will be selected to minimize the confounding by indication bias. The variable "referral to asthma education" is the only variable that was systematically documented in our databases and could be used to select patients in need of the interventions of interest; therefore, it will be used to as an inclusion criterion to select the cohort of at-risk patients.

1.10.3 Attrition

Attrition takes place when all the study participants do not have the same follow-up period, since some of them are lost to follow-up. Attrition can cause a bias when there are different rates of loss to follow-up in the exposure groups and when the characteristics of participants changed as a result, rendering the exposure groups not comparable.[200] In this thesis, we will deal with attrition by excluding patients without provincial medical services coverage for at least one year preceding and one year following the study entry. In this way, we will ensure access to complete medical services use during the 1-year follow-up period for all patients from the study cohort and therefore, no patients will be lost to follow-up.

1.10.4 Censoring

In the main analysis of the present thesis, administrative censoring will take place in patients who do not experience the event of interest during the 1-year follow-up period. No censoring due to lost to follow-up or withdrawal from the study will take place due to the exclusion of patients without provincial medical services coverage for at least one year preceding and one year following the study entry.

1.10.5 Missing values

Different methods for handling missing values have been proposed in the literature. The most practical method is a complete case analysis, which implies including only patients with complete information in the analysis. The disadvantage of using this method is that some data is lost if there is censoring prior to the end of follow-up or due to missing values. Other more complex methods including maximum likelihood estimation, multiple imputation and weighted estimating equations.[201] However, when a large proportion of the data is missing, complete case analysis is not recommended.[201] Therefore in this thesis, a complete case analysis will be performed if there is little missing data. Multiple imputation methods will be used if there is an important amount of missing values.

Chapter 2: Objectives

In children referred to the Asthma Education Centre following an emergency department (ED) visit for an acute asthma exacerbation, the objective of this thesis is to evaluate the impact of asthma education received at the Montreal Children's Hospital's Asthma Education Centre (AEC) and/or of a specialized asthma care (SAC) visit on asthma morbidity in the subsequent 12 months in real-life practice.

2.1 Primary objective

To examine the impact of an AEC and/or a SAC visit (individually and in combination) on the risk of an earlier subsequent asthma emergency visit in the 12 months following an ED visit for an acute asthma or asthma-like exacerbation in children aged 0 to 17 years.

2.2 Secondary objectives

In the subcohort of patients covered by the public drug plan, to investigate the impact of an AEC and/or a SAC visit, individually or in combination, after the index ED visit on subsequent:

- Asthma control level
- Use of asthma rescue medication, that is, short-acting β2-agonists (SABA)
- Use of rescue oral corticosteroids (OCS) for asthma exacerbation

In the subcohort of patients covered by the public drug plan, to explore the impact of an AEC and/or a SAC visit, individually or in combination, after the index ED visit on subsequent adherence to inhaled corticosteroids

Chapter 3: Methodology

3.1 Data sources

The study used data obtained from three hospital databases of Montreal Children's Hospital (MCH) and three Quebec health administrative databases.

3.1.1 Montreal Children's Hospital (MCH) databases

The **Emergency department (ED) database** contains the information concerning all the ED visits, irrespective of the physician's payment scheme. For this study, we obtained data on all respiratory-related ED visits (defined as a discharge diagnosis of "asthma/reactive airway disease", "asthma and otitis", "asthma and pneumonia", "allergic rhinitis and asthma", "bronchiolitis", "bronchitis" and "bronchospasm") occurring between 2000 and 2007. Information included patient demographics (such as age, gender and residential postal code), the date and time of arrival to, and disposition from, the emergency department, disposition (discharge or hospital admission), the Canadian Triage and Acuity Scale level at presentation, and the 'in-house' diagnostic code at discharge.

The Asthma Education Centre (AEC) database comprises documentation of all the referral requests, the referral source (ED, hospitalization units, asthma clinic, community physicians, or self-referral), the date of referral, the attendance code (presence, absence, contacted but no answer) and the date of the educational visit.

The Asthma Centre (AC) database includes the date of the visit, the attendance code, patients' demographics, anthropometric measures, confirmation (or not) of asthma diagnosis by a specialist, morbidity in the previous year, asthma control and severity, asthma symptoms and triggers, atopic conditions, spirometry test results, physician treatment plan including prescribed controller and rescue medication.

3.1.2 The Régie de l'assurance maladie du Québec (RAMQ) databases

RAMQ is Quebec's universal health insurance agency, whose mission is to manage the provincial's public medical services health insurance and prescription drug insurance plans.[202]

All Quebec' residents benefit of free of charge medical services, including medical visits and hospital admissions, and investigation under Quebec's universal public health insurance plan. In addition, RAMQ offers a public prescription drug insurance plan for beneficiaries of the social assistance program,[203] families of individuals who are not eligible for a private drug insurance plan, and those aged 65 years and older; which represent approximately 44% of the Quebec population.[204] RAMQ databases have been validated for their usage in asthma studies [205,206,207,208] and are widely used in medical research. Additionally, RAMQ provides files containing the admissibility periods to the public health insurance and the prescription drug insurance plans, described hereafter.

The Régie de l'assurance maladie (RAMQ) medical services database contains information obtained from the claims of physicians who are remunerated for medical services on a fee-for-service basis. Of note, between 2000 and 2009, 68% of generalists and 77% of specialists were remunerated on fee for service in Quebec.[209] More specifically, this database includes the physician's specialty, the type of establishment where the medical service was performed (medical clinic, emergency department, hospital visit), the date of the service, and the ICD-9 (International Classification of diseases) diagnostic code.

The **Régie de l'assurance maladie (RAMQ) public prescription claims database** comprises information about the prescription medications dispensed by community pharmacies to patients covered by the public drug insurance plan. It includes the type of beneficiary, information about the prescribed medication (class of medication, the non-proprietary name, form, dosage, amount, Drug Identification Number [DIN], duration of prescription, cost), the type of prescription (new or refill), the dispensation date, the number of allowed refills, and the physician's specialty.

3.1.3 The Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière (MED-ECHO) database

MED-ECHO is a database from the Quebec's Ministry of Health and Social Services, which contains information about hospital admissions and outpatient surgeries; it is used for the evaluation, planning and organization of the services.[210] This database contains the dates of admission and discharge, the type of care provided (short term or long term), the type of

admission (urgent, semi-urgent, non urgent), the length of the stay, the International Classification of Diseases (ICD) 9th version of the primary and secondary (up to 16) discharge diagnostic codes until March 31, 2006 and ICD-10th version ever since. Under Quebec's universal public healthcare system, all Quebec residents are covered for hospital admissions.

3.2 Ethical considerations

The Research Ethics Boards of Montreal Children's Hospital and then of CHU Sainte-Justine approved the study protocol (Appendix I). The authorization to access the governmental health databases for this study was granted by the Commission d'accès à l'information du Québec (file number: #080185), the provincial organization responsible for the access to documents from the public sector and the protection of personal information.

3.3 Study design

A retrospective cohort study was performed by linking the three governmental health administrative databases and the three MCH databases by using a unique patient identifier number.

The cohort entry (index) visit corresponded to the emergency visit date on which the child met all inclusion criteria. If the eligibility criteria were met on multiple emergency visits during the study period, the earlier presentation date was chosen as the cohort entry (index) visit. For the main outcome, patients were followed until their first subsequent ED visit or for 12 months following the index ED date (if they did not have a subsequent ED visit). The secondary outcomes (OCS use, SABA use, and asthma control) and the exploratory outcome (adherence to ICS) were documented over the 7^{th} to 12^{th} months following the index ED visit.

3.4 Inclusion criteria

Children were eligible if they presented to the emergency department of the Montreal Children's Hospital between January 1st 2001 and December 31st 2006 with the following criteria:

1) Aged 0 to 17 years

2) Received discharge diagnosis of asthma (ICD-9: 493) or, if aged 1 year and over (as per the 2015 Canadian Position Paper[6]) a discharge diagnosis of an asthma-related condition, defined as acute bronchiolitis (ICD-9: 466.1), bronchospasm (ICD-9: 519.1), acute bronchitis (ICD-9: 466.0) or bronchitis not specified as acute or chronic (ICD-9: 490.9), as registered in the RAMQ medical services database. For visits with a missing diagnostic code in the RAMQ database and for those not recorded in the RAMQ database due to the physician not being remunerated by fee-for-service, the corresponding hospital diagnostic codes were used (see Appendix II)
3) Had medical services coverage in Quebec for at least 12 months preceding, and 12 months following, the index ED visit
4) Were referred to the AEC in the 12 months following the index ED visit

For the secondary and exploratory outcomes, full medication coverage for at least 12 months preceding and 12 months following the index ED visit was also required.

- Justification for inclusion criteria 2:

Of note, patients with an 'asthma-like diagnosis' were included *as per* the '2015 Canadian Position paper on the diagnosis and management of asthma in preschoolers' that listed common misnomers for asthma in young children ("repeated bronchiolitis", "bronchospasm", "recurrent bronchitis) that should be avoided and replaced with diagnosis of 'asthma' or 'suspected asthma in children aged 1 year and older. We applied this approach due to lack of a standardized approach to define asthma in preschoolers in place during the study period (between 2000 and 2007). At that time, asthma-like diagnoses were commonly used because of the previously perceived ambiguity in the role of an ED physician in making an asthma diagnosis and initiating long-term controller treatment in an ED setting. This was a role that was often delegated to the treating physician at follow-up.[150] Delayed diagnosis associated with delayed therapy, in combination with low rates of medical follow-ups[144,145] probably contributed to delayed management and ongoing preventable morbidity.

The selection of the asthma-like diagnostic codes was performed after (i) verifying the concordance between asthma/asthma-like diagnostic codes in the RAMQ database and asthma/asthma-like diagnosis in the hospital ED database (and vice-versa) and (ii) the likelihood of having a subsequent medical visit with an asthma diagnosis in the year following an ED visit. Based on these preliminary analyses (see Appendix III), asthma-like diagnostic codes included "acute bronchiolitis", "bronchospasm", "acute bronchitis" and "bronchitis not specified as acute or chronic" in children aged 1 year and over.

- Justification for inclusion criteria 4:

The last entry criterion was selected, as it is the only systematically documented marker in our databases of the perceived need for specialized asthma education (and probably specialized care) in the view of the ED physician. A referral was required to attend an asthma education session at the AEC and to see a specialist. Since there is no "referral to specialist" variable in the databases, only the "referral to AEC" variable could be used to select high-risk patients.

3.5 Exclusion criteria

Patients were excluded if they had made a visit to the Montreal Children's Hospital's Asthma Education Centre or Asthma Centre or to an asthma specialist (allergist or respirologist) in the 12 months preceding the index ED visit; this was specified to ensure that we selected patients naïve to the interventions of interest.

3.6 Exposure variables

3.6.1 Asthma education

Patients were considered as 'exposed' to asthma education if they attended an AEC session at the Montreal Children's Hospital within 12 months of the index ED visit. Patients were considered 'exposed' from the day of their first visit to the AEC until cohort exit. The dates of AEC visits were documented in the AEC database.

3.6.2 Specialized asthma care (SAC)

Patients were considered 'exposed' to a specialized asthma care if they made a documented medical visit either to the Montreal Children's Hospital's Asthma Centre or to an asthma specialist (allergist or respirologist) in the Province of Quebec, within 12 months of the index ED visit. Patients were considered 'exposed' from the day of their SAC. The dates of SAC visits were documented in the Asthma clinic database and/or in the RAMQ medical services database.

3.6.3 Asthma education and specialized asthma care

If the patient made a documented visit to both the AEC and SAC during the follow-up period, he/she was considered exposed to both from the day of the latest intervention exposure.

3.7 Outcome variables

3.7.1 Main outcome

The main outcome variable was the time to the first subsequent ED visit (with or without hospital admission) for asthma (ICD-9: 493) or (if the patient is 1 year of age or older) for asthma or an asthma-related condition in the 12 months following the index ED visit. Asthma related conditions were defined as: acute bronchiolitis (ICD-9: 466.1), bronchospasm (ICD-9: 519.1), acute bronchitis (ICD-9: 466.0) or bronchitis not specified as acute or chronic (ICD-9: 490.9). Patients were followed until the first subsequent ED visit, or for 12 months following the index ED visit (if they didn't experience a subsequent ED visit).

3.7.2 Secondary outcomes

Secondary outcomes included asthma control, use of short-acting beta-agonists (SABA) and rescue oral corticosteroids (OCS) use. Taking into account the delay to access asthma education and specialized asthma care in real-life, we considered a 182-day window (6 months) to access the intervention exposures. Secondary outcomes were measured from the 183rd to the 365th day of follow-up (from the beginning of the 7th month to the end of the 12th

month after the index ED visit). A 6-month observation period for these secondary outcomes was appropriate as our indicator of asthma control (see below) is measured over a 6-month period, which is also sufficient long for accurate ascertainment of SABA and OCS use.

3.7.2.1 Asthma control

Asthma control was measured by using the Pharmacoepidemiologic Pediatric Asthma Control Index (PPACI), a validated 4-category index developed for use in administrative health databases[75] (Table 5). The PPACI is based on the average weekly number of doses of short-acting B2-agonists (SABA), prescriptions of short course oral corticosteroids (OCS) with a duration of less than 14 days (the latter two from drug claims), ED visits and hospital admissions for asthma (ICD-9: 493) and, in children aged ≥1 year, for asthma-like symptoms (acute bronchiolitis [ICD-9: 466.1] acute bronchitis [ICD-9: 466.0], and bronchitis, not specified as acute or chronic [ICD-9: 490.9]).[75]

For hospital admissions that took place from April 1, 2006, the corresponding ICD-10 codes were used for asthma [ICD-10: J45] and asthma-like symptoms (acute bronchiolitis [ICD-10: J21], acute bronchitis [ICD-10: J20], and bronchitis, not specified as acute or chronic [ICD-10: J40]). To ensure that the OCS were prescribed for the asthma symptoms, only the prescriptions filled within 10 days of a medical service for asthma or asthma-like symptoms were included. The average weekly number of SABA doses was calculated using an algorithm developed by our research group, based on the quantity of dispensed medications where two 100 μg salbutamol inhalations from a metered-dose inhaler were considered equivalent to one SABA dose.[75] We applied a modification to the calculation of PPACI, hereafter referred to as modified PPACI, using a follow-back period of six, instead of twelve, months for the calculation of the average weekly number of SABA doses. Preliminary analyses showed that this modification overestimates the proportion of patients with controlled asthma by only 3%, a reasonable adaptation to minimize the additional exclusions of children without drug coverage over the 18 months prior to index ED visit, which would have resulted in the loss of 100 additional patients.

Table 5. Definition of asthma control levels, as measured by the PPACI[75]

Level of asthma control	Definitions (over a 6-month period)
Controlled	<4 SABA doses/week and no OCS/ED/Hospital admission
Partly controlled	≥4 to <7 SABA doses/week and no OCS/ED/Hospital admission
Poorly controlled	(≥7 SABA doses/week or ≥1 OCS of ≥1 ED) and no hospital admission
Very poorly controlled	≥1 Hospital admission

3.7.2.2 Use of short-acting beta-agonists (SABA)

The average weekly number of doses of short-acting beta-agonists (SABA) was calculated using the algorithm developed for the calculation of the PPACI and using a follow-back period of six months instead of twelve months. The results were then categorised as "Average of less than four SABA doses per week" vs. "Average of four or more SABA doses per week", one of the markers of poor asthma control.[9]

3.7.2.3 Use of oral corticosteroids (OCS)

Only OCS prescriptions with a duration of less than 14 days and filled within 10 days of a medical service for asthma (ICD-9: 493) or an asthma-related condition, defined as acute bronchiolitis (ICD-9: 466.1), bronchospasm (ICD-9: 519.1), acute bronchitis (ICD-9: 466.0) or bronchitis not specified as acute or chronic (ICD-9: 490.9), were included to ensure that these claims were not made for other conditions. The values were then categorized as "no OCS prescriptions" vs. "1 or more OCS prescriptions" over the 6-month observation period.

3.7.3 Exploratory outcome

Adherence to inhaled corticosteroids (ICS) was explored over a six-month period, which is sufficient for accurate ascertainment of ICS adherence.[211] It was calculated by using the Proportion of days covered (PDC), which is defined as the total days' supply dispensed (i.e., the sum of the duration of new dispensed, and refills of, ICS prescriptions) divided by the total number of days of follow-up.[212] Patients were provided with a 182-day window (approximately six months) to access the intervention exposures and the use of inhaled corticosteroids was evaluated during the 183rd to the 365th day of follow-up (the six subsequent months). Given the known decrease in ICS use with time[213] and for information purposes, the PDC will also be presented in the first six months and the last six months of follow-up, irrespective of intervention exposure.

3.8 Potential confounding variables

Potential confounding variables were chosen based on the literature review and their ability to be obtained from the Quebec health administrative databases and/or Montreal Children's Hospital (MCH) databases. For the main and secondary outcomes, the following covariates were considered for adjustment:

a) Patient characteristics at the index ED visit: gender (female, male), age (in years), Pampalon social and material deprivation index (in quintiles, obtained by using the patient's residential postal code as a proxy[214]), and prior morbidity, namely atopy (dermatitis, allergic rhinitis, urticaria), emergency visits and hospital admissions for asthma in the 12 previous months. As always, asthma-like diagnoses were included for patients aged 1 year or older.

b) Index emergency visit characteristics: triage level (resuscitation, emergent, urgent, less urgent, non-urgent) and season (winter, spring, summer, fall) and diagnosis at the index visit (asthma or asthma-like condition)

The main analysis was also adjusted for season of follow-up (winter, spring, summer, fall), which was included as a time-varying covariate. This allowed accounting for seasons of asthma exacerbations, such as the September peak and seasonal allergies.[215]

For the secondary outcomes, to avoid multicollinearity, emergency visits and hospital admissions for asthma (or asthma-like diagnoses) in the 12 previous months were replaced by asthma control, measured by the modified PPACI in the 6 months preceding the index visit.

3.9 Statistical analysis

Missing data was found only for Pampalon social and material deprivation indices (in 6.2% of patients from the study cohort and 4.2% from the subcohort), and these patients were excluded from the analyses. Therefore, a complete case analysis was performed for the primary, secondary and exploratory outcomes, meaning that only patients with complete data were analyzed. The primary and secondary outcome analyses were adjusted for all documented potential confounding variables. For all analyses, statistical significance was defined using a threshold of two-sided $P < 0.05$. Analyses were performed using SAS Enterprise Guide 5.1 (SAS Institute, Cary, NC) and R Studio software (version 3.5.0).

3.9.1 Main outcome

A Cox proportional hazards model with time-varying AEC and SAC exposures was constructed to analyze the association between the intervention exposures and the time to first subsequent ED visit for asthma or asthma-like conditions in the 12 months following the index ED visit. The proportional hazards assumption was verified for the intervention exposure variables and the covariates by using Schoenfeld residuals plots and by generating time dependent variables. Interactions with the appropriate survival time function (log, linear or squared) were included in the models for covariates that violated the proportional hazards assumption. For morbidity covariates measured in the previous 12 months, ED visits and hospital admissions taking place within 7 days of each other were only counted once, assuming that they pertained to the same exacerbation.

Several sensitivity analyses of the main outcome were performed first in the unselected cohort of children 0-17 years old who experienced an index ED visit for an asthma or asthma-like condition during the study period (with or without referral to the AEC); secondly, in the subcohort of children covered by the public drug prescription plan; and thirdly, in the

subcohort of children with a confirmed asthma diagnosis at the index ED visit (one hospital admission for asthma and/or two asthma physician visits occurring at least 14 days apart within the previous year). The latter definition of asthma diagnosis was a slightly modified version of an asthma case definition developed for research and surveillance purposes in Ontario (using one year as an observation period instead of two years).[37,38]

The first sensitivity analysis was performed to assess the magnitude of the confounding by indication associated with analyzing the outcomes in an unselected cohort of patients. The second sensitivity analysis was undertaken to verify the impact of accounting for the use of rescue medications in the 6 months preceding the index ED visit. The third sensitivity analysis allowed us to verify the robustness of our results in the subgroup of patients with a confirmed asthma diagnosis at the index ED visit.

3.9.2 Secondary outcomes

Modified Poisson regression models for binary outcomes[216] were used to analyze the use of short-acting beta-agonist (SABA) use, the use of rescue oral corticosteroids (OCS) for asthma and asthma control. These modified Poisson regression models include a robust error variance procedure to avoid overestimating the error for the relative risk that takes place when Poisson regression models are used for binary data.[216]

3.9.3 Exploratory outcome: Adherence to inhaled corticosteroids

The median (25%, 75%) PDC of inhaled corticosteroids was calculated. A Kruskal-Wallis test allowed the global comparison of ICS adherence among the intervention exposure groups.

Chapter 4: Results

4.1 Preamble

The main results of this research project are presented in the form of a manuscript, which will be submitted for publication to the Journal of Allergy and Clinical Immunology (JACI): In Practice.

4.2 Contribution of authors

I confirm my original contribution to the present manuscript. More specifically, I conducted the literature review, assembled the study cohort, performed the data analysis, interpreted the findings and wrote the manuscript.

Dr. Cristina Longo provided guidance with respect to methodology and creation of the statistical programs required for cohort assembly and statistical data analysis.

Dr. Francine M. Ducharme conceptualized the study and provided overall guidance in all aspects of the work conducted by Pamela Mondragon. Moreover, Dr. Francine M. Ducharme obtained access to the hospital and provincial databases, and obtained ethics approval for their use in this research project.

4.3 Manuscript

Asthma education and specialized care after a pediatric emergency department visit: Real-life impact.

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4.3.1 Abstract

Background: Although asthma education and medical follow-up improved asthma control in efficacy trials, difficulty in implementation may affect their real-life effectiveness.

Objectives: To ascertain the real-life individual and combined impact of asthma education and specialized asthma care (SAC), in children referred to the Asthma Education Centre (AEC) following an emergency department (ED) visit for asthma.

Methods: Using hospital and provincial administrative databases, we conducted a retrospective cohort of children aged 0-17 years, discharged from the ED between 2001-2006 with an asthma/asthma-like diagnosis and referred to the AEC. Patients were considered *exposed* to AEC or SAC from their first visit to the service, *exposed* to both AEC and SAC at the date of the latest service, and *unexposed* otherwise. . A Cox proportional hazards model model was used to estimate the association of AEC and/or SAC with time to an asthma ED visit during a 1-year follow-up period).

Results: Of the 1233 cohort children, 63.5% were male and the mean age was 4.4 years. Overall, 19% of children received AEC alone, 8% received SAC alone, and 46% received both AEC and SAC. Compared to *unexposed* children, the likelihood (Hazard Ratio [95% CI]) of a subsequent ED visit was significantly lower in children receiving AEC with SAC (0.43 [0.34, 0.53]) and AEC alone (HR=0.68 [0.53, 0.86]), but not in those receiving SAC alone (HR=0.85 [0.64, 1.14]).

Conclusion: In a real-life setting of children referred to asthma education following an ED visit, exposure to AEC alone and with SAC, but not SAC alone, was associated with a decreased likelihood of a subsequent ED visit, underlying the effectiveness of asthma education, yet suboptimal patient attendance.

4.3.2 Introduction

Despite evidence-based guidelines, most asthmatic children remain poorly controlled worldwide.[1,2] In Canada, there were 28,830 pediatric asthma emergency department (ED) visits in 2017-2018,[3] with approximately 20% of them resulting in hospital admissions.[4,5] Asthma guidelines recommend regular medical follow-up, asthma education and a written action plan to prevent future asthma exacerbations.[6-8] However, in North America, fewer than 30% of children presenting to the ED have an action plan at home[9-11] or receive prior asthma education.[9,12] Moreover, approximately 60% of children had received regular care prior to their ED visit[12] or hospital admission[13] and barely 12%[14] to 33%[15] of children had a medical follow-up visit within two months of the ED visit. Organizational barriers contributing to these persistent care gaps[16] include delay for the provision of asthma education and a written action plan, suboptimal physician proficiency in providing guidelines-recommended care, and insufficient access to regular medical care.[17,18] An ED visit could offer an opportunity to break the cycle of poor management by referring high-risk asthmatic children to the appropriate asthma care services.

A 2009 landmark Cochrane review established that asthma education, with or without other self-management interventions, following a pediatric asthma ED visit was associated with a 25% risk reduction of subsequent ED visits compared to usual care or lower intensity education.[19] Although the individual contribution of co-existing interventions including medical visits by general practitioners or specialists, could not be ascertained, these findings clearly supported referral to asthma education as the preferred intervention.[19] Most included trials reported attendance rates of 70% to 100% to asthma education within up to 6 months of the index ED visit,[19] yet in real-life practice, patient uptake of offered services is clearly inferior. In non-randomized studies, 42% of patients (children or adults) referred to an asthma education centre (AEC) after an ED visit attended their scheduled appointment;[20] only 36% to 59% of children referred to an asthma specialist, received specialized care over the following year.[21,22] Furthermore, when both education and medical follow-up are offered, they are often provided in different settings and time periods, challenging the real-life implementation and resulting in delays that may interfere with expected benefits.

Our primary objective was thus to examine the real-world effectiveness of the individual and combined exposure to asthma education and specialized asthma care on the likelihood of subsequent ED visit for asthma over the next year in children referred to the AEC following an ED visit for asthma. Secondarily, we aimed to examine the impact of these interventions on asthma control and rescue medication use and, as an exploratory outcome, on inhaled corticosteroid (ICS) use.

4.3.3 Methods

Study design

We conducted a retrospective cohort study of children who presented to the ED of the Montreal Children's Hospital, a tertiary care academic centre. The Research Ethics Boards of CHU Sainte-Justine and Montreal Children's Hospital approved the study protocol. Permission to access medical records without patient consent and to link them to governmental administrative databases was granted by the Director of Professional services and the Commission d'accès à l'information du Québec.

Data sources

From the Emergency Department (ED) database, we extracted respiratory-related visits data including patient demographics, visit dates, hospital-specific diagnostic codes, and disposition (admitted vs. discharged). The database was linked by an unique identifier to the two additional hospital databases, namely that of: (i) the Asthma Education Centre (AEC), where patients benefited from a one-on-one hour-long standardized asthma education session provided by a certified nurse or respiratory technologist trained by the Quebec Respiratory Health Education Network (*Réseau québecois d'éducation en santé respiratoire)*[23,24] and (ii) the Asthma Centre (AC), staffed by pediatric asthma specialists, including pediatricians, allergists and respirologists. The AEC database comprised all referral requests, as well as referral source, visit date and attendance status; the AC database recorded visit date, diagnosis, and management.[25-27] These three hospital databases were then linked to three validated[28-30] governmental health administrative databases namely: (i) the MED-ECHO database, which contained the hospital admission dates, diagnostic codes from the International Classification of Diseases (ICD) 9th version (until 31 March 2006) and ICD-10th version thereafter; (ii) the

Régie de l'assurance maladie du Québec (RAMQ) medical services database, pertaining to all medical visit claims of physicians remunerated on a fee-for-service basis, that included the visit date and the ICD-9th version diagnostic codes; and (iii) the RAMQ public prescription claims database that included duration, strength and dispensation date of all prescriptions dispensed by pharmacies to insured Quebec residents, representing approximately 43% of the Quebec population, i.e., those not eligible for a private drug insurance plan.[31] Under the Canadian universal public healthcare system, all Quebec residents benefit from free-of-charge medical consultations and hospital admissions, and for children covered by the Quebec drug insurance, free medication. Of note, although most (77%) specialists are remunerated on a fee-for-service basis in Quebec,[32] the hospital databases allowed us to also capture medical visits made to salaried physicians.

Study population

Children were eligible if they presented to the ED of the Montreal Children's Hospital between January 1st 2001 and December 31st 2006, (1) were aged 0 to 17 years; (2) received a discharged diagnosis of asthma (ICD-9: 493) or, if aged one year and over, of an asthma-like condition including acute bronchiolitis (ICD-9: 466.1), bronchospasm (ICD-9: 519.1), acute bronchitis (ICD-9: 466.0) or bronchitis not specified as acute or chronic (ICD-9: 490.9), as registered in the RAMQ medical services database; and (3) were referred to the AEC in the 12 months following the index ED visit. The latter entry criterion was chosen to identify patients at high-risk of relapse, as asthma education is the recommended preferred service for needing families, is widely accessible in accredited centres in Quebec since 1994[33] and is documented through our hospital AEC's records.

Patients were excluded if they: did not have full RAMQ medical services coverage for at least 12 months preceding and following the index ED visit or if they had made a visit to the AEC, Asthma Centre or an asthma specialist visit (allergist or respirologist) in the year prior to the index ED visit.

Of note, whereas a systematic referral program to the AEC was in place for children hospitalized for asthma, referral to AEC following an ED visit was left to the physicians'

discretion, usually based on the frequency of ED visits, perceived patient misunderstanding of disease, assessment or management, and /or poor continuity of care.

The cohort entry visit (index ED visit) corresponded to the first ED visit on which the child first met all eligibility criteria. The cohort exit date corresponded to the first asthma or asthma-like related emergency visit, or to 12 months, after cohort entry, which ever occurred first. A drug claim subcohort pertained to the subgroup of cohort patients who also had full public drug coverage in the 12 months prior to, and after, the index ED visit, to quantify the impact of intervention exposures on medication use and asthma control.

Intervention exposures

Exposure to asthma education was defined as the first visit to the hospital AEC while exposure to specialized asthma care (SAC) pertained to the first visit to an asthma specialist (allergist or respirologist) or to the hospital Asthma Centre, provided either occurred within 12 months of the index ED visit. For patients visiting both the AEC and SAC, exposure to both was deemed to have occurred on the day of the latest exposure. Patients were considered *exposed* from the date of their intervention exposures until the end of the 12-month observation period.

Outcomes

The main outcome was a subsequent ED visit for asthma/asthma-like condition (with or without hospital admission) occurring within 12 months of the index ED visit. A sensitivity analysis of the main outcome was performed in children with an asthma diagnosis at the index ED visit as per Dr. To's modified pharmacoepidemiologic asthma case definition (one hospital admission for asthma and/or two asthma physician visits occurring at least 14 days apart),[34,35] using one year as an observation period instead of two years.

In the drug claim subcohort, secondary outcomes included weekly short-acting beta-agonist (SABA) use; rescue oral corticosteroids (OCS) use for asthma, that is, dispensed within 10 days of a medical visit with an asthma/asthma-like diagnosis; and asthma control ascertained over 6 months using the Pharmacoepidemiologic Pediatric Asthma Control Index (PPACI),[34] a validated index that classifies asthma control in 4 categories (controlled, partly controlled, not well controlled and very poorly controlled) based on SABA use, OCS use, ED

visits and hospital admissions.[36] A modified version of PPACI, including a look-back period of six, instead of twelve, months prior to the index ED visit, was used to calculate the average weekly number of SABA doses. As exploratory outcome, inhaled corticosteroid use was examined by using the Proportion of days covered (PDC) defined as the total number of days for which the drug was dispensed, divided by the total number of days of follow-up.[37] Secondary and exploratory outcomes were measured in the last 6 months (months 7 to 12) to provide patients a 6-month window to receive the interventions and because both medication use and asthma control are adequately measured over 6-month periods.[38,39]

Statistical analyses

Cox proportional hazards models with time-varying exposures were used to analyze the association between the individual and combined exposures to AEC and SAC with the time to first subsequent ED visit for an asthma or asthma-like exacerbation. Covariates included factors related to the: (1) child namely, age at cohort entry, gender, Pampalon social and material deprivation indexes,[40] atopy−defined as eczema (ICD-9 codes 691.8 692.0 - 692.9), urticaria (708.0, 708.1 708.8, 708.9) or allergic rhinitis (477.0, 477.8, 477.9), ED visits, and hospital admissions for asthma/asthma-like (493, 466.0, 466.1, 519.1) in the 12 months preceding the index visit; and (2) index ED visit namely, triage category, season, and disposition (discharge or hospital admission). ED visits occurring within 7 days of each other were counted only once. The proportional hazards assumption was verified using Schoenfeld residuals plots and by generating time-dependent covariates. For covariates that violated the proportional hazards assumption, interactions with the appropriate survival time function (e.g., log, linear or squared) were included in the model. We adjusted the analysis for the season of follow up (i.e., September peak and/or allergy seasons) by adding it as a time-varying covariate.

In the drug claim subcohort, we used modified Poisson models[41] to analyze secondary outcomes namely, average SABA weekly use (<4 vs. ≥ 4 doses per week), oral corticosteroid courses use (yes vs. no), and PPACI (controlled/partly controlled vs. not well controlled/very poorly controlled). The mean ±SD and the median (25%, 75%) PDC were reported. The median PDC was compared globally among the intervention exposure groups using the Kruskal-Wallis test. Statistical significance was assumed at a two-sided $P < 0.05$, for all the

analyses. Analyses were performed using SAS Enterprise Guide 5.1 (SAS Institute, Cary, NC) and R Studio software (version 3.5.0).

4.3.4 Results

Of the 40,272 patients presenting with a respiratory-related ED visit, 1233 children met eligibility criteria and were referred to the AEC. Of these, 432 children covered by the Quebec drug insurance, comprised the drug claim subcohort (Figure 2). Eligible children were predominantly male and preschoolers. In the year preceding the index visit, approximately 20% of participants had experienced at least one ED visit for an asthma or asthma-like exacerbation or had a medical claim for atopy. At the index ED visit, the overwhelming majority (87%) of children received a diagnosis of asthma and 58% were admitted to hospital. The baseline characteristics of children included in the main cohort and the drug claim subcohort were similar in all aspects (Table 6), with the exception of a higher proportion of patients in the lower quintiles of material and social deprivation in the drug claim subcohort.

In the 12 months following the index visit, 563 (46%) children attended both the AEC and the SAC, 234 (19%) attended only the AEC, 97 (8%) received only SAC and 27% attended neither service. By design, all recorded AEC were made at our hospital, whereas most (65%) SAC occurred at our Asthma Centre. Moreover, 56% of the AEC visits alone, 30% of the visits to both services and 27% of the SAC visits only, occurred within one month of the index ED visit (Figure 2).

Overall, 59% (731/1233) of patients from the main cohort experienced one or more subsequent ED visits. Compared to unexposed children, the risk of an earlier subsequent ED visit for an asthma/asthma-like exacerbation was significantly reduced by 57% in children receiving both interventions and by 32% in those attending only the AEC, whereas no statistically significant impact of SAC alone was observed (Table 7). Higher triage priority categories at the index ED visit and ≥ 2 ED visits for asthma/asthma-like exacerbations in the preceding year were significantly associated with an increased risk of an earlier subsequent ED visit; index exacerbation occurring in the spring or fall and older age were protective (Supplemental data: Table 10). Of interest, sex, social and material deprivation, atopy, were not significantly associated with time to subsequent ED visit (Supplemental data: Table 10). In

the sensitivity analysis focused on patients meeting To's asthma diagnosis criteria, only combined exposure to the interventions was significantly associated with a decreased risk of an earlier subsequent ED visit (Supplemental data: Table 11).

Compared to unexposed children receiving a referral to the AEC, those attending both SAC and AEC in the first 6 months after the index ED visit experienced a reduction by more than half of the risk of rescue OCS use and by 12%, that of poor asthma control in the last 6 months of the follow-up period; no clinically relevant effect was observed for either AEC or SAC alone (Table 8). Neither intervention alone or combined was associated with a significant effect on subsequent SABA use.

In children from the drug claim subcohort with at least one ICS serving during the 7-12 months of follow-up, there was no statistically significant difference between the crude median Proportion of days covered (PDC) across exposure groups (p=0.72) (Table 9).

4.3.5 Discussion

In this real-world retrospective cohort study of children referred to the AEC following an ED for an asthma or asthma-like exacerbation, about two thirds attended an AEC (usually in conjunction with an asthma specialist visit) over the next 12 months; a quarter attended neither service and fewer than 10% received only specialized care. Asthma education, with or without specialized care, was associated with a 57% and 32 % decrease in the likelihood of a subsequent asthma/asthma-like ED visit, respectively, underlying the benefit of asthma education in this high-risk group of patients.

Clearly, the strongest protective effect against subsequent ED visits was observed when patients received both interventions, which were also associated with reduced risk of poor asthma control and rescue OCS use. To our knowledge, only two trials tested the impact of combined exposure to asthma education and specialist care on subsequent morbidity using usual care as the control group. Consistent with our findings, they both reported significant beneficial effects, reporting a 46% reduction in the risk of unscheduled visits for asthma[42] and a 1.4 times lower risk of a subsequent ED visit[43] compared to controls (asthma educational booklet or usual care). Neither reported data on subsequent OCS and SABA use.

Exposure to asthma education alone was associated with a 32% decrease in the likelihood of a subsequent ED visit. However, it had no statistically significant impact on subsequent asthma control, SABA use and OCS use. The magnitude of effect is in agreement with the 2009 Cochrane systematic review of 38 trials[19] where asthma education alone or as part of a comprehensive self-management program was associated with a 27% risk reduction in subsequent ED visits, compared to usual care/lower intensity asthma education, confirming the robustness of findings. Two subsequent randomized controlled trials examining the impact of asthma education alone in children following an ED visit, showed a protective[44] or no effect[45] on subsequent ED visits. Consistent with our findings, no association between asthma education alone and subsequent SABA use was observed in another randomized controlled trial,[46] although asthma education over 4 to 8 weeks was associated with 20% to 36% lower likelihood of subsequent OCS use.[44,45] Consequently, asthma education appears to have its primary preventive effect on exacerbations severe enough to require an ED visit, with or without rescue OCS.

Receiving specialized asthma care alone had no significant impact on any of the outcomes of interest. We did not identify any clinical trials testing the impact of specialized asthma care alone following an acute care visit, however our results are in agreement with cohort studies reporting that asthma specialist care alone had no significant impact on a subsequent ED visit[47] or readmission[22] for children admitted to the hospital for asthma. Of note, our statistical power to detect a 30% to 47% risk reduction varied from 40.7% to 81.4%, respectively.

It is unclear why individual exposure to AEC and SAC did not succeed in decreasing overall SABA use. It is possible that, in our crude analysis, the suboptimal ICS use observed in all groups was only sufficient to achieve a reduction in exacerbations, without a significant impact on daily symptoms and rescue bronchodilator use that require higher ICS adherence. This finding is in line with prior observations of an earlier impact effect of ICS on most severe outcomes (e.g., death and hospitalizations) than less severe outcomes (e.g., symptom control).[48,49] Yet, the consistent marked reduction of combined AEC and SAC on exacerbations requiring ED visits and/or rescue OCS argues in favour of this approach.

In our cohort of high-risk children referred to asthma education, several determinants associated with an earlier subsequent ED visit were in line with prior studies of children in similar settings namely, 2 or more ED visits in the preceding year,[12,15,50,51] and higher triage codes.[15,52] Our observation contrasts with previous studies reporting that hospital admissions prior to the index ED visit[15,52,53] and lower socioeconomic levels[15,47] increased the risk or likelihood of repeat ED visits. Of note, in our study, there was no statistically significant difference in the distribution of Pampalon material (p=0.29) and social deprivation indexes (p=0.64) at cohort entry among children who subsequently attended the AEC session and those who did not. The effect of deprivation was perhaps partially compensated and diluted by access to free health care services and, for children of family with predominantly lower socioeconomic status, free asthma drugs in Quebec.

The study must be interpreted in light of strengths and limitations. Our observational study reflects the real-world effectiveness of individual and combined exposure to the interventions on a subsequent ED visit. While we cannot rule out the possibility that in absence of randomization, patients who did not attend their asthma education session had milder asthma than those that did, this would have diluted the observed effect. Access to institutional databases and validated Quebec administrative databases avoided the recall bias associated with patient-reported outcomes. Although misclassification may have occurred if children referred to our AEC visited another AEC or were seen by a specialist with an alternate reimbursement plan, prior studies confirmed that nearly 90% of our patients return to our main institution[54] and 77% of Quebec specialists are remunerated on a fee-for-service basis,[32] such that exposure misclassification would have affected a small proportion of children. We *a priori* included asthma-like conditions as per the 2015 Canadian Position paper on preschool asthma[7] recommendation to consider as 'suspected asthma' recurrent episodes of asthma-like symptoms in children aged 1 year and over, provided that airway obstruction and reversibility were documented; the later two criteria could not be confirmed in administrative databases, such that it is possible that non-asthmatic children were included in our cohort. Yet, the sensitivity analysis excluding 'asthma-like' diagnoses showed similar results. The use of time-varying exposures of asthma education and specialized care for the main outcome analysis is a clear strength. However, we focused on exposures occurring within 6 months

following the index ED visit for the secondary and exploratory outcomes; thus, 20% of children who received these services after 6 months were considered as part of control group, which could have diluted the effect of the interventions. Moreover, a look-back period of 6 months was used in the calculation of the PPACI because a 12-month look-back period would have led to the exclusion of 100 additional children (23% of the drug claim subcohort); this modification slightly overestimated the proportion of controlled asthma by 3%.

We adjusted for all potential confounder variables available in the databases: however, we couldn't adjust for lung function, asthma severity, obesity, ethnicity and other variables related to socioeconomic status, which may have resulted in residual confounding. The study was conducted in Quebec, Canada where children have free access to medical visits, and asthma education at the AEC, and to heavily subsidized drug access. Secondary outcomes were analyzed in children insured by a public drug plan, which resulted, as expected, in an overrepresentation of children with lower socioeconomic status. Our findings may thus not be generalized to other health care settings and populations.

In conclusion, in a real-life setting of children referred to the AEC following an asthma emergency visit, receiving asthma education with or without specialized asthma care is associated with a marked decreased likelihood of a subsequent ED visit. Children receiving both asthma education and specialized care experienced the largest risk reduction in earlier subsequent ED visit as well as in rescue oral corticosteroid use and poor asthma control. Our results confirm the benefit of these services in high-risk population and would argue against referral to specialized care without offering concurrent asthma education. Identification of characteristics of children that would benefit most from, and strategies to increase attendance to both, asthma education and specialized care, should be key research priorities.

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4.3.7 References

1. McGhan SL, MacDonald C, James DE, Naidu P, Wong E, Sharpe H, et al. Factors associated with poor asthma control in children aged five to 13 years. *Can Respir J.* 2006;13(1):23-29.
2. Cope SF, Ungar WJ, Glazier RH. Socioeconomic factors and asthma control in children. *Pediatr Pulmonol.* 2008;43(8):745-752.
3. Canadian Institute for Health Information (CIHI). NACRS Emergency Department (ED) Visits: Volumes and Median Length of Stay by Triage Level, Visit Disposition, and Main Problem 2017-2018. Retrieved from https://www.cihi.ca/en/quick-stats.
4. Stanford RH, Buikema AR, Riedel AA, Camargo CA, Rey GG, Chapman KR. Asthma controller delay and recurrence risk after an emergency department visit or hospitalization. *Respir Med.* 2012;106(12):1631-1638.
5. Camp PG, Norton SP, Goldman RD, Shajari S, Smith MA, Heathcote S, et al. Emergency department visits for children with acute asthma: discharge instructions, parental plans, and follow-through of care--a prospective study. *CJEM.* 2014;16(6):467-476.
6. Lougheed MD, Lemiere C, Ducharme FM, Licskai C, Dell SD, Rowe BH, et al. Canadian Thoracic Society 2012 guideline update: diagnosis and management of asthma in preschoolers, children and adults. *Can Respir J.* 2012;19(2):127-164.
7. Ducharme FM, Dell SD, Radhakrishnan D, Grad RM, Watson WT, Yang CL, et al. Diagnosis and management of asthma in preschoolers: A Canadian Thoracic Society and Canadian Paediatric Society position paper. *Can Respir J.* 2015;22(3):135-143.
8. Global Initiative for Asthma. 2018 GINA Report, Global Strategy for Asthma Management and Prevention. 2018. Retrieved from https://ginasthma.org/wp-content/uploads/2018/04/wms-GINA-2018-report-V1.3-002.pdf.
9. Ducharme FM, Zemek RL, Chalut D, McGillivray D, Noya FJ, Resendes S, et al. Written action plan in pediatric emergency room improves asthma prescribing, adherence, and control. *Am J Respir Crit Care Med.* 2011;183(2):195-203.

10. Macy ML, Davis MM, Clark SJ, Stanley RM. Parental health literacy and asthma education delivery during a visit to a community-based pediatric emergency department: a pilot study. *Pediatr Emerg Care.* 2011;27(6):469-474.
11. Pade KH, Agnihotri NT, Vangala S, Thompson LR, Wang VJ, Okelo SO. Asthma specialist care preferences among parents of children receiving emergency department care for asthma. *J Asthma.* 2019:1-8.
12. To T, Wang C, Dell S, Fleming-Carroll B, Parkin P, Scolnik D, et al. Risk factors for repeat adverse asthma events in children after visiting an emergency department. *Ambul Pediatr.* 2008;8(5):281-287.
13. Brittan M, Richardson T, Kenyon C, Sills MR, Fieldston E, Hall M, et al. Association between Postdischarge Oral Corticosteroid Prescription Fills and Readmission in Children with Asthma. *J Pediatr.* 2017;180:163-169.e161.
14. Andrews AL, Teufel RJ, Basco WT. Low rates of controller medication initiation and outpatient follow-up after emergency department visits for asthma. *J Pediatr.* 2012;160(2):325-330.
15. Li P, To T, Guttmann A. Follow-up care after an emergency department visit for asthma and subsequent healthcare utilization in a universal-access healthcare system. *J Pediatr.* 2012;161(2):208-213.e201.
16. Boulet LP, Bourbeau J, Skomro R, Gupta S. Major care gaps in asthma, sleep and chronic obstructive pulmonary disease: a road map for knowledge translation. *Can Respir J.* 2013;20(4):265-269.
17. Boulet LP. Asthma education: an essential component in asthma management. *Eur Respir J.* 2015;46(5):1262-1264.
18. Miles C, Arden-Close E, Thomas M, Bruton A, Yardley L, Hankins M, et al. Barriers and facilitators of effective self-management in asthma: systematic review and thematic synthesis of patient and healthcare professional views. *NPJ Prim Care Respir Med.* 2017;27(1):57.
19. Boyd M, Lasserson TJ, McKean MC, Gibson PG, Ducharme FM, Haby M. Interventions for educating children who are at risk of asthma-related emergency department attendance. *Cochrane Database Syst Rev.* 2009(2):CD001290.

20. Robichaud P, Laberge A, Allen MF, Boutin H, Rossi C, Lajoie B, et al. Evaluation of a program aimed at increasing referrals for asthma education of patients consulting at the emergency department for acute asthma. *Chest.* 2004;126(5):1495-1501.
21. Aragona E, Wang J, Scheckelhoff T, Hyacinthe A, Nino G, Pillai KG. Asthma specialty clinics decrease emergency department visits in inner-city children hospitalized for asthma exacerbation. *Am J Respir Crit Care Med.* 2014; s: 189, A3838.
22. Drewek R, Mirea L, Rao A, Touresian P, Adelson PD. Asthma treatment and outcomes for children in the emergency department and hospital. *J Asthma.* 2018;55(6):603-608.
23. Boulet LP, Chapman KR. Asthma education: the Canadian experience. *Chest.* 1994;106(4 Suppl):206S-210S.
24. Bérubé D, Chirron R. Asthma education: the impact on care: the Quebec experience. *Pediatr Pulmonol.* 2001;Suppl 23:16-17.
25. Ducharme FM, Davis GM, Noya F, Rich H, Ernst P. The Asthma Quiz for Kidz: a validated tool to appreciate the level of asthma control in children. *Can Respir J.* 2004;11(8):541-546.
26. Ducharme FM, Noya FJ, Allen-Ramey FC, Maiese EM, Gingras J, Blais L. Clinical effectiveness of inhaled corticosteroids versus montelukast in children with asthma: prescription patterns and patient adherence as key factors. *Curr Med Res Opin.* 2012;28(1):111-119.
27. Longo C, Bartlett G, Schuster T, Ducharme FM, MacGibbon B, Barnett TA. The obese-asthma phenotype in children: An exacerbating situation? *J Allergy Clin Immunol.* 2018;141(4):1239-1249.e1234.
28. Blais L, Vilain A, Kettani FZ, Forget A, Lalonde G, Beauchesne MF, et al. Accuracy of the days' supply and the number of refills allowed recorded in Québec prescription claims databases for inhaled corticosteroids. *BMJ Open.* 2014;4(11):e005903.
29. Delfino RJ, Becklake MR, Hanley JA. Reliability of hospital data for population-based studies of air pollution. *Arch Environ Health.* 1993;48(3):140-146.
30. Blais L, Lemière C, Menzies D, Berbiche D. Validity of asthma diagnoses recorded in the Medical Services database of Quebec. *Pharmacoepidemiol Drug Saf.* 2006;15(4):245-252.

31. Régie de l'assurance maladie du Québec - Rapport annuel de gestion 2010-2011. Régie de l'assurance maladie du Québec. 2011.
32. Boulenger, S., & Castongay, J. Portrait de la rémuneration des médecins de 2000 à 2009. Rapport Série Scientifique. Quebec : CIRANO. 2012
33. Boulet LP, Dorval E, Labrecque M, Turgeon M, Montague T, Thivierge RL. Towards Excellence in Asthma Management: final report of an eight-year program aimed at reducing care gaps in asthma management in Quebec. *Can Respir J.* 2008;15(6):302-310.
34. To T, Dell S, Dick PT, Cicutto L, Harris JK, MacLusky IB, et al. Case verification of children with asthma in Ontario. *Pediatr Allergy Immunol.* 2006;17(1):69-76.
35. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying patients with physician-diagnosed asthma in health administrative databases. *Can Respir J.* 2009;16(6):183-188.
36. Despres F, Ducharme FM, Forget A, Sze Man T, Kettani FZ, Blais L. Development and Validation of a Pharmacoepidemiologic Pediatric Asthma Control Index Using Information from Administrative Database. American Thoracic Society 2017 International Conference.Washington DC, United States. May 2017.
37. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Ann Pharmacother.* 2006;40(7-8):1280-1288.
38. McGhan SL, Wong E, Sharpe HM, Hessel PA, Mandhane P, Boechler VL, et al. A children's asthma education program: Roaring Adventures of Puff (RAP), improves quality of life. *Can Respir J.* 2010;17(2):67-73.
39. Feehan M, Ranker L, Durante R, Cooper DK, Jones GJ, Young DC, et al. Adherence to controller asthma medications: 6-month prevalence across a US community pharmacy chain. *J Clin Pharm Ther.* 2015;40(5):590-593.
40. Pampalon R, Hamel D, Gamache P, Philibert MD, Raymond G, Simpson A. An area-based material and social deprivation index for public health in Québec and Canada. *Can J Public Health.* 2012;103(8 Suppl 2):S17-22.
41. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol.* 2004;159(7):702-706.

42. Teach SJ, Crain EF, Quint DM, Hylan ML, Joseph JG. Improved asthma outcomes in a high-morbidity pediatric population: results of an emergency department-based randomized clinical trial. *Arch Pediatr Adolesc Med.* 2006;160(5):535-541.
43. Kelly CS, Morrow AL, Shults J, Nakas N, Strope GL, Adelman RD. Outcomes evaluation of a comprehensive intervention program for asthmatic children enrolled in medicaid. *Pediatrics.* 2000;105(5):1029-1035.
44. Watson WT, Gillespie C, Thomas N, Filuk SE, McColm J, Piwniuk MP, et al. Small-group, interactive education and the effect on asthma control by children and their families. *CMAJ.* 2009;181(5):257-263.
45. Otsuki M, Eakin MN, Rand CS, Butz AM, Zuckerman IH, Ogborn J, et al. Adherence feedback to improve asthma outcomes among inner-city children: a randomized trial. *Pediatrics.* 2009;124(6):1513-1521.
46. Cowie RL, Underwood MF, Little CB, Mitchell I, Spier S, Ford GT. Asthma in adolescents: a randomized, controlled trial of an asthma program for adolescents and young adults with severe asthma. *Can Respir J.* 2002;9(4):253-259.
47. Johnson LH, Beck AF, Kahn RS, Huang B, Ryan PH, Olano KK, et al. Characteristics of Pediatric Emergency Revisits After an Asthma-Related Hospitalization. *Ann Emerg Med.* 2017;70(3):277-287.
48. Suissa S, Ernst P. Inhaled corticosteroids: impact on asthma morbidity and mortality. *J Allergy Clin Immunol.* 2001;107(6):937-944.
49. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med.* 2000;343(5):332-336.
50. To T, Cicutto L, Degani N, McLimont S, Beyene J. Can a community evidence-based asthma care program improve clinical outcomes?: a longitudinal study. *Med Care.* 2008;46(12):1257-1266.
51. Tolomeo C, Savrin C, Heinzer M, Bazzy-Asaad A. Predictors of asthma-related pediatric emergency department visits and hospitalizations. *J Asthma.* 2009;46(8):829-834.
52. Guttmann A, Zagorski B, Austin PC, Schull M, Razzaq A, To T, et al. Effectiveness of emergency department asthma management strategies on return visits in children: a population-based study. *Pediatrics.* 2007;120(6):e1402-1410.

53. Hall AB, Novotny A, Bhisitkul DM, Melton J, Regan T, Leckie M. Association of emergency department albuterol dispensing with pediatric asthma revisits and readmissions. *J Asthma.* 2017;54(5):498-503.

54. Ducharme FM, Noya F, Rich H, Davis GM, Resendes S, Khomenko L, et al. Randomized controlled trial of a multi-faceted intervention initiated in the emergency department (ED) to improve asthma control. Pediatric Academic Societies. 2009

Table 6. Baseline characteristics

Characteristic	Main cohort (N=1233)	Drug claim subcohort (N=432)
DEMOGRAPHICS		
Male sex −*n* (%)	783 (63.50)	285 (65.97)
Age in years at index ED visit −mean ± SD	4.38 ± 4.04	4.69 ± 4.02
Pampalon material deprivation index −*n* (%)		
Missing value	76 (6.16)	18 (4.17)
1st quintile (most privileged)	172 (13.95)	46 (10.65)
2nd quintile- 3rd quintile	389 (31.55)	106 (24.54)
4th quintile -5th quintile	596 (48.34)	262 (60.65)
Pampalon social deprivation index −*n* (%)		
Missing value	76 (6.16)	18 (4.17)
1st quintile (most privileged)	212 (17.19)	60 (13.89)
2nd quintile- 3rd quintile	473 (38.36)	152 (35.19)
4th quintile -5th quintile	472 (38.28)	202 (46.76)
PRIOR MORBIDITY IN PAST 12 MONTHS		
Atopy−*n* (%)	254 (20.60)	81 (18.75)
# of Asthma/asthma-like ED visits† −*n* (%)		
0	985 (79.89)	352 (81.48)
1	196 (15.90)	60 (13.89)
≥2	52 (4.22)	20 (4.63)
# of Asthma/asthma-like hospital admissions† −*n* (%)		
0	1168 (94.73)	407 (94.21)
≥1	65 (5.27)	25 (5.79)
PPACI in the previous 6 months‡		
Controlled	–	252 (58.33)
Partly controlled	–	41 (9.49)
Poorly controlled	–	118 (27.31)
Very poorly controlled	–	21 (4.86)
INDEX EMERGENCY VISIT		
Epidemiological-based diagnosis of asthma‖ −*n* (%)	849 (68.86)	302 (69.91)
Diagnosis¶ −*n* (%)		
Asthma (ICD-9: 493)	1080 (87.59)	382 (88.43)
Bronchiolitis (ICD-9: 466.11)	92 (7.46)	27 (6.25)
Bronchitis (ICD-9: 466.01, 490.91)	1 (0.08)	1 (0.23)
Bronchospasm (ICD-9: 519.11)	60 (4.87)	22 (5.09)

Season −*n* (%)		
Winter	277 (22.47)	111 (25.69)
Spring	329 (26.68)	114 (26.39)
Summer	162 (13.14)	52 (12.04)
Fall	465 (37.71)	155 (35.88)
Canadian Triage and Acuity Scale −*n* (%)		
1 (Resuscitation) or 2 (Emergent)	600 (48.66)	189 (43.75)
3 (Urgent)	551 (44.69)	210 (48.61)
4 (Less urgent) or 5 (Non-urgent)	82 (6.65)	33 (7.64)
Disposition −*n* (%)		
Discharged	513 (41.61)	175 (40.51)
Hospital admission	720 (58.39)	257 (59.49)

[†]For patients aged ≥1 year, the following asthma-like ICD-9 diagnostic codes (466.11, 466.01, 490.91 and 519.11) were included. For past hospital admissions of patients aged ≥ 1 year, the following asthma-like ICD-10 diagnostic codes (J20, J21, J40, J98.01) were also used.

[‡]A modified version of To et al.[37,38] epidemiological asthma diagnosis was used; defined as "at least one hospitalization with an asthma diagnosis code (ICD-9 : 493, ICD-10: J45) or at least two medical claims with an asthma diagnosis (ICD-9 : 493, ICD-10: J45) since birth, with at least 15 days and a maximum period of 2 years between the diagnostic codes." The modifications pertained to the retrospective, rather than prospective, application of this diagnostic approach, applied to events in the 12 months preceding the index ED visit (including the index ED visit), instead of since birth.

[ʃ]PPACI: Pediatric Pharmacoepidemiologic Asthma Control Index[75]. 'Controlled' was defined as < 4 SABA doses per week and no OCS/ED/Hospital admissions for asthma, and 'partly controlled' as ≥ 4 to < 7 SABA doses per week and no OCS/ED/Hospital admissions for asthma. 'Poorly controlled' was defined as (≥ 7 SABA doses/week or ≥1 OCS of ≥ 1 ED) and no hospital admission, and 'very poorly controlled' as at least one hospital admission.

[¶]For visits not recorded in the RAMQ database, that is, for visits to a physician not remunerated by fee-for-service, the corresponding hospital diagnostic codes were used.

Table 7. Cox proportional hazards model for the main outcome

	Hazard Ratio[†] (95% CI)
Intervention exposure	
AEC and SAC	0.43 (0.34-0.53)
AEC only	0.68 (0.53-0.86)
SAC only	0.85 (0.64-1.14)
none	reference

[†]Model was adjusted for sex, age, morbidity in the 12 months preceding the index ED visit (ED visits and hospital admissions with an asthma diagnosis), atopy, Pampalon social and material deprivation index, triage code, season at index ED visit and season of follow-up

Table 8. Secondary outcomes in the drug claim subcohort

Intervention exposure [†]	N=414	OCS use[‡] Rate Ratio (95% CI)	SABA use ≥4 doses/week [‡] Rate Ratio (95% CI)	Poor asthma control[‡,∫] Rate Ratio (95% CI)
AEC and SAC	n=140 (33.82%)	0.48 (0.31-0.75)	1.00 (0.96-1.05)	0.88 (0.83-0.94)
AEC only	n=68 (16.43%)	0.83 (0.53-1.30)	1.04 (0.99-1.09)	0.94 (0.86-1.02)
SAC only	n=30 (7.25%)	0.57 (0.26-1.22)	1.01 (0.95-1.08)	0.94 (0.84-1.04)
none	n=176 (42.51%)	reference	reference	reference

[†] In the 6 months following the index ED visit

[‡]Analyzed by Poisson regression models modified for use with binary outcomes.[216] Adjusted for sex, age at index ED visit, asthma control measured by the PPACI in the 6 months preceding the index ED visit, atopy, Pampalon social and material deprivation index, triage code, season and diagnosis at index ED visit

[∫] Poor asthma control was defined as PPACI=not well controlled or very poorly controlled. As per the PPACI, patients were deemed not well controlled if they did not experience a hospital admission with an asthma/asthma-like diagnosis, but used at least 7 weekly doses of SABA, filled at least 1 OCS prescription, or had at least 1 ED visit for asthma during the 6-month follow-up periodPatients who had at least 1 hospital admission with an asthma/asthma-like diagnosis were deemed very poorly controlled.

Table 9. Use of inhaled corticosteroids in the 7-12 months following the index ED visit – crude analysis

Intervention exposure in the first 6 months	N=258	PDC[†]-median (25%, 75%)
AEC and SAC	n=89 (34.50%)	27.47 (16.48-38.46)
AEC only	n=42 (16.28%)	16.48 (16.48-34.62)
SAC only	n=19 (7.36%)	32.97 (16.48-49.45)
None	n=108 (41.86%)	18.41 (16.48-32.97)

[†]Proportion of days covered (PDC)

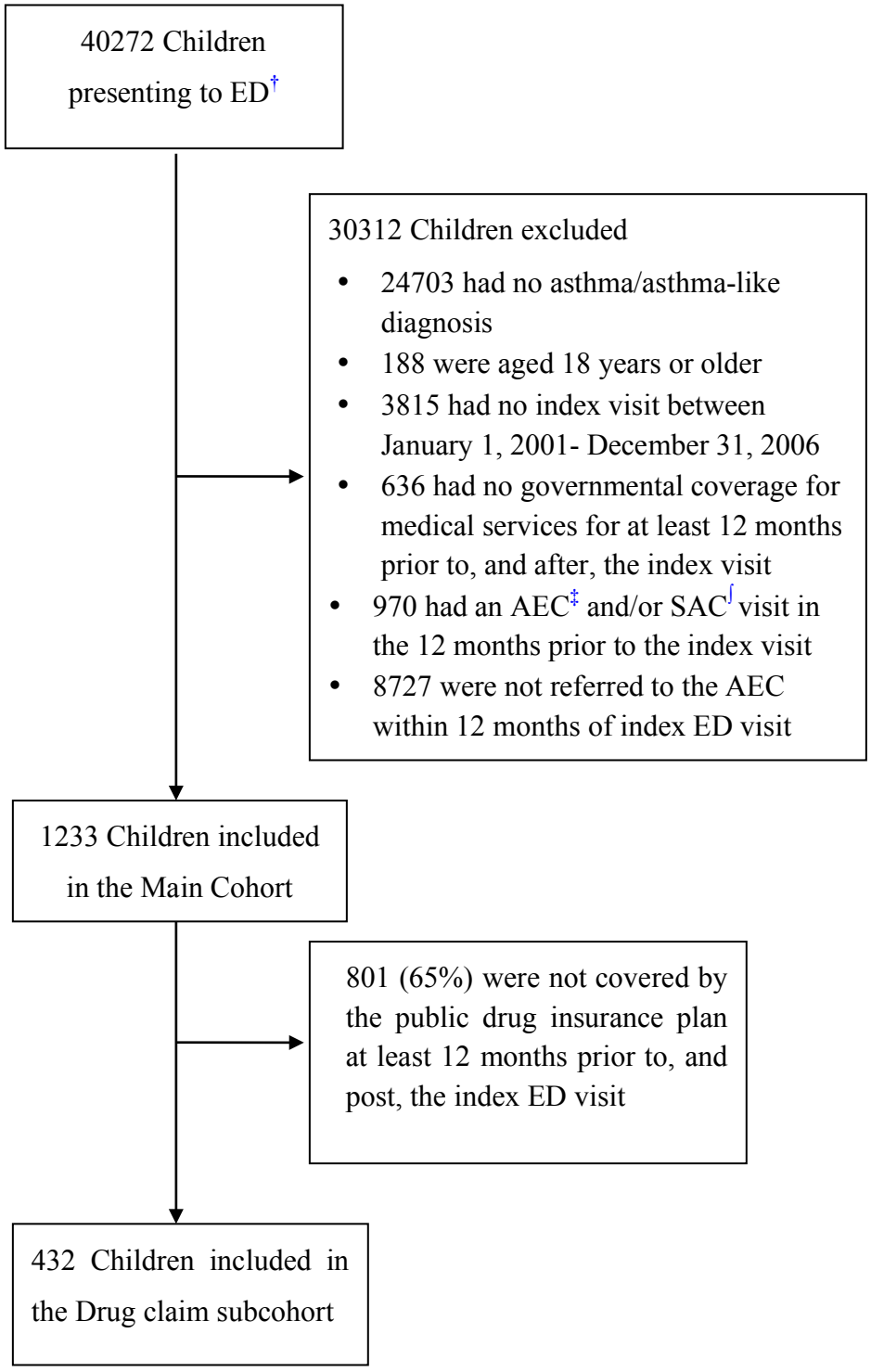
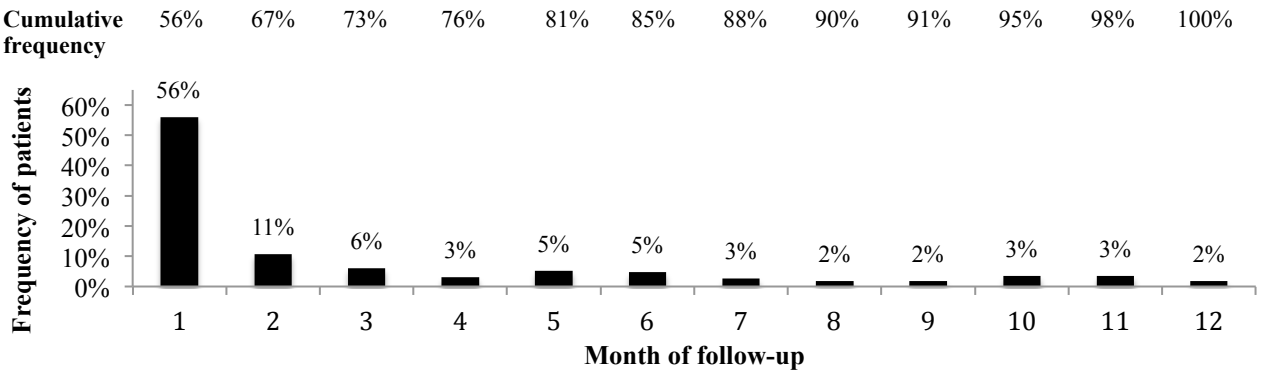
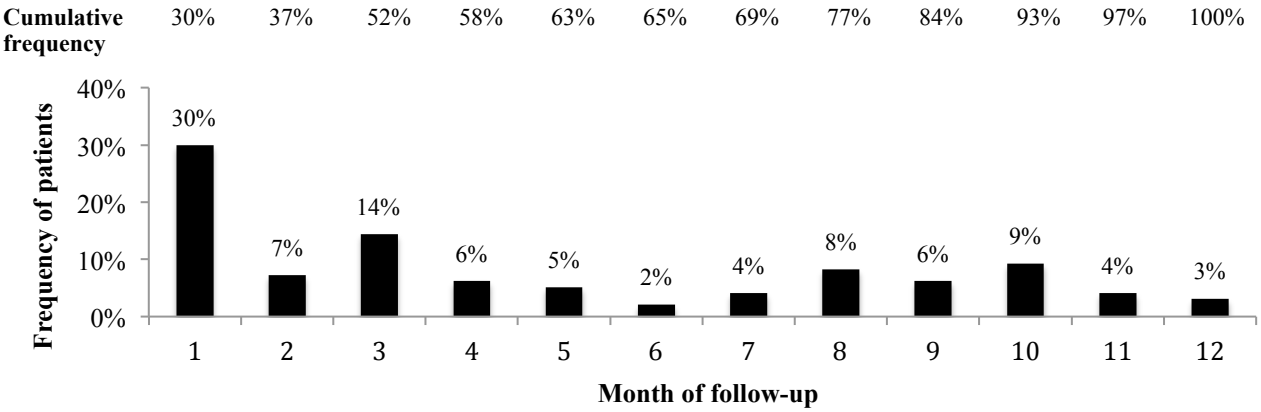


Figure 2. Patient selection. †ED: Emergency Department. ‡AEC: Asthma Education Centre. ∫SAC: Specialized Asthma Care

a)



b)



c)

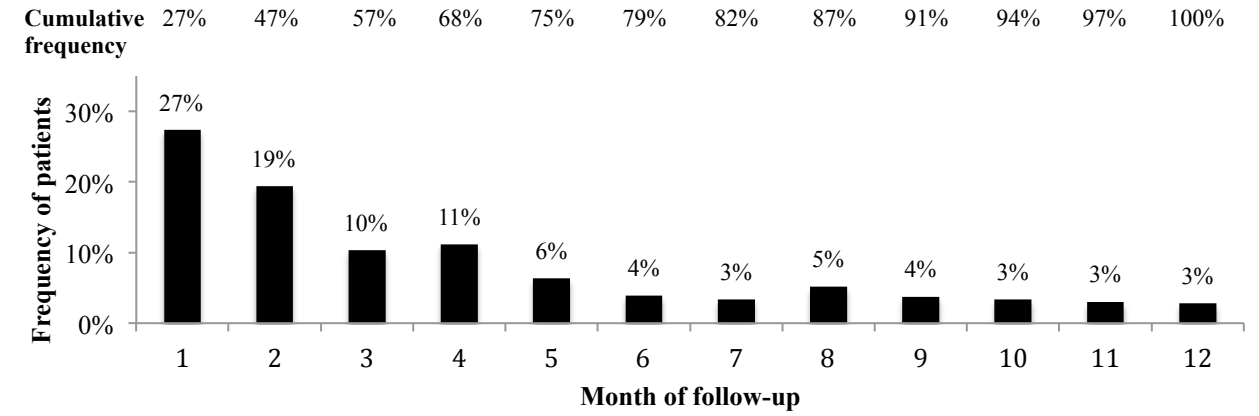


Figure 3. Distribution of the delay between the index ED visit and the intervention exposures. The distribution of the delay to the first AEC visit alone is depicted in a), for first SAC visit alone in b) and, for those with combined AEC and SAC exposure, for the last of AEC or SAC visit date in c). The frequency and cumulative frequency of patients who received the intervention exposure during the follow-up period are shown.

4.2.8 Supplemental data

Table 10. Complete Cox proportional hazards model for the main outcome

	Main cohort (N=1157)
Variable	**Hazard Ratio (95% CI)**
DEMOGRAPHICS	
Intervention exposure	
AEC and SAC	0.43 (0.34-0.53)
AEC only	0.68 (0.53-0.86)
SAC only	0.85 (0.64-1.14)
none	reference
Male sex	0.93 (0.80-1.09)
Age at index ED visit	0.89 (0.86-0.93)
Age*time	1.00 (1.00-1.00)
Pampalon material deprivation index	
1st quintile (most privileged)	reference
2nd or 3rd quintile	1.05 (0.86-1.29)
4th or 5th quintile	1.02 (0.84-1.22)
Pampalon social deprivation index	
1st quintile (most privileged)	reference
2nd or 3rd quintile	0.98 (0.79-1.23)
4th or 5th quintile	1.01 (0.86-1.19)
MORBIDITY IN THE PRECEDING 12 MONTHS	
Atopy	1.08 (0.91-1.29)
1 asthma/asthma-like ED visit	0.84 (0.60-1.18)
1 asthma/asthma-like ED visit*time	1.00 (1.00-1.00)
≥2 asthma/ asthma-like ED visit	1.65 (1.17-2.34)
1 or more Hospital admissions	0.93 (0.64-1.34)
INDEX ED VISIT CHARACTERISTICS	
Diagnosis	
asthma	0.84 (0.68-1.03)
asthma-like	reference
Season	
winter	1.24 (0.99-1.55)
spring	1.65 (1.26-2.16)
fall	1.36 (1.10-1.67)

summer	reference
Canadian Triage and Acuity Scale	
Triage 1-2 (most urgent)	1.41 (0.99-2.01)
Triage 3	1.09 (0.77-1.53)
Triage 4-5 (less urgent)	reference
Disposition	
Hospital admission	0.94 (0.45-1.95)
Hospital admission*log(time)	0.84 (0.72-0.99)
Discharge	reference
FOLLOW-UP SEASON	
winter	0.99 (0.80-1.23)
spring	0.67 (0.52-0.86)
fall	1.40 (1.15-1.71)
summer	reference

Table 11. Main outcome in patients with an alternative definition of asthma

	Hazard Ratio[†] (95% CI)
Intervention exposure	
AEC and SAC	0.41 (0.31-0.55)
AEC only	0.77 (0.57-1.03)
SAC only	0.84 (0.58-1.20)
none	reference

[†]Model was adjusted for sex, age, morbidity in the 12 months preceding the index ED visit (ED visits and hospital admissions with an asthma diagnosis), atopy, Pampalon social and material deprivation index, triage code, season at index ED visit and season of follow-up

Chapter 5: Supplemental results

The following chapter includes the results of two sensitivity analyses of the main outcome that were not included in the scientific article and describes in more detail the sensitivity analyses performed in children with an alternative definition of asthma. The sensitivity analysis in the *unselected cohort* allowed the ascertainment of the magnitude of the 'confounding by indication' bias in the absence of an appropriate selection of study subjects.[217] Two additional sensitivity analyses allowed the assessment of the robustness of our findings when *restricting to children meeting an alternative definition of asthma* and to *those covered by the public drug prescription plan*. Only patients with complete data were included in the sensitivity analyses.

5.1 Main outcome in the *unselected cohort* of children

In the *unselected cohort* composed of 9960 children (9399 with complete data) presenting to the ED with an asthma or asthma-like diagnosis, exposure to AEC alone (adjusted HR=1.47, 95% CI 1.17-1.84) or in combination with SAC (adjusted HR=1.21, 95% CI 0.99-1.48) was associated with an increased risk of an earlier ED return visit (Table 12). Exposure to SAC alone had no statistically significant impact on the risk of an earlier ED return (adjusted HR=1.08, 95% CI 0.95-1.24). The complete Cox proportional hazards model for this sensitivity is found in Appendix IV.

Table 12. Main outcome in the unselected cohort of patients

	Hazard Ratio[†] (95% CI)
Intervention exposure	
AEC and SAC	1.21 (0.99-1.48)
AEC only	1.47 (1.17-1.84)
SAC only	1.09 (0.95-1.24)
none	reference

[†]Hazard ratios were adjusted for sex, age, morbidity in the 12 months preceding the index ED visit (ED visits and hospital admissions with an asthma diagnosis), atopy, Pampalon social and material deprivation index, triage code, season at index ED visit and season of follow-up

5.2 Main outcome in the *alternative definition* of asthma

Criteria for the diagnosis of asthma in children 6 years and older have remained stable for over 2 decades[9,218], whereas they have evolved for preschoolers.[6] As for any billing diagnosis, there are no requirements and no means to confirm the criteria diagnosis applied by the physician. This sensitivity analysis explored a modified version of a case definition of asthma case developed for epidemiological studies by Teresa To consisting of one hospital admission for asthma and/or two asthma physician visits with a diagnosis of asthma occurring at least 14 days apart within 2 consecutive years.[37,38] This definition is also based on recorded diagnosis in the medical chart and subsequently, in our case, in the RAMQ database. The definition was meant to be applied prospectively from birth but in our case, we were limited by a 12-month look-back period. Thus use of this definition may have underestimated the proportion of children with asthma due to its requirement for 2 medical visits, the shorter applicability period (12 months instead of since birth) and the shorter observation period (12 months instead of 24 months). Our application of Dr. To's definition would thus be expected to increase specificity, while reducing sensitivity.

In total, 750 (61% of the study cohort) of the eligible patients (243 younger than 6 years old and 507 of age 6 years or older) fit the modified Dr. To's definition when applied in the 12 months preceding the index ED visit (including the index ED visit). Of these, 699 had complete data. As described in the manuscript, exposure to AEC alone (adjusted HR=0.77, 95% CI 0.57-1.03) and in combination with SAC (adjusted HR=0.41, 95% CI 0.31-0.55) showed similar effect sizes as observed in the original cohort, although only the combination of AEC and SAC was associated with a statistically significant decreased risk of an earlier ED subsequent visit (See Table 11 in Chapter 4). Again, no statistically significant association was found between the specialized care and the risk of an earlier ED return visit (adjusted HR=0.84, 95% CI 0.58-1.20) as observed in our main analysis with a similar effect size. The complete Cox proportional hazards model for this sensitivity analysis is found in Appendix V.

5.3 Main outcome in children covered by the *public prescription drug plan*

There were 432 children (35% of the study cohort) covered by the *public drug prescription plan* in the 12 months preceding, and the 12 months following, the index ED visit. Of these, 414 had complete data. Children exposed to AEC only (HR=0.58, 95% CI 0.37-0.90) and those exposed to both AEC and SAC (HR=0.30, 95% CI 0.19-0.47) exhibited a decreased risk of an earlier ED return visit (Table 7). Exposure only to SAC was not associated with a statistically significant subsequent risk of an earlier ED return visit (HR=0.96, 95% CI 0.60-1.54). Including the Pharmacoepidemiologic pediatric asthma control index (based on ED, hospital admissions, SABA and OCS use) in the 6 months preceding the index ED visit as a covariate provided similar results to those obtained in the study cohort, with slightly larger protective effects of exposure to asthma education alone and in combination with specialized care on the likelihood of a subsequent ED visit (Table 13). The complete Cox proportional hazards model is found in Appendix VI.

Table 13. Main outcome in the subcohort covered by the public prescription drug plan

	Hazard Ratio[†] (95% CI)
Intervention exposure	
AEC and SAC	0.30 (0.19-0.47)
AEC only	0.58 (0.37-0.90)
SAC only	0.96 (0.60-1.54)
none	reference

[†]Hazard ratios were adjusted for sex, age, asthma control in the 6 months preceding the index ED visit (based on ED visits, hospital admissions, SABA use and OCS use), atopy, Pampalon social and material deprivation index, triage code, season at index ED visit and season of follow-up

5.4 Post-hoc exploratory analyses of potential interactions between age, Pampalon social and material deprivation indexes and intervention group

We briefly examined whether the interactions between age and the intervention exposure group (Table 14), Pampalon social deprivation index and the intervention exposure group (Table 15), and Pampalon material deprivation index and the intervention exposure group (Table 16) would have been worth exploring. Patients with missing data for Pampalon material and social deprivation index were excluded from the last two of these analyses. Given the similar distributions of age, Pampalon material deprivation index and Pampalon social deprivation index among the intervention groups, interactions of these variables with the intervention exposure group. These results suggest that such interactions were unlikely to be of importance and thus, they were not considered for inclusion in the final model.

Table 14. Distribution of the patients' age among the intervention exposure groups in the main cohort (N=1233)

	Intervention exposure				
Age group	AEC alone n (%)	SAC alone n (%)	AEC and SAC n (%)	None n (%)	TOTAL
0 to 5 years	168 (71.79%)	66 (68.04 %)	361 (64.12%)	258 (76.11%)	853
6 to 17 years	66 (28.21%)	31 (31.96%)	202 (35.88%)	81 (23.89%)	380
TOTAL	234	97	563	339	1233

Table 15. Distribution of the patients' Pampalon social deprivation index among the intervention exposure groups in the main cohort (N=1157)

	Intervention exposure				
Pampalon social deprivation index	AEC alone n (%)	SAC alone n (%)	AEC and SAC n (%)	None n (%)	TOTAL
1st quintile	34 (15.32%)	18 (19.57%)	97 (18.48%)	63 (19.81%)	212
2nd quintile	43 (19.37%)	19 (20.65%)	107 (20.38%)	61 (19.18%)	230
3rd quintile	49 (22.07%)	19 (20.65%)	110 (20.95%)	65 (20.44%)	243
4th quintile	41 (18.47%)	14 (15.22%)	127 (24.19%)	66 (20.75%)	248
5th quintile	55 (24.77%)	22 (23.91%)	84 (16.00%)	63 (19.81%)	224
TOTAL	222	92	525	318	1157

Table 16. Distribution of the patients' Pampalon material deprivation index among the intervention exposure groups in the main cohort (N=1157)

	Intervention exposure				
Pampalon material deprivation index	AEC alone n (%)	SAC alone n (%)	AEC and SAC n (%)	None n (%)	TOTAL
1st quintile	41 (18.47%)	16 (17.39%)	80 (15.24%)	35 (11.01%)	172
2nd quintile	34 (15.32%)	10 (10.87%)	81 (15.43%)	44 (13.84%)	169
3rd quintile	37 (16.67%)	20 (21.74%)	103 (19.62%)	60 (18.87%)	220
4th quintile	50 (22.52%)	17 (18.48%)	122 (23.24%)	85 (26.73%)	274
5th quintile	60 (27.03%)	29 (31.52%)	139 (26.48%)	94 (29.56%)	232
TOTAL	222	92	525	318	1157

Chapter 6: Discussion

The main objective of this dissertation was to examine the impact of individual and combined exposure to asthma education (AEC) and specialized asthma care (SAC) on the time to subsequent ED return visit in the real-life setting of children identified by the ED physician as being in need for asthma education. Asthma emergency visits were chosen as the main outcome because they represent a significant burden at the patient, family, and health-care system levels, due to their detrimental effect on quality of life and the associated resources and costs.[7]

Additionally, we aimed to determine the effect of the individual and combined exposure to AEC and SAC on other (secondary) health outcomes reflective of asthma control: namely asthma control measured by the pharmacoepidemiologic pediatric asthma control index (PPACI), the use of short-acting beta-agonists (SABA) and the use of oral corticosteroids (OCS). The PPACI is a 4-category asthma control index (controlled, partly controlled, not well controlled and very poorly controlled) measured over a 6-month period, based on the occurrence of an emergency department (ED) visit, hospital admission, filled prescriptions of OCS and the average number of weekly doses of SABA as recorded in administrative health services databases.[75] In our study, asthma control was treated as binary variable (controlled/partly controlled vs. not well-controlled/very poorly controlled). The use of SABA (less than 4 weekly doses of SABA, ≥4 weekly doses of SABA) and OCS (no OCS, at least one OCS prescription claim) were also treated as individual binary variables. Finally, we aimed to explore one of the mechanisms by which the exposures of interest may protect patients against ED relapse, that is, by increasing the appropriate use of ICS.

The following section includes the interpretation of findings pertaining to the main, secondary and exploratory outcomes.

6.1 Main outcome

In our study, children exposed to both AEC and SAC (adjusted HR=0.43, 95% CI 0.34-0.53) had a lower risk of an earlier subsequent ED visit than those exposed to AEC alone. To our knowledge, no previous studies compared the impact of asthma education with vs.

without specialized care on subsequent morbidity. Indeed, as described in the manuscript, most previous studies compared combined exposure to asthma education and specialized care to usual care,[190,219] where the latter may have included follow-up by a primary care physician or education provided by ED physicians or nurses prior to discharge. Previous studies have shown that receiving both asthma education and specialized asthma care is associated with a decreased likelihood of a subsequent ED visit compared to usual care,[190,219] to primary care follow-up,[192] to an asthma education booklet,[191] or to lower intensity education.[220] Furthermore, children followed by specialists are more likely to receive a written asthma action plan[221,222] and guideline-based controller medication use[129] than those who do not receive specialized care. Therefore, the synergistic effect of asthma education and specialized care could be mediated in part by the optimal self-management recommendations by specialists complemented by education reinforcing these recommendations by both asthma educators and specialists.

The beneficial effect associated with exposure to asthma education alone in our study is concordant with the findings from the 2009 Cochrane review of the impact of asthma education in children following an asthma emergency visit.[11] Due to the heterogeneity among the studies included in this Cochrane review, the authors were not able to determine the exact components of effective asthma education.[11] A previous randomized controlled trial (RCT) of four weeks of small-group multicomponent age-adapted asthma education program at the AEC (facilitator-led presentations, group discussion and peer sharing) was associated a reduced risk of subsequent emergency department visits (RR=0.62, 95% CI 0.48-0.81).[185] Another RCT showed that an 8-week home-based asthma education program had no effect on subsequent ED visits when used alone, but was associated with a protective effect when combined with medication adherence feedback (IRR=0.85, 95% CI 0.74-0.97).[186] In all studies and ours, asthma education provided at the AEC was likely effective because it was personalized (targeted to the needs of patients)[120] and used a standardized approach that is regularly updated to ensure adherence to clinical guidelines' recommendations.[119] Asthma education can also reduce the risk of subsequent morbidity by increasing patients' asthma knowledge and helping them to improve their inhaler technique.[223] Although some authors argue for an ED visit as the teachable moment,[224,225] it could also be argued that the AEC

offers a more appropriate setting for motivating patients to change their behaviour. The effectiveness associated with exposure to asthma education may also have been diluted by the variability in patients' adherence to the self-management recommendations from asthma educators.

Given that patients followed by an allergist for example report a higher asthma self-management knowledge than those without a regular source of asthma care or those followed by a primary care physician,[226] it appears paradoxical that exposure to specialized care alone would not be beneficial in our study. These findings are not the due to regression towards the mean, since the number of patients with ED visits increased in all the exposure groups in the 12 months following the index ED visit, compared to the 12 preceding months (Appendix VII) There are four main potential reasons that could explain the null/minimal (and non statistically significant) effect related to individual exposure to specialized care on the primary and secondary outcomes. First, we cannot firmly conclude that specialized care has no impact on a subsequent ED visit because the large confidence interval of the hazard ratio reflects insufficient statistical power, likely associated to the low proportion of patients who received asthma specialist care alone (8%) compared to asthma education alone (19%) and both exposures (46%). Indeed, the statistical power to detect a 30%, 35% and 47% absolute risk reduction of subsequent ED visits associated with exposure to specialized asthma care in our study cohort was 40.7%, 53.4% and 81.4%, respectively. Moreover, it has been reported that unequal group sample sizes can greatly distort the power level.[227] Second, the effectiveness of specialized asthma care alone may have been diluted by the variability in physicians' adherence to asthma guidelines regarding pharmacologic treatment, as well as the quantity and quality of the physician-patient exchanges. Indeed, there is likely variability in the explanations (asthma education provided to patients to explain the disease, role of medication, means of appropriate intake of medication and self-management action plan) provided by physicians to ensure adequate understanding of self-management by patients. Even if specialists are 1.5 times more likely to prescribe appropriate daily controller use than primary care physicians, there could still be improvements to be made regarding the appropriate assessment of needs and prescription, as well as written self-management action plan provision and regular review.[125] Third, it is possible that specialized care is truly not sufficient

to change behaviour if not provided in conjunction with sufficient asthma education. Fourth, variability in patient's adherence to recommendations from asthma specialists regarding disease management may dilute the effectiveness of specialized care. As discussed in the manuscript, our findings are in accordance with previous cohort studies where exposure to specialist care alone had no significant impact on subsequent ED visit[165] or readmission.[146] However, preliminary results from two abstracts reported lower risk of subsequent ED visits following exposure to specialized care in patients with moderate-severe asthma and at least 1 ED visit prior to the index admission,[147] and in patients with an index exacerbation associated with a prescription of oral corticosteroids,[154] both identifying patients with higher morbidity. Collectively, these findings suggest that further research is required to confirm the effectiveness of SAC alone and the pre-requisites for effectiveness. Until then most implementation efforts should focus on offering asthma education and SAC to high-risk patients, when feasible.

6.2 Sensitivity analyses of the main outcome

Similar results were obtained in two sensitivity analyses of children with an *alternative asthma case definition* at the index ED visit and in children *covered by the public drug plan*. These results attest to the robustness of our findings in patients meeting a modified pharmacoepidemiologic asthma case definition at the index ED visit and when adjusting for prior rescue medication use. This suggests that the inclusion of children with an asthma-like diagnosis was an appropriate methodological choice.

In contrast, opposite results, that is, apparent harm, were found in the *unselected cohort*, where asthma education with and without specialized asthma care was associated with an increased risk of earlier return ED visit. These results most probably reflect a confounding by indication bias that could not be corrected by adjustment for previous morbidity in terms of ED visits and hospital admissions. While it is intuitively likely that the most severe children will be the ones referred to, and attending, asthma education and specialized care, these children are also at higher risk of returning to the ED due to their baseline severity. Indeed, in the unselected cohort, the referral rate to the AEC was more than 6 times higher in the hospitalized children compared to those discharged at the index ED visit (39% vs. 6%,

respectively). This confounding by indication was prevented in our study cohort by restriction to a higher morbidity group, that is, by limiting to children who were referred to AEC by a physician. The results found in the unselected cohort of children are in agreement with a previous retrospective cohort study which found that asthma education increased the likelihood of a subsequent ED visit in patients admitted for asthma.[228] The authors of this study concluded that beneficial effects of asthma education may be obtained when selecting patients with histories of frequent utilization.[228] There is also possible that the paradoxical increase in subsequent ED visits is related to increased parental anxiety and misinterpretation of asthma symptoms, both leading to unnecessary ED visits. Even if these children would be discharged with simple reassurance and no treatment, the ED visit would be considered an exacerbation in our study. Indeed, a previous study showed that parental anxiety greatly influences the decision of parents to seek pediatric asthma care in the emergency department.[229]

Currently, it seems reasonable to reserve asthma education and specialized care to those appearing to need it, where it has a strong beneficial effect, consistent with that observed in efficacy trials. Yet, it appears worthwhile, for standardization purposes, to better identify those in need for asthma education and specialized asthma care and to investigate means to improve attendance to these services following the index ED visit, as only 65% of those referred attended their AEC appointment.

6.3 Secondary outcomes

The main interest of performing the analyses of the secondary outcomes was to better adjust for prior asthma control by including SABA use (most sensitive marker of control) and OCS use to health care resources utilization (ED and hospital admission), which was not possible without drug claims coverage. Of note, the subgroup of children in whom drug claims data were available (35% of the main cohort) and the main cohort had similar baseline characteristics, except for an overrepresentation of lower socioeconomic levels in the subcohort. This was expected because beneficiaries of the public drug plan are children whose parents do not have access to private drug insurance though their employment or are beneficiaries of last-resort financial assistance.

In the *drug claim* subcohort (n=432 in total, 414 with complete data), our results showed that only the combination of asthma education with specialist care was associated with a statistically significant decreased risk of subsequent OCS use and poor asthma control (not well controlled/very poorly controlled). Neither individual nor combined exposure to AEC and SAC had a statistically significant effect on subsequent SABA use, which is not likely an issue of statistical power since the effect size was close to 1 and the confidence intervals were small for all exposure groups. These observations would suggest that SAC is crucial for the optimal selection of the personalized written action plan and mediation prescription while AEC is essential to ensure adequate self-monitoring and guided self-management skills. However, achieving optimal asthma control requires regular medical follow-up and asthma education to achieve sustained asthma controller use and environmental control, a status that is usually obtained with more than a single encounter.

Although individual exposure to AEC and SAC did not have a statistically significant impact on subsequent OCS use, there is a trend towards protective effect of these interventions on this secondary outcome. Given that the effect sizes of the individual exposures had the same direction and similar magnitude in the main cohort and the subcohort, the non-statistically significant effect size of asthma education alone on the subsequent OCS use could be related to insufficient statistical power, given the low sample size of the subcohort and the large confidence interval of the effect size. For the same reasons, there seems to be a small trend of a small protective effect of the individual exposures on reduced risk of subsequent poor asthma control. Collectively, these results attest to the essential synergy of the interventions and suggest that both interventions are required for the strongest protection against subsequent morbidity.

6.4 Exploratory outcome

The use of inhaled corticosteroids was analyzed during the second 6-month follow-up period in the patients from the subcohort who had at least one ICS prescription claimed (n=258, 60% of the subcohort). We aimed to explore whether individual and combined exposure to asthma education and specialized care were associated with better use of asthma controller medications compared to none of the interventions. The difference in median ICS

use measured by the Proportion of Days Covered (PDC) among the exposure groups was not statistically significant in the crude (unadjusted) exploratory outcome analysis, but further analyses with adjustment for confounding variables and covariates would be required to confirm these findings.

Only one previous study of the impact of asthma education in combination with specialized care on subsequent ICS use was found, reporting beneficial effects on this outcome at 6 months following study entry.[191] In contrast, our findings are in accordance with three previous studies reporting no significant impact of asthma education alone on ICS use in the year following study entry.[186,188,230] However, one of these studies reported beneficial effects of asthma education alone on ICS use when measured on a shorter delay, namely at 6 months following study entry.[188] No previous studies examining the impact of specialized care alone on subsequent ICS use were found. Although further research is required to confirm the individual and combined effectiveness of AEC and SAC on controller medication use, the previous studies collectively suggest asthma education with or without specialized care may be effective to improve ICS use in the short term. Of note, rapid decreases in adherence to prescribed ICS have been reported following an ED visit in several studies from 90% on day 1 to 50% on day 14,[90] and in ICS claim rates from 89% within the first 30 days to 34% during day 31 to 60.[231] Therefore, the low PDC of ICS observed during the 7 to 12 months of follow-up may be in part explained by the expected decrease in ICS adherence and thus use, following an index ED visit or following medical visit.

6.5 Limitations

We acknowledge several study limitations.

6.5.1 Timing of the intervention exposures

It is important to take into account that, in real-life conditions, patients may not be referred to AEC and SAC at the index exacerbation, but at a subsequent medical encounter. Therefore, for patients receiving AEC and/or SAC during the last months of the follow-up period, there may not have been sufficient follow-up time to study the individual and combined impact of the interventions.

Furthermore, most randomized controlled trials included in the 2009 Cochrane review of the impact of asthma education with or without medical follow-up and other self-management components reported attendance rates of at least 70%.[11] However, patient-related factors (misbeliefs about the need for asthma education,[110] perception that ED care is sufficient for the management of asthma[105]) and provider-related factors (long waiting times,[142] limited hours of operation,[141] lack of access to specialty care[105]) are constraints that could delay access to asthma education and specialty care and may explain the lower rates of attendance to AEC and SAC observed in real-life. Thus, the observed beneficial effect of AEC with and without SAC may thus represent a conservative estimate of their maximal potential impact had these services been used more rapidly following the index acute care visit.

6.5.2 Survival bias

We acknowledge the inherent survival bias related to the use of a Cox proportional hazards model. Survival bias refers to the artificial survival advantage associated with the exposure of interest due to the fact that patients need to remain event free in order to be classified as exposed.[232] As a consequence of this inherent survival bias, the hazard ratios associated with the exposures of interest may be underestimated. However, similar effect sizes or trends were found for the individual and combined impact of AEC and SAC on the secondary outcomes, which were not subject to survival bias.

6.5.3 Information bias

First, misclassification of asthma education exposure may have taken place if children received asthma education outside of the Montreal Children's hospital, resulting in information bias. Considering that 9 out of 10 pediatric patients receive their asthma care at their main institution,[233] this misclassification would have affected approximately 10% of our cohort. If this misclassification took place, the beneficial effects of AEC alone or in combination with SAC would have been underestimated.

Moreover, we only had access to information about asthma specialist visits remunerated by fee-for-service by the RAMQ in the province of Quebec in addition to those made to the AC of the MCH, where we had complete data irrespective of remuneration

scheme. As a consequence of this, patients who received specialized asthma care by physicians with other types of remuneration schemes in other institutions may have been misclassified. Considering that 77% of specialists were remunerated on fee-for-service scheme in Quebec between 2000 and 2009,[209] this misclassification may only affect the expected small proportion of patients seen by specialists outside of the MCH.

Furthermore, in the subgroup of patients with drug claims data, we assumed that all drugs dispensed were used until the next service; but it is possible that patients have claimed the ICS medications from the pharmacy but not used them completely or at all (lost, expired, forgotten). However, the impact of this would be non-differential (i.e., it would affect the exposure groups in a similar way), overestimating the ICS use in patients who actually did not consume the ICS medications completely or at all, but without a systematic bias. The same applies to SABA and OCS use, as one cannot use a drug that has not first been dispensed. Indeed, previous studies have reported that OCS prescriptions received during an ED visit are only filled by 40%[234] of to 60%[90] of children in the month following discharge. Consequently, the use of drug claims from pharmacy records over medical records of prescription was a clear advantage of our study design, resulting in a better ascertainment of potential use.

Only AEC and SAC exposures that took place within the initial 6 months were taken into account in the analyses of the secondary and exploratory outcomes. For these analyses, children who received any exposures in the 7 to 12 months of follow up (which represent 20% of the subcohort) would have be misclassified as part of the control group, thus contributing to an underestimation of effect.

6.5.4 Residual confounding

Our primary and secondary outcome analyses were adjusted for potential confounder variables that were available in the hospital and governmental databases. However, residual confounding may still be present in our results since we were unable to adjust for some demographic, family and clinical variables that have been associated with the risk of a subsequent ED visit in other studies, such as lung function, asthma severity, obesity, race, frequency of asthma symptoms, asthma knowledge, and home/outdoor irritant or allergen exposure. Had we been able to include these variables, our estimates of the effect of the

exposures would be have been more precise. Future studies should also include other variables related to socioeconomic status, such as parental education level, income and tenant status, which have been shown to be important determinants of asthma exacerbations even when children have free access to health care services.[61] Furthermore, including information regarding the levels of ambient air pollutants in patients' residential areas[235] as covariates in future studies would also provide more precise estimates of the effects of asthma education and specialized asthma care.

6.5.5 External validity

The results of the present study may not be generalized to other populations in terms of person, time and place. The results of the main outcome analysis are representative of the residents of Quebec (Canada), who benefit from free-of -charge medical visits, medical tests, hospitalizations, and asthma education sessions at the AEC. Therefore, these findings are not necessarily generalized to other countries where there are greater disparities in access to healthcare services. Moreover, secondary outcomes and exploratory analysis were performed in the subcohort of children covered by the public drug plan, whose parents were self-employed, beneficiaries of social assistance or whose employers did not offer drug insurance. Therefore, in theory, the drug data findings may not apply to children with higher socioeconomic status, as we observed an overrepresentation of children of lower status in this subcohort, as evidenced in the table of characteristics. However, the effect sizes of the main outcome were similar in the study cohort and the subcohort (except for AEC alone), reflecting the robustness of our findings irrespective of the distribution of socioeconomic status.

By design, our cohort study was retrospective and covered 2000 to 2007. Although, the Canadian Asthma guidelines released in 1996, 2005, 2012 and 2015 consistently highlighted the importance of daily controller medication, their emphasis on asthma education and early controller therapy had increased over the years such that the management patterns may have improved ever since. Therefore, our findings may not be reflective of the current impact of individual and combined exposure to asthma education and specialized asthma care that may be mediated in part via better patient use of controller medications.

6.6 Implications for clinical practice

In our retrospective study, the greatest protection against a subsequent ED visit was obtained when both asthma education and specialized care were provided in children referred to the AEC following an emergency department visit for an asthma/asthma-like condition. Moreover, only exposure to both interventions was effective in reducing subsequent risk of poor asthma control and oral corticosteroids use. We thus conclude that it seems reasonable to consider concurrent referral to specialized care whenever children are referred to the AEC. Given the low real-life attendance to asthma education and specialized asthma care following an ED visit, priority should be given to finding ways to improve attendance to both of these services in children referred to the AEC.

6.7 Implications for future research

First, the low referral rate to the Asthma Education Centre in children presenting to the emergency department for an asthma/asthma-like condition (12.4%=1233/9960) and the strong effectiveness of receiving both interventions in protecting against subsequent emergency visits in children referred to the AEC highlights the need to better identify the characteristics of the high-risk children who would benefit the most from asthma education and specialized asthma care. Second, prospective studies with a larger number of patients exposed to the interventions should be performed to better understand the mechanism conferring the effectiveness of asthma education and specialized care, taking into account the appropriateness of the prescription, and exploring the critical time period at which the interventions are the most effective.

Three studies could be undertaken to address these objectives. The first study would be an effectiveness study (perhaps using the same cohort as ours) to identify the determinants of subsequent ED visits in a larger group of children presenting to the ED for an asthma/asthma-like exacerbation. This would allow us to identify the characteristics of children at high risk of ED relapse in real life and provide insights about which children would benefit the most from asthma education and specialized asthma care.

Once identified, the group of high-risk children would be randomly allocated in a 1:1:1 ratio to receive the interventions (AEC only, SAC only, both AEC and SAC or none) prior to discharge in a second study (a randomized controlled trial). Access to the provincial database of prescriptions claimed by patients with a private as well as public drug insurance would allow us to determine the impact of the interventions on subsequent medication use in patients from all socioeconomic levels. The outcomes of interest would include emergency visits, hospital admissions, rescue medication use (OCS and SABA) and use of controller medications by using different measures of adherence.

A third study would be a randomized controlled trial including a sufficiently large number of high-risk children receiving the interventions (AEC only, SAC only, both AEC and SAC or none) at different time periods from the index ED visit. This would allow us to identify the critical time period at which the interventions provide the greatest protection.

Future studies should also take into account the number of AEC or SAC visits, which would provide more precise estimates of the effects of these exposures. Indeed, it is likely that the impact of asthma education and specialized care depends on the number of visits received.

Conclusion

This thesis provides solid evidence of the beneficial real-life impact of asthma education offered at the Asthma Education Centre (AEC) with and without specialized asthma care (SAC) in children referred to the AEC following an emergency visit for an asthma/asthma-like exacerbation, with an effect size in the same order as that observed in randomized controlled trials. In our study cohort, combined exposure to AEC and SAC offered the greatest protective effects against subsequent morbidity. To our knowledge, this is the first study to evaluate simultaneously the individual and combined impact of asthma education and specialized asthma care in the real-life pediatric setting.

Our findings support an approach consisting of the combination of asthma education and specialized asthma care for clinical management in children presenting to the ED and deemed in need of asthma education. Moreover, our findings constitute a solid basis to plan future real-life effectiveness studies and randomized controlled trials to further improve care of children discharged from the ED following an acute asthma/asthma-like exacerbation.

References

1. Public Health Agency of Canada. Report from the Canadian Chronic Disease Surveillance System: Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Canada, 2018.
2. Public Health Agency of Canada. Canadian Chronic Disease Indicators, 2017 Edition. 2017. Retrieved from https://infobase.phac-aspc.gc.ca/ccdi-imcc/data-tool/.
3. Lougheed MD, Garvey N, Chapman KR, Cicutto L, Dales R, Day AG, et al. The Ontario Asthma Regional Variation Study: emergency department visit rates and the relation to hospitalization rates. *Chest.* 2006;129(4):909-917.
4. Garner R, Kohen D. Changes in the prevalence of asthma among Canadian children. *Health Rep.* 2008;19(2):45-50.
5. Larsen K, Zhu J, Feldman LY, Simatovic J, Dell S, Gershon AS, et al. The Annual September Peak in Asthma Exacerbation Rates. Still a Reality? *Ann Am Thorac Soc.* 2016;13(2):231-239.
6. Ducharme FM, Dell SD, Radhakrishnan D, Grad RM, Watson WT, Yang CL, et al. Diagnosis and management of asthma in preschoolers: A Canadian Thoracic Society and Canadian Paediatric Society position paper. *Can Respir J.* 2015;22(3):135-143.
7. Ismaila AS, Sayani AP, Marin M, Su Z. Clinical, economic, and humanistic burden of asthma in Canada: a systematic review. *BMC Pulm Med.* 2013;13:70.
8. Cost Risk Analysis for Chronic Lung Disease in Canada, The Conference Board of Canada, Louis Theriault, Gregory Hermus, Danielle Goldfarb, Carole Stonebridge, Fares Bounajm, 2012. Retrieved from http://www.conferenceboard.ca/elibrary/abstract.aspx?did=4585.
9. Lougheed MD, Lemiere C, Ducharme FM, Licskai C, Dell SD, Rowe BH, et al. Canadian Thoracic Society 2012 guideline update: diagnosis and management of asthma in preschoolers, children and adults. *Can Respir J.* 2012;19(2):127-164.
10. Global Initiative for Asthma. 2018 GINA Report, Global Strategy for Asthma Management and Prevention. 2018. Retrieved from https://ginasthma.org/wp-content/uploads/2018/04/wms-GINA-2018-report-V1.3-002.pdf.

11. Boyd M, Lasserson TJ, McKean MC, Gibson PG, Ducharme FM, Haby M. Interventions for educating children who are at risk of asthma-related emergency department attendance. *Cochrane Database Syst Rev.* 2009(2):CD001290.
12. Schatz M, Casale TB, Pace W, Walters R, Turner P, Elward KS. Characteristics of Asthma Visits to Specialists Compared to Primary Care Physicians. *Journal of Allergy and Clinical Immunology.* 2013;131(2, Supplement):AB34.
13. Edwards ST, Mafi JN, Landon BE. Trends and quality of care in outpatient visits to generalist and specialist physicians delivering primary care in the United States, 1997-2010. *J Gen Intern Med.* 2014;29(6):947-955.
14. Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, et al. After asthma: redefining airways diseases. *Lancet.* 2018;391(10118):350-400.
15. Raedler D, Schaub B. Immune mechanisms and development of childhood asthma. *Lancet Respir Med.* 2014;2(8):647-656.
16. Restori KH, Srinivasa BT, Ward BJ, Fixman ED. Neonatal Immunity, Respiratory Virus Infections, and the Development of Asthma. *Front Immunol.* 2018;9:1249.
17. Sokolowska M, Frei R, Lunjani N, Akdis CA, O'Mahony L. Microbiome and asthma. *Asthma Res Pract.* 2018;4:1.
18. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med.* 2012;18(5):716-725.
19. Debley J, Filbrun AG, Subbarao P. Clinical applications of pediatric pulmonary function testing: lung function in recurrent wheezing and asthma. *Pediatric Allergy, Immunology, and Pulmonology.* 2011;24(2):69-76.
20. Mallol J, García-Marcos L, Solé D, Brand P, EISL Study Group. International prevalence of recurrent wheezing during the first year of life: variability, treatment patterns and use of health resources. *Thorax.* 2010;65(11):1004-1009.
21. Dela Bianca AC, Wandalsen GF, Mallol J, Solé D. Prevalence and severity of wheezing in the first year of life. *J Bras Pneumol.* 2010;36(4):402-409.
22. Bisgaard H, Szefler S. Prevalence of asthma-like symptoms in young children. *Pediatr Pulmonol.* 2007;42(8):723-728.

23. Cano Garcinuño A, Mora Gandarillas I, SLAM Study Group. Early patterns of wheezing in asthmatic and nonasthmatic children. *Eur Respir J.* 2013;42(4):1020-1028.
24. Brehm JM. Toward improved diagnosis of early asthma. *Am J Respir Crit Care Med.* 2015;191(2):126-127.
25. Østergaard MS. Childhood asthma: reasons for diagnostic delay and facilitation of early diagnosis--a qualitative study. *Prim Care Respir J.* 2005;14(1):25-30.
26. Saglani S, Payne DN, Zhu J, Wang Z, Nicholson AG, Bush A, et al. Early detection of airway wall remodeling and eosinophilic inflammation in preschool wheezers. *Am J Respir Crit Care Med.* 2007;176(9):858-864.
27. Bush A. How early do airway inflammation and remodeling occur? *Allergol Int.* 2008;57(1):11-19.
28. Boulet LP. Airway remodeling in asthma: update on mechanisms and therapeutic approaches. *Curr Opin Pulm Med.* 2018;24(1):56-62.
29. Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med.* 2005;172(10):1253-1258.
30. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med.* 1995;332(3):133-138.
31. Ma H, Li Y, Tang L, Peng X, Jiang L, Wan J, et al. Impact of childhood wheezing on lung function in adulthood: A meta-analysis. *PLoS One.* 2018;13(2):e0192390.
32. O'Byrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW, START Investigators Group. Severe exacerbations and decline in lung function in asthma. *Am J Respir Crit Care Med.* 2009;179(1):19-24.
33. Bui DS, Lodge CJ, Burgess JA, Lowe AJ, Perret J, Bui MQ, et al. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *Lancet Respir Med.* 2018;6(7):535-544.
34. Bisgaard H, Jensen SM, Bonnelykke K. Interaction between asthma and lung function growth in early life. *Am J Resp Crit Care Med.* 2012;185(11):1183-1189.

35. Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe asthma in adults. *Lancet.* 2006;368(9537):780-793.
36. Cave AJ, Atkinson LL. Asthma in preschool children: a review of the diagnostic challenges. *J Am Board Fam Med.* 2014;27(4):538-548.
37. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying patients with physician-diagnosed asthma in health administrative databases. *Can Respir J.* 2009;16(6):183-188.
38. To T, Dell S, Dick PT, Cicutto L, Harris JK, MacLusky IB, et al. Case verification of children with asthma in Ontario. *Pediatr Allergy Immunol.* 2006;17(1):69-76.
39. Yang CL, Simons E, Foty RG, To T, Dell SD. Administrative Databases Useful For Asthma Surveillance But Overestimate Asthma Prevalence. In: *B61. PEDIATRIC ASTHMA.* American Thoracic Society; 2012:A3363-A3363.
40. Kozyrskyj AL, HayGlass KT, Sandford AJ, Pare PD, Chan-Yeung M, Becker AB. A novel study design to investigate the early-life origins of asthma in children (SAGE study). *Allergy.* 2009;64(8):1185-1193.
41. Trevethan R. Sensitivity, Specificity, and Predictive Values: Foundations, Pliabilities, and Pitfalls in Research and Practice. *Front Public Health.* 2017;5:307.
42. Nissen F, Quint JK, Wilkinson S, Mullerova H, Smeeth L, Douglas IJ. Validation of asthma recording in electronic health records: a systematic review. *Clin Epidemiol.* 2017;9:643-656.
43. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health.* 2012;12:204.
44. Lai CK, Beasley R, Crane J, Foliaki S, Shah J, Weiland S, et al. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax.* 2009;64(6):476-483.
45. Public Health Agency of Canada. Canadian Chronic Disease Surveillance System 2016. Retrieved from https://infobase.phac-aspc.gc.ca/datalab/asthma-blog-en.html.
46. Pignataro FS, Bonini M, Forgione A, Melandri S, Usmani OS. Asthma and gender: The female lung. *Pharmacol Res.* 2017;119:384-390.

47. Postma DS. Gender differences in asthma development and progression. *Gend Med.* 2007;4 Suppl B:S133-146.
48. Almqvist C, Worm M, Leynaert B, working group of GA2LEN WP 2.5 'Gender'. Impact of gender on asthma in childhood and adolescence: a GA2LEN review. *Allergy.* 2008;63(1):47-57.
49. Vos T, Allen C, Arora M, Barber RM, Bhutta ZA, Brown A, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet.* 2016;388(10053):1545-1602.
50. Most Recent Asthma Data (Webpage last updated: June 2017) - Centers for Disease Control and Prevention (CDC). Retrieved from https://www.cdc.gov/asthma/most_recent_data.htm.
51. Forno E, Celedon JC. Asthma and ethnic minorities: socioeconomic status and beyond. *Curr Opin Allergy Clin Immunol.* 2009;9(2):154-160.
52. Drake KA, Galanter JM, Burchard EG. Race, ethnicity and social class and the complex etiologies of asthma. *Pharmacogenomics.* 2008;9(4):453-462.
53. Assari S, Moghani Lankarani M. Poverty Status and Childhood Asthma in White and Black Families: National Survey of Children's Health. *Healthcare (Basel).* 2018;6(2).
54. Lajoie P, Lévesque B, Rhainds M, Rochette L. respiratory health: Frequency of asthma, wheezing and allergies in inuit children in relation to indoor air quality. *Epidemiology.* 2008;19(6):S217.
55. Kovesi T, Giles BL, Pasterkamp H. Long-term management of asthma in First Nations and Inuit children: A knowledge translation tool based on Canadian paediatric asthma guidelines, intended for use by front-line health care professionals working in isolated communities. *Paediatr Child Health.* 2012;17(7):e46-64.
56. Zomer-Kooijker K, Uiterwaal CS, Verschueren KJ, Maitland-vd Zee AH, Balemans WA, van Ewijk BE, et al. Respiratory tract infections and asthma control in children. *Respir Med.* 2014;108(10):1446-1452.
57. Dondi A, Calamelli E, Piccinno V, Ricci G, Corsini I, Biagi C, et al. Acute Asthma in the Pediatric Emergency Department: Infections Are the Main Triggers of Exacerbations. *Biomed Res Int.* 2017:9687061.

58. de Groot EP, Nijkamp A, Duiverman EJ, Brand PL. Allergic rhinitis is associated with poor asthma control in children with asthma. *Thorax.* 2012;67(7):582-587.
59. Vanker A, Gie RP, Zar HJ. The association between environmental tobacco smoke exposure and childhood respiratory disease: a review. *Expert Rev Respir Med.* 2017;11(8):661-673.
60. Guarnieri M, Balmes JR. Outdoor air pollution and asthma. *Lancet.* 2014;383(9928):1581-1592.
61. Jacques L, Plante C, Goudreau S, Deger L, Fournier M, Smargiassi A, et al. Rapport synthèse régional de l'étude sur la santé respiratoire des jeunes Montréalais de 6 mois à 12 ans. Montréal: Direction de santé publique. Agence de la santé et des Services Sociaux de Montréal; 2011.
62. Deliu M, Belgrave D, Simpson A, Murray CS, Kerry G, Custovic A. Impact of rhinitis on asthma severity in school-age children. *Allergy.* 2014;69(11):1515-1521.
63. Murray CS, Simpson A, Custovic A. Allergens, viruses, and asthma exacerbations. *Proc Am Thorac Soc.* 2004;1(2):99-104.
64. Sears MR. Epidemiology of asthma exacerbations. *J Allergy Clin Immunol.* 2008;122(4):662-668; quiz 669-670.
65. Busse WW, Lemanske RF, Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. *Lancet.* 2010;376(9743):826-834.
66. Akinbami LJ, Parker JD, Merkle S. Factors associated with school absence among children with symptomatic asthma, United States, 2002–2003. *Pediatric Allergy, Immunology, and Pulmonology.* 2010;23(3):191-200.
67. Centers for Disease Control and Prevention. National Center for Health Statistics: National Health Interview Survey raw data. CDC Software. Atlanta, GA; 2011.
68. Sullivan PW, Ghushchyan V, Navaratnam P, Friedman HS, Kavati A, Ortiz B, et al. The national burden of poorly controlled asthma, school absence and parental work loss among school-aged children in the United States. *J Asthma.* 2018;55(6):659-667.
69. Le AV, Simon RA. The Difficult-to-Control Asthmatic: A Systematic Approach. *Allergy Asthma Clin Immunol.* 2006;2(3):109-116.

70. Chapman KR, Boulet LP, Rea RM, Franssen E. Suboptimal asthma control: prevalence, detection and consequences in general practice. *Eur Respir J.* 2008;31(2):320-325.
71. Pedersen S. From asthma severity to control: a shift in clinical practice. *Prim Care Respir J.* 2010;19(1):3-9.
72. Carroll WD, Wildhaber J, Brand PL. Parent misperception of control in childhood/adolescent asthma: the Room to Breathe survey. *Eur Respir J.* 2012;39(1):90-96.
73. Koster ES, Wijga AH, Koppelman GH, Postma DS, Brunekreef B, De Jongste JC, et al. Uncontrolled asthma at age 8: the importance of parental perception towards medication. *Pediatr Allergy Immunol.* 2011;22(5):462-468.
74. Firoozi F, Lemière C, Beauchesne MF, Forget A, Blais L. Development and validation of database indexes of asthma severity and control. *Thorax.* 2007;62(7):581-587.
75. Despres F, Ducharme FM, Forget A, Sze Man T, Kettani FZ, Blais L. Development and Validation of a Pharmacoepidemiologic Pediatric Asthma Control Index Using Information from Administrative Database. American Thoracic Society 2017 International Conference.Washington DC, United States. May 2017.
76. McIvor RA, Boulet LP, FitzGerald JM, Zimmerman S, Chapman KR. Asthma control in Canada: no improvement since we last looked in 1999. *Can Fam Physician.* 2007;53(4):672-677.
77. Cope SF, Ungar WJ, Glazier RH. Socioeconomic factors and asthma control in children. *Pediatr Pulmonol.* 2008;43(8):745-752.
78. McGhan SL, MacDonald C, James DE, Naidu P, Wong E, Sharpe H, et al. Factors associated with poor asthma control in children aged five to 13 years. *Can Respir J.* 2006;13(1):23-29.
79. Price D, Fletcher M, van der Molen T. Asthma control and management in 8,000 European patients: the REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey. *NPJ Prim Care Respir Med.* 2014;24:14009.
80. Zahran HS, Bailey CM, Qin X, Moorman JE. Assessing asthma control and associated risk factors among persons with current asthma - findings from the child and adult Asthma Call-back Survey. *J Asthma.* 2015;52(3):318-326.

81. Tolomeo C, Savrin C, Heinzer M, Bazzy-Asaad A. Predictors of asthma-related pediatric emergency department visits and hospitalizations. *J Asthma.* 2009;46(8):829-834.
82. CIHI Quickstats, Emergency Department (ED) Visits: Volumes and Median Length of Stay by Triage Level, Visit Disposition and Main Problem (Asthma). 2017
83. Cree M, Bell NR, Johnson D, Carriere KC. Increased continuity of care associated with decreased hospital care and emergency department visits for patients with asthma. *Dis Manag.* 2006;9(1):63-71.
84. Huang ST, Wu SC, Hung YN, Lin IP. Effects of continuity of care on emergency department utilization in children with asthma. *Am J Manag Care.* 2016;22(1):e31-37.
85. Johnson LH, Chambers P, Dexheimer JW. Asthma-related emergency department use: current perspectives. *Open Access Emerg Med.* 2016;8:47-55.
86. Fleetcroft R, Noble M, Martin A, Coombes E, Ford J, Steel N. Emergency hospital admissions for asthma and access to primary care: cross-sectional analysis. *Br J Gen Pract.* 2016;66(650):e640-646.
87. To T, Wang C, Dell S, Fleming-Carroll B, Parkin P, Scolnik D, et al. Risk factors for repeat adverse asthma events in children after visiting an emergency department. *Ambul Pediatr.* 2008;8(5):281-287.
88. FitzGerald JM, Lemiere C, Lougheed MD, Ducharme FM, Dell SD, Ramsey C, et al. Recognition and management of severe asthma: A Canadian Thoracic Society position statement. Taylor & Francis; 2017.
89. Gibson PG. Monitoring the patient with asthma: an evidence-based approach. *J Allergy Clin Immunol.* 2000;106(1 Pt 1):17-26.
90. Ducharme FM, Zemek RL, Chalut D, McGillivray D, Noya FJ, Resendes S, et al. Written action plan in pediatric emergency room improves asthma prescribing, adherence, and control. *Am J Respir Crit Care Med.* 2011;183(2):195-203.
91. Chen YZ, Busse WW, Pedersen S, Tan W, Lamm CJ, O'Byrne PM. Early intervention of recent onset mild persistent asthma in children aged under 11 yrs: the Steroid Treatment As Regular Therapy in early asthma (START) trial. *Pediatr Allergy Immunol.* 2006;17 Suppl 17:7-13.

92. World Health Organization. Adherence to long-term therapies: evidence for action. 2003.
93. Kozyrskyj AL, Mustard CA, Simons FE. Inhaled corticosteroids in childhood asthma: Income differences in use. *Pediatr Pulmonol.* 2003;36(3):241-247.
94. Morton RW, Everard ML, Elphick HE. Adherence in childhood asthma: the elephant in the room. *Arch Dis Child.* 2014;99(10):949-953.
95. Gong T, Lundholm C, Rejnö G, Mood C, Långström N, Almqvist C. Parental socioeconomic status, childhood asthma and medication use-a population-based study. *PLoS One.* 2014;9(9):e106579.
96. Peláez S, Lamontagne AJ, Collin J, Gauthier A, Grad RM, Blais L, et al. Patients' perspective of barriers and facilitators to taking long-term controller medication for asthma: a novel taxonomy. *BMC Pulm Med.* 2015;15:42.
97. Farnesi BC, Ducharme FM, Blais L, Collin J, Lavoie KL, Bacon SL, et al. Guided asthma self-management or patient self-adjustment? Using patients' narratives to better understand adherence to asthma treatment. *Patient Prefer Adherence.* 2019;13:587-597.
98. Klok T, Lubbers S, Kaptein AA, Brand PL. Every parent tells a story: why non-adherence may persist in children receiving guideline-based comprehensive asthma care. *J Asthma.* 2014;51(1):106-112.
99. Cooper V, Metcalf L, Versnel J, Upton J, Walker S, Horne R. Patient-reported side effects, concerns and adherence to corticosteroid treatment for asthma, and comparison with physician estimates of side-effect prevalence: a UK-wide, cross-sectional study. *NPJ Prim Care Respir Med.* 2015;25:15026.
100. Desager K, Vermeulen F, Bodart E. Adherence to asthma treatment in childhood and adolescence - a narrative literature review. *Acta Clin Belg.* 2018;73(5):348-355.
101. DeWalt DA, Dilling MH, Rosenthal MS, Pignone MP. Low parental literacy is associated with worse asthma care measures in children. *Ambul Pediatr.* 2007;7(1):25-31.
102. Hoover EL, Pierce CS, Spencer GA, Britten MX, Neff-Smith M, James GD, et al. Relationships among functional health literacy, asthma knowledge and the ability to

care for asthmatic children in rural dwelling parents. *Online Journal of Rural Nursing and Health Care.* 2012;12(2):30-40.

103. Wood MR, Price JH, Dake JA, Telljohann SK, Khuder SA. African American parents'/guardians' health literacy and self-efficacy and their child's level of asthma control. *Journal of pediatric nursing.* 2010;25(5):418-427.

104. Fiks AG, Mayne SL, Karavite DJ, Suh A, O'Hara R, Localio AR, et al. Parent-reported outcomes of a shared decision-making portal in asthma: a practice-based RCT. *Pediatrics.* 2015;135(4):e965-973.

105. Miles C, Arden-Close E, Thomas M, Bruton A, Yardley L, Hankins M, et al. Barriers and facilitators of effective self-management in asthma: systematic review and thematic synthesis of patient and healthcare professional views. *NPJ Prim Care Respir Med.* 2017;27(1):57.

106. McQuaid EL. Barriers to medication adherence in asthma: The importance of culture and context. *Ann Allergy Asthma Immunol.* 2018;121(1):37-42.

107. Wilson SR, Strub P, Buist AS, Knowles SB, Lavori PW, Lapidus J, et al. Shared treatment decision making improves adherence and outcomes in poorly controlled asthma. *Am J Respir Crit Care Med.* 2010;181(6):566-577.

108. D'Auria JP. All about asthma: top resources for children, adolescents, and their families. *J Pediatr Health Care.* 2013;27(4):e39-42.

109. Drummond D, Monnier D, Tesnière A, Hadchouel A. A systematic review of serious games in asthma education. *Pediatr Allergy Immunol.* 2017;28(3):257-265.

110. Boulet LP. Asthma education: an essential component in asthma management. *Eur Respir J.* 2015;46(5):1262-1264.

111. Roddis JK, Holloway I, Bond C, Galvin KT. Living with a long-term condition: Understanding well-being for individuals with thrombophilia or asthma. *Int J Qual Stud Health Well-being.* 2016;11:31530.

112. McDonald VM, Gibson PG. Asthma self-management education. *Chron Respir Dis.* 2006;3(1):29-37.

113. Horne R, Price D, Cleland J, Costa R, Covey D, Gruffydd-Jones K, et al. Can asthma control be improved by understanding the patient's perspective? *BMC Pulm Med.* 2007;7:8.

114. Jones MA. Asthma Self-Management Patient Education. *Respiratory Care.* 2008;53(6):778-786.
115. Rance KS. Helping patients attain and maintain asthma control: reviewing the role of the nurse practitioner. *J Multidiscip Healthc.* 2011;4:299-309.
116. Rank MA, Volcheck GW, Li JT, Patel AM, Lim KG. Formulating an effective and efficient written asthma action plan. *Mayo Clin Proc.* 2008;83(11):1263-1270.
117. Schatz M, Rachelefsky G, Krishnan JA. Follow-up after acute asthma episodes: what improves future outcomes? *J Emerg Med.* 2009;37(2 Suppl):S42-50.
118. Gibson PG, Powell H. Written action plans for asthma: an evidence-based review of the key components. *Thorax.* 2004;59(2):94-99.
119. Boulet LP, Chapman KR. Asthma education: the Canadian experience. *Chest.* 1994;106(4 Suppl):206S-210S.
120. Bérubé D, Chirron R. Asthma education: the impact on care: the Quebec experience. *Pediatr Pulmonol.* 2001;Suppl 23:16-17.
121. Division of General Pediatrics - McGill University. Retrieved from https://www.mcgill.ca/peds/divisions/generalpediatrics.
122. Ortiz-Alvarez O, Mikrogianakis A, Canadian Paediatric Society Acute Care Committee. Managing the paediatric patient with an acute asthma exacerbation. *Paediatr Child Health.* 2012;17(5):251-262.
123. Martin MA, Press VG, Nyenhuis SM, Krishnan JA, Erwin K, Mosnaim G, et al. Care transition interventions for children with asthma in the emergency department. *J Allergy Clin Immunol.* 2016;138(6):1518-1525.
124. Lamontagne AJ, Peláez S, Grad R, Blais L, Lavoie KL, Bacon SL, et al. Facilitators and solutions for practicing optimal guided asthma self-management: the physician perspective. *Can Respir J.* 2013;20(4):285-293.
125. Cloutier MM, Salo PM, Akinbami LJ, Cohn RD, Wilkerson JC, Diette GB, et al. Clinician Agreement, Self-Efficacy, and Adherence with the Guidelines for the Diagnosis and Management of Asthma. *J Allergy Clin Immunol Pract.* 2018;6(3):886-894.e884.

126. Gagné ME, Boulet LP. Implementation of asthma clinical practice guidelines in primary care: A cross-sectional study based on the Knowledge-to-Action Cycle. *J Asthma.* 2018;55(3):310-317.
127. Hudgins JD, Neuman MI, Monuteaux MC, Porter J, Nelson KA. Provision of Guideline-Based Pediatric Asthma Care in US Emergency Departments. *Pediatr Emerg Care.* 2019.
128. Chamberlain JM, Teach SJ, Hayes KL, Badolato G, Goyal MK. Practice Pattern Variation in the Care of Children With Acute Asthma. *Acad Emerg Med.* 2016;23(2):166-170.
129. Butz A, Morphew T, Lewis-Land C, Kub J, Bellin M, Ogborn J, et al. Factors associated with poor controller medication use in children with high asthma emergency department use. *Ann Allergy Asthma Immunol.* 2017;118(4):419-426.
130. Filler G, Kovesi T, Bourdon E, Jones SA, Givelichian L, Rockman-Greenberg C, et al. Does specialist physician supply affect pediatric asthma health outcomes? *BMC Health Serv Res.* 2018;18(1):247.
131. Boulet LP, Bourbeau J, Skomro R, Gupta S. Major care gaps in asthma, sleep and chronic obstructive pulmonary disease: a road map for knowledge translation. *Can Respir J.* 2013;20(4):265-269.
132. Lingner H, Burger B, Kardos P, Criée CP, Worth H, Hummers-Pradier E. What patients really think about asthma guidelines: barriers to guideline implementation from the patients' perspective. *BMC Pulm Med.* 2017;17(1):13.
133. Cross E, Villa-Roel C, Majumdar SR, Bhutani M, Rosychuk RJ, Couperthwaite S, et al. Action plans in patients presenting to emergency departments with asthma exacerbations: Frequency of use and description of contents. *Can Respir J.* 2014;21(6):351-356.
134. Garro AC, Asnis L, Merchant RC, McQuaid EL. Frequency of prescription of inhaled corticosteroids to children with asthma in U.S. emergency departments. *Acad Emerg Med.* 2011;18(7):767-770.
135. Lougheed MD, Garvey N, Chapman KR, Cicutto L, Dales R, Day AG, et al. Variations and gaps in management of acute asthma in Ontario emergency departments. *Chest.* 2009;135(3):724-736.

136. Price C, Agarwal G, Chan D, Goel S, Kaplan AG, Boulet LP, et al. Large care gaps in primary care management of asthma: a longitudinal practice audit. *BMJ Open.* 2019;9(1):e022506.
137. Braido F. Failure in asthma control: reasons and consequences. *Scientifica (Cairo).* 2013;2013:549252.
138. Al-Muhsen S, Horanieh N, Dulgom S, Al Aseri Z, Vazquez-Tello A, Halwani R, et al. Poor asthma education and medication compliance are associated with increased emergency department visits by asthmatic children. *Ann Thorac Med.* 2015;10(2):123-131.
139. Sampayo EM, McLoughlin RJ, Tsevdos D, Alam S, Zorc JJ. Pediatricians Support Initiation of Asthma Controller Medications in the Emergency Department: A National Survey. *Pediatr Emerg Care.* 2015;31(8):545-550.
140. Wahabi HA, Alziedan RA. Reasons behind non-adherence of healthcare practitioners to pediatric asthma guidelines in an emergency department in Saudi Arabia. *BMC Health Serv Res.* 2012;12:226.
141. Cicutto L, Murphy S, Coutts D, O'Rourke J, Lang G, Chapman C, et al. Breaking the access barrier: evaluating an asthma center's efforts to provide education to children with asthma in schools. *Chest.* 2005;128(4):1928-1935.
142. Robichaud P, Laberge A, Allen MF, Boutin H, Rossi C, Lajoie B, et al. Evaluation of a program aimed at increasing referrals for asthma education of patients consulting at the emergency department for acute asthma. *Chest.* 2004;126(5):1495-1501.
143. Krishnan S, Rohman A, Welter J, Dozor AJ. Relationship Between Health Literacy in Parents and Asthma Control in Their Children: A Prospective Study in a Diverse Suburban Population. *Pediatric Allergy, Immunology, and Pulmonology.* 2018;31(4):221-225.
144. Li P, To T, Guttmann A. Follow-up care after an emergency department visit for asthma and subsequent healthcare utilization in a universal-access healthcare system. *J Pediatr.* 2012;161(2):208-213.e201.
145. Williams KW, Word C, Streck MR, Titus MO. Parental education on asthma severity in the emergency department and primary care follow-up rates. *Clin Pediatr (Phila).* 2013;52(7):612-619.

146. Drewek R, Mirea L, Rao A, Touresian P, Adelson PD. Asthma treatment and outcomes for children in the emergency department and hospital. *J Asthma.* 2018;55(6):603-608.
147. Aragona E, Wang J, Scheckelhoff T, Hyacinthe A, Nino G, Pillai KG. Asthma specialty clinics decrease emergency department visits in inner-city children hospitalized for asthma exacerbation. *Am J Respir Crit Care Med.* 2014; s: 189, A3838.
148. Herndon JB, Mattke S, Evans Cuellar A, Hong SY, Shenkman EA. Anti-inflammatory medication adherence, healthcare utilization and expenditures among Medicaid and children's health insurance program enrollees with asthma. *Pharmacoeconomics.* 2012;30(5):397-412.
149. Blais L, Kettani FZ, Forget A, Beauchesne MF, Lemière C, Ducharme FM. Assessing adherence to inhaled corticosteroids in asthma patients using an integrated measure based on primary and secondary adherence. *Eur J Clin Pharmacol.* 2017;73(1):91-97.
150. Andrews AL, Teufel RJ, Basco WT. Initiating inhaled steroid treatment for children with asthma in the emergency room: current reported prescribing rates and frequently cited barriers. *Pediatr Emerg Care.* 2013;29(9):957-962.
151. Scarfone RJ, Zorc JJ, Angsuco CJ. Emergency physicians' prescribing of asthma controller medications. *Pediatrics.* 2006;117(3):821-827.
152. Klok T, Kaptein AA, Duiverman E, Oldenhof FS, Brand PL. General practitioners' prescribing behaviour as a determinant of poor persistence with inhaled corticosteroids in children with respiratory symptoms: mixed methods study. *BMJ Open.* 2013;3(4).
153. Gillette C, Rockich-Winston N, Kuhn JA, Flesher S, Shepherd M. Inhaler Technique in Children With Asthma: A Systematic Review. *Acad Pediatr.* 2016;16(7):605-615.
154. McNamara K, Stukus DR. Differences in Oral Corticosteroid Prescribing Regimens for Asthma Exacerbations Between Primary Care and Specialty Pediatricians. In. Vol 137, no. 2: *Journal of Allergy and Clinical Immunology*; 2016.
155. D'Amato G, Vitale C, Molino A, Stanziola A, Sanduzzi A, Vatrella A, et al. Asthma-related deaths. *Multidiscip Respir Med.* 2016;11:37.
156. Ducharme FM, Tse SM, Chauhan B. Diagnosis, management, and prognosis of preschool wheeze. *Lancet.* 2014;383(9928):1593-1604.

157. Seung SJ, Mittmann N. Urgent care costs of uncontrolled asthma in Canada, 2004. *Can Respir J.* 2005;12(8):435-436.

158. To T, Gershon A, Wang C, Dell S, Cicutto L. Persistence and remission in childhood asthma: a population-based asthma birth cohort study. *Arch Pediatr Adolesc Med.* 2007;161(12):1197-1204.

159. Stanford RH, Buikema AR, Riedel AA, Camargo CA, Rey GG, Chapman KR. Asthma controller delay and recurrence risk after an emergency department visit or hospitalization. *Respir Med.* 2012;106(12):1631-1638.

160. To T, Cicutto L, Degani N, McLimont S, Beyene J. Can a community evidence-based asthma care program improve clinical outcomes?: a longitudinal study. *Med Care.* 2008;46(12):1257-1266.

161. Guttmann A, Zagorski B, Austin PC, Schull M, Razzaq A, To T, et al. Effectiveness of emergency department asthma management strategies on return visits in children: a population-based study. *Pediatrics.* 2007;120(6):e1402-1410.

162. Hall AB, Novotny A, Bhisitkul DM, Melton J, Regan T, Leckie M. Association of emergency department albuterol dispensing with pediatric asthma revisits and readmissions. *J Asthma.* 2017;54(5):498-503.

163. Engelkes M, Janssens HM, de Ridder MA, Sturkenboom MC, de Jongste JC, Verhamme KM. Real life data on incidence and risk factors of severe asthma exacerbations in children in primary care. *Respir Med.* 2016;119:48-54.

164. Hanson JR, Lee BR, Williams DD, Murphy H, Kennedy K, DeLurgio Sr SA, et al. Developing a risk stratification model for predicting future health care use in asthmatic children. *Ann Allergy Asthma Immunol.* 2016;116(1):26-30.

165. Johnson LH, Beck AF, Kahn RS, Huang B, Ryan PH, Olano KK, et al. Characteristics of Pediatric Emergency Revisits After an Asthma-Related Hospitalization. *Ann Emerg Med.* 2017;70(3):277-287.

166. Walsh-Kelly CM, Kelly KJ, Drendel AL, Grabowski L, Kuhn EM. Emergency department revisits for pediatric acute asthma exacerbations: association of factors identified in an emergency department asthma tracking system. *Pediatr Emerg Care.* 2008;24(8):505-510.

167. Haselkorn T, Fish JE, Zeiger RS, Szefler SJ, Miller DP, Chipps BE, et al. Consistently very poorly controlled asthma, as defined by the impairment domain of the Expert Panel Report 3 guidelines, increases risk for future severe asthma exacerbations in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. *J Allergy Clin Immunol.* 2009;124(5):895-902.e891-894.

168. Robinson LD, Calmes DP, Bazargan M. The impact of literacy enhancement on asthma-related outcomes among underserved children. *J Natl Med Assoc.* 2008;100(8):892-896.

169. Ahmadizar F, Vijverberg SJ, Arets HG, de Boer A, Lang JE, Kattan M, et al. Childhood obesity in relation to poor asthma control and exacerbation: a meta-analysis. *Eur Respir J.* 2016;48(4):1063-1073.

170. Rust G, Zhang S, Reynolds J. Inhaled corticosteroid adherence and emergency department utilization among Medicaid-enrolled children with asthma. *J Asthma.* 2013;50(7):769-775.

171. Yonas MA, Lange NE, Celedón JC. Psychosocial stress and asthma morbidity. *Curr Opin Allergy Clin Immunol.* 2012;12(2):202-210.

172. Yamamoto N, Nagano J. Parental stress and the onset and course of childhood asthma. *Biopsychosoc Med.* 2015;9:7.

173. Lange NE, Bunyavanich S, Silberg JL, Canino G, Rosner BA, Celedón JC. Parental psychosocial stress and asthma morbidity in Puerto Rican twins. *J Allergy Clin Immunol.* 2011;127(3):734-740.e731-737.

174. Wilhelm M, Meng YY, Rull RP, English P, Balmes J, Ritz B. Environmental public health tracking of childhood asthma using California health interview survey, traffic, and outdoor air pollution data. *Environ Health Perspect.* 2008;116(9):1254-1260.

175. Wang Z, May SM, Charoenlap S, Pyle R, Ott NL, Mohammed K, et al. Effects of secondhand smoke exposure on asthma morbidity and health care utilization in children: a systematic review and meta-analysis. *Ann Allergy Asthma Immunol.* 2015;115(5):396-401.e392.

176. Gold DR, Wright R. Population disparities in asthma. *Annu Rev Public Health.* 2005;26:89-113.

177. Liu SY, Pearlman DN. Hospital readmissions for childhood asthma: the role of individual and neighborhood factors. *Public Health Rep.* 2009;124(1):65-78.

178. Lougheed MD, Lemière C, Dell SD, Ducharme FM, FitzGerald JM, Leigh R, et al. Canadian Thoracic Society Asthma Management Continuum-2010 Consensus Summary for children six years of age and over, and adults. *Can Respir J.* 2010;17(1):15-24.

179. Zorc JJ, Scarfone RJ, Li Y, Hong T, Harmelin M, Grunstein L, et al. Scheduled follow-up after a pediatric emergency department visit for asthma: a randomized trial. *Pediatrics.* 2003;111(3):495-502.

180. Zorc JJ, Chew A, Allen JL, Shaw K. Beliefs and barriers to follow-up after an emergency department asthma visit: a randomized trial. *Pediatrics.* 2009;124(4):1135-1142.

181. Smith SR, Jaffe DM, Highstein G, Fisher EB, Trinkaus KM, Strunk RC. Asthma coaching in the pediatric emergency department. *Acad Emerg Med.* 2006;13(8):835-839.

182. Farber HJ, Oliveria L. Trial of an Asthma Education Program in an Inner-City Pediatric Emergency Department. *Pediatric Asthma, Allergy & Immunology.* 2004;17(2):107-115.

183. Sockrider MM, Abramson S, Brooks E, Caviness AC, Pilney S, Koerner C, et al. Delivering tailored asthma family education in a pediatric emergency department setting: a pilot study. *Pediatrics.* 2006;117(4 Pt 2):S135-144.

184. Gorelick MH, Meurer JR, Walsh-Kelly CM, Brousseau DC, Grabowski L, Cohn J, et al. Emergency department allies: a controlled trial of two emergency department-based follow-up interventions to improve asthma outcomes in children. *Pediatrics.* 2006;117(4 Pt 2):S127-134.

185. Watson WT, Gillespie C, Thomas N, Filuk SE, McColm J, Piwniuk MP, et al. Small-group, interactive education and the effect on asthma control by children and their families. *CMAJ.* 2009;181(5):257-263.

186. Otsuki M, Eakin MN, Rand CS, Butz AM, Zuckerman IH, Ogborn J, et al. Adherence feedback to improve asthma outcomes among inner-city children: a randomized trial. *Pediatrics.* 2009;124(6):1513-1521.

187. Indinnimeo L, Bonci E, Capra L, La Grutta S, Monaco F, Paravati F, et al. Clinical effects of a Long-term Educational Program for children with asthma - Aironet. A 1-yr randomized controlled trial. *Pediatr Allergy Immunol.* 2009;20(7):654-659.
188. Bruzzese JM, Sheares BJ, Vincent EJ, Du Y, Sadeghi H, Levison MJ, et al. Effects of a school-based intervention for urban adolescents with asthma. A controlled trial. *Am J Respir Crit Care Med.* 2011;183(8):998-1006.
189. Gaudreau K, Stryhn H, Sanford C, Cheverie C, Conklin J, Hansen J, et al. Use of emergency departments and primary care visits for asthma related conditions in the 3 years following an asthma education program. *J Asthma.* 2014;51(3):288-293.
190. Kelly CS, Morrow AL, Shults J, Nakas N, Strope GL, Adelman RD. Outcomes evaluation of a comprehensive intervention program for asthmatic children enrolled in medicaid. *Pediatrics.* 2000;105(5):1029-1035.
191. Teach SJ, Crain EF, Quint DM, Hylan ML, Joseph JG. Improved asthma outcomes in a high-morbidity pediatric population: results of an emergency department-based randomized clinical trial. *Arch Pediatr Adolesc Med.* 2006;160(5):535-541.
192. Snyder DA, Thomas OW, Gleeson SP, Stukus DR, Jones LM, Regan C, et al. Reducing emergency department visits utilizing a primary care asthma specialty clinic in a high-risk patient population. *J Asthma.* 2017:1-10.
193. Andrews AL, Teufel RJ, Basco WT. Low rates of controller medication initiation and outpatient follow-up after emergency department visits for asthma. *J Pediatr.* 2012;160(2):325-330.
194. Singal AG, Higgins PD, Waljee AK. A primer on effectiveness and efficacy trials. *Clin Transl Gastroenterol.* 2014;5:e45.
195. Steckler A, McLeroy KR. The importance of external validity. *Am J Public Health.* 2008;98(1):9-10.
196. Gartlehner G, Hansen RA, Nissman D, Lohr KN, Carey TS. Criteria for Distinguishing Effectiveness From Efficacy Trials in Systematic Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2006 Apr. (Technical Reviews, No. 12.) Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK44029/
197. Silverman SL. From randomized controlled trials to observational studies. *Am J Med.* 2009;122(2):114-120.

198. Suissa S. Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol.* 2008;167(4):492-499.
199. Pazzagli L, Linder M, Zhang M, Vago E, Stang P, Myers D, et al. Methods for time-varying exposure related problems in pharmacoepidemiology: An overview. *Pharmacoepidemiol Drug Saf.* 2018;27(2):148-160.
200. Catalogue of Bias Collaboration, Bankhead C, Aronson JK, Nunan D. Attrition bias. Catalogue Of Bias 2017. Retrieved from https://catalogofbias.org/biases/attrition-bias/.
201. Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. *Am J Epidemiol.* 1995;142(12):1255-1264.
202. Régie de l'assurance maladie du Québec. The Régie: Mission. Retrieved from http://www.ramq.gouv.qc.ca/en/regie/Pages/mission.aspx.
203. Public Prescription Drug Insurance Plan. Retrieved from http://www.ramq.gouv.qc.ca/en/citizens/prescription-drug-insurance/Pages/registration-deregistration.aspx.
204. Régie de l'assurance maladie du Québec - Rapport annuel de gestion 2010-2011. Régie de l'assurance maladie du Québec. 2011.
205. Blais L, Vilain A, Kettani FZ, Forget A, Lalonde G, Beauchesne MF, et al. Accuracy of the days' supply and the number of refills allowed recorded in Québec prescription claims databases for inhaled corticosteroids. *BMJ Open.* 2014;4(11):e005903.
206. Delfino RJ, Becklake MR, Hanley JA. Reliability of hospital data for population-based studies of air pollution. *Arch Environ Health.* 1993;48(3):140-146.
207. Blais L, Lemière C, Menzies D, Berbiche D. Validity of asthma diagnoses recorded in the Medical Services database of Quebec. *Pharmacoepidemiol Drug Saf.* 2006;15(4):245-252.
208. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Québec. *J Clin Epidemiol.* 1995;48(8):999-1009.
209. Boulenger S, Castongay J. Portrait de la rémuneration des médecins de 2000 à 2009. Rapport Série Scientifique. Quebec : CIRANO. 2012

210. Ministère de la Santé et des Services Sociaux. Sources de données et metadonnées. Retrieved from http://www.msss.gouv.qc.ca/professionnels/documentation-sources-de-donnees-et-indicateurs/sources-de-donnees-et-metadonnees/med-echo/.
211. Normansell R, Kew KM, Stovold E. Interventions to improve adherence to inhaled steroids for asthma. *Cochrane Database Syst Rev.* 2017;4:CD012226.
212. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Ann Pharmacother.* 2006;40(7-8):1280-1288.
213. Zheng S, Yu Q, Zeng X, Sun W, Sun Y, Li M. The influence of inhaled corticosteroid discontinuation in children with well-controlled asthma. *Medicine (Baltimore).* 2017;96(35):e7848.
214. Pampalon R, Hamel D, Gamache P, Philibert MD, Raymond G, Simpson A. An area-based material and social deprivation index for public health in Québec and Canada. *Can J Public Health.* 2012;103(8 Suppl 2):S17-22.
215. Johnston NW, Johnston SL, Duncan JM, Greene JM, Kedabze T, Keith PK, et al. The September epidemic of asthma exacerbations in children: a search for etiology. *J Allergy Clin Immunol.* 2005;115(1):132-138.
216. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol.* 2004;159(7):702-706.
217. Skelly AC, Dettori JR, Brodt ED. Assessing bias: the importance of considering confounding. *Evid Based Spine Care J.* 2012;3(1):9-12.
218. Becker A, Bérubé D, Chad Z, Dolovich M, Ducharme F, D'Urzo T, et al. Canadian pediatric asthma consensus guidelines, 2003 (updated to December 2004): introduction. *Cmaj.* 2005;173(6 suppl):S12-S14.
219. Harish Z, Bregante AC, Morgan C, Fann CS, Callaghan CM, Witt MA, et al. A comprehensive inner-city asthma program reduces hospital and emergency room utilization. *Ann Allergy Asthma Immunol.* 2001;86(2):185-189.
220. Greineder DK, Loane KC, Parks P. A randomized controlled trial of a pediatric asthma outreach program. *J Allergy Clin Immunol.* 1999;103(3 Pt 1):436-440.

221. Agnihotri NT, Pade KH, Vangala S, Thompson LR, Wang VJ, Okelo SO. Predictors of prior asthma specialist care among pediatric patients seen in the emergency department for asthma. *J Asthma.* 2018:1-7.

222. Flores G, Snowden-Bridon C, Torres S, Perez R, Walter T, Brotanek J, et al. Urban minority children with asthma: substantial morbidity, compromised quality and access to specialists, and the importance of poverty and specialty care. *J Asthma.* 2009;46(4):392-398.

223. Barthwal MS, Katoch CD, Marwah V. Impact of optimal asthma education programme on asthma morbidity, inhalation technique and asthma knowledge. *J Assoc Physicians India.* 2009;57:574-576, 579.

224. Volerman A, Chin MH, Press VG. Solutions for Asthma Disparities. *Pediatrics.* 2017;139(3).

225. Singer AJ, Camargo CA, Lampell M, Lewis L, Nowak R, Schafermeyer RW, et al. A call for expanding the role of the emergency physician in the care of patients with asthma. *Ann Emerg Med.* 2005;45(3):295-298.

226. Schatz M, Zeiger RS, Mosen D, Apter AJ, Vollmer WM, Stibolt TB, et al. Improved asthma outcomes from allergy specialist care: a population-based cross-sectional analysis. *J Allergy Clin Immunol.* 2005;116(6):1307-1313.

227. Shieh G. Power and sample size calculations for comparison of two regression lines with heterogeneous variances. *PLoS One.* 2018;13(12):e0207745.

228. Davis AM, Benson M, Cooney D, Spruell B, Orelian J. A matched-cohort evaluation of a bedside asthma intervention for patients hospitalized at a large urban children's hospital. *J Urban Health.* 2011;88 Suppl 1:49-60.

229. Mudd SS, Ogborn CJ, Bollinger ME, Morphew T, Kub J, Lewis-Land C, et al. Parental decision making associated with pediatric emergency department use for asthma. *Ann Allergy Asthma Immunol.* 2016;117(5):490-494.

230. McGhan SL, Wong E, Sharpe HM, Hessel PA, Mandhane P, Boechler VL, et al. A children's asthma education program: Roaring Adventures of Puff (RAP), improves quality of life. *Can Respir J.* 2010;17(2):67-73.

231. Adams SN, Abel M, Fowler D, Braden J, Ebeling MD, Simpson AN, et al. Inhaled corticosteroid prescribing in a pediatric emergency department: Sustained success and prescription filling rates. *J Asthma.* 2018;55(3):252-258.

232. Zhou Z, Rahme E, Abrahamowicz M, Pilote L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. *Am J Epidemiol.* 2005;162(10):1016-1023.

233. Ducharme FM, Noya F, Rich H, Davis GM, Resendes S, Khomenko L, et al. Randomized controlled trial of a multi-faceted intervention initiated in the emergency department (ED) to improve asthma control. Pediatric Academic Societies. 2009

234. Blais L, Beauchesne MF. Use of inhaled corticosteroids following discharge from an emergency department for an acute exacerbation of asthma. *Thorax.* 2004;59(11):943-947.

235. Tétreault LF, Doucet M, Gamache P, Fournier M, Brand A, Kosatsky T, et al. Severe and Moderate Asthma Exacerbations in Asthmatic Children and Exposure to Ambient Air Pollutants. *Int J Environ Res Public Health.* 2016;13(8).

Appendix I. Ethics approval

Le 22 mars 2016

Docteure Francine Ducharme
CHU Sainte-Justine

Objet	Renouvellement de l'approbation éthique - CÉR
	2009-206, 2779 Impact de la référence systématique des enfants avec une crise d'asthme au Centre d'enseignement sur l'asthme (CEA) et/ou au Centre d'asthme, sur l'utilisation des services de santé et l'adhérence aux médicaments antiasthmatiques prescrits Francisco Noya; Lucie Blais

Docteure,

L'approbation éthique de votre projet cité en rubrique a été renouvelée par le Comité d'éthique de la recherche du CHU Sainte-Justine en date du 02 mars 2016 et les documents suivants ont été approuvés:

- Protocole de recherche non daté

Tous les projets de recherche impliquant des sujets humains doivent être réévalués annuellement. La durée de votre approbation sera effective jusqu'au **02 mars 2017**. Il est de votre responsabilité de soumettre une demande au comité pour que l'approbation éthique soit renouvelée avant la date d'expiration. Il est également de votre responsabilité d'aviser le comité dans les plus brefs délais de toute modification au projet et/ou de tout événement grave et inattendu susceptible d'augmenter le niveau de risque ou d'influer sur le bien-être du participant.

En vous souhaitant une bonne poursuite de votre projet,

Carolina Martin
Conseillère en éthique,
Comité d'éthique de la recherche

CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant

Université de Montréal

Le 23 février 2017

Francine Ducharme
CHU Sainte-Justine

Objet	Renouvellement de l'approbation éthique - CÉR
	2009-206, 2779 Impact de la référence systématique des enfants avec une crise d'asthme au Centre d'enseignement sur l'asthme (CEA) et/ou au Centre d'asthme, sur l'utilisation des services de santé et l'adhérence aux médicaments antiasthmatiques prescrits Co-chercheurs : Francisco Noya; Lucie Blais

Bonjour,

Les membres du comité restreint du Comité d'éthique de la recherche du CHU Sainte-Justine ont examiné votre demande de renouvellement de l'approbation éthique de votre projet cité en rubrique à leur réunion du 15 février 2017. L'approbation éthique de votre projet a été renouvelée par le Comité en date du 15 février 2017 et le document suivant a été approuvé :

- Protocole de recherche non daté

Tous les projets de recherche impliquant des sujets humains doivent être réévalués annuellement. La durée de votre approbation sera effective jusqu'au **15 février 2018**. Il est de votre responsabilité de soumettre une demande au comité pour que l'approbation éthique soit renouvelée avant la date d'expiration. Il est également de votre responsabilité d'aviser le comité dans les plus brefs délais de toute modification au projet et/ou de tout événement grave et inattendu susceptible d'augmenter le niveau de risque ou d'influer sur le bien-être du participant.

En vous souhaitant une bonne poursuite de votre projet,

Carolina Martin
Conseillère en éthique,
Comité d'éthique de la recherche

CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant

Université de Montréal

Le 14 février 2018

Docteure Francine Ducharme
CHU Sainte-Justine

Objet	Renouvellement de l'approbation éthique - CÉR
	2009-206, 2779 Impact de la référence systématique des enfants avec une crise d'asthme au Centre d'enseignement sur l'asthme (CEA) et/ou au Centre d'asthme, sur l'utilisation des services de santé et l'adhérence aux médicaments anti-asthmatiques prescrits. **Co-chercheurs: Lucie Blais; Francisco Noya**

Docteur,

Les membres du comité restreint du Comité d'éthique de la recherche du CHU Sainte-Justine ont examiné votre demande de renouvellement de l'approbation éthique de votre projet cité en rubrique à leur réunion du 07 février 2018. L'approbation éthique de votre projet a été renouvelée par le Comité en date du 07 février 2018 et le document suivant a été approuvé :

- Protocole de recherche non daté

Tous les projets de recherche impliquant des sujets humains doivent être réévalués annuellement. La durée de votre approbation sera effective jusqu'au **07 février 2019**. Il est de votre responsabilité de soumettre une demande au comité pour que l'approbation éthique soit renouvelée avant la date d'expiration. Il est également de votre responsabilité d'aviser le comité dans les plus brefs délais de toute modification au projet et/ou de tout événement grave et inattendu susceptible d'augmenter le niveau de risque ou d'influer sur le bien-être du participant.

En vous souhaitant une bonne poursuite de votre projet,

Carolina Martin
Conseillère en éthique,
Comité d'éthique de la recherche

CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant
Université de Montréal

Le 13 février 2019

Docteure Francine Ducharme
CHU Sainte-Justine

Objet	Renouvellement de l'approbation éthique - CÉR
	2009-206, 2779 Impact de la référence systématique des enfants avec une crise d'asthme au Centre d'enseignement sur l'asthme (CEA) et/ou au Centre d'asthme, sur l'utilisation des services de santé et l'adhérence aux médicaments anti-asthmatiques prescrits. Co-chercheurs: Francisco Noya; Lucie Blais

Docteure,

Les membres du comité restreint du Comité d'éthique de la recherche du CHU Sainte-Justine ont examiné votre demande de renouvellement de l'approbation éthique de votre projet cité en rubrique à leur réunion du 06 février 2019. L'approbation éthique de votre projet a été renouvelée par le Comité en date du 06 février 2019 et le document suivant a été approuvé:

- Protocole de recherche non daté

Tous les projets de recherche impliquant des sujets humains doivent être réévalués annuellement. La durée de votre approbation sera effective jusqu'au **06 février 2020**. Il est de votre responsabilité de soumettre une demande au comité pour que l'approbation éthique soit renouvelée avant la date d'expiration. Il est également de votre responsabilité d'aviser le comité dans les plus brefs délais de toute modification au projet et/ou de tout événement grave et inattendu susceptible d'augmenter le niveau de risque ou d'influer sur le bien-être du participant.

En vous souhaitant une bonne poursuite de votre projet,

Carolina Martin
Conseillère en éthique,
Comité d'éthique de la recherche

Appendix II. Hospital diagnostic codes

Asthma and asthma-like hospital diagnostic codes
0403 Asthma/reactive airway disease
0437 Asthma and Otitis
0438 Asthma and pneumonia
0442 Allergic rhinitis and asthma
0405 Bronchiolitis
0406 Bronchitis
0407 Bronchospasm

Appendix III. Preliminary analyses of diagnostic codes

1. Global concordance between diagnostic codes from the RAMQ medical services database and the hospital ED visits database

The following analyses were performed in the 16,016 children aged 0 to 17 years old who had an index ED visit with a valid (non-missing) ICD-9 diagnostic code between 2001-01-01 and 2006-12-31.

The following diagnostic codes were used:

Eligible ICD-9 diagnostic codes from the RAMQ medical services database

-asthma (ICD-9: 493)

If ≥1 year old :

-acute bronchiolitis (ICD-9: 466.1)

-bronchospasm (ICD-9: 519.1)

-acute bronchitis (ICD-9: 466.0) or bronchitis not specified as acute or chronic (ICD-9: 490.9)

Eligible hospital diagnostic codes

-asthma (0403, 0437, 0438, 0442)

If ≥1 year old :

-bronchiolitis (0405)

-bronchospasm (0407)

-bronchitis (0406)

Results:

-Of the 8599 patients with an index ED visit with an eligible hospital diagnostic code, 73% also had an eligible ICD-9 diagnostic code

-Of the 6642 patients with an index ED visit with an eligible ICD-9 diagnostic code, 94.4% also had an eligible hospital diagnostic code

2. Predictive value analysis

The following table shows the proportion of patients aged 1 to 17 years old who experienced subsequent medical visit with an asthma diagnosis (ICD-9: 493) in the year following an index ED visit with an asthma-like diagnosis.

Asthma-like diagnosis code at the index ED visit	Results
acute bronchiolitis (ICD-9: 466.1) n=854	42% of patients (360/854) experienced a medical visit with an asthma diagnosis (ICD-9: 493) in the subsequent year
bronchospasm (ICD-9: 519.1) n=210	61% of patients (127/210) experienced a medical visit with an asthma diagnosis (ICD-9: 493) in the subsequent year
acute bronchitis (ICD-9: 466.0) or bronchitis not specified as acute or chronic (ICD-9: 490.9) n=72	53% of patients (38/72) experienced a medical visit with an asthma diagnosis (ICD-9: 493) in the subsequent year

Appendix IV. Complete Cox proportional hazards model for the main outcome in the unselected cohort

	n=9399
Variable	**Hazard Ratio (95% CI)**
DEMOGRAPHICS	
Intervention exposure	
AEC and SAC	1.21 (0.99-1.48)
AEC only	1.47 (1.17-1.84)
SAC only	1.09 (0.95-1.24)
none	reference
Male sex	1.03 (0.96-1.11)
Age at index ED visit	0.91 (0.90-0.93)
Age*time	1.00 (1.00-1.00)
Pampalon material deprivation index	
1st quintile (most privileged)	reference
2nd or 3rd quintile	1.39 (0.95-2.05)
2nd or 3rd quintile *log(time)	0.92 (0.85-1.00)
4th or 5th quintile	1.12 (1.01-1.24)
Pampalon social deprivation index	
1st quintile (most privileged)	reference
2nd or 3rd quintile	1.02 (0.92-1.12)
4th or 5th quintile	1.05 (0.97-1.14)
MORBIDITY IN THE PRECEDING 12 MONTHS	
Atopy	1.29 (1.16-1.45)
Atopy *$(time)^2$	1.00 (1.00-1.00)
1 asthma/asthma-like ED visit	1.35 (1.15-1.59)
1 asthma/asthma-like ED visit *(time)	1.00 (1.00-1.00)
≧2 asthma/ asthma-like ED visit	2.89 (2.46-3.41)
1 or more Hospital admissions	1.12 (0.93-1.34)
INDEX ED VISIT CHARACTERISTICS	
Diagnosis	
asthma	1.07 (0.97-1.18)
asthma-like	reference
Season	
winter	1.31 (1.18-1.45)
spring	1.24 (1.10-1.40)
fall	1.17 (1.06-1.29)
summer	reference
Canadian Triage and Acuity Scale	
Triage 1-2 (most urgent)	2.15 (1.88-2.47)

Triage 3	1.55 (1.31-1.82)
Triage 3 *(time)	1.00 (1.00-1.00)
Triage 4-5 (less urgent)	reference
Disposition	
Hospital admission	1.06 (0.97-1.17)
Discharge	reference
FOLLOW-UP SEASON	
winter	0.95 (0.85-1.05)
spring	0.59 (0.52-0.66)
fall	1.36 (1.23-1.49)
summer	reference

Appendix V. Complete Cox proportional hazards model for the main outcome in patients with an alternative definition of asthma

	n=699
Variable	**Hazard Ratio (95% CI)**
DEMOGRAPHICS	
Intervention exposure	
AEC and SAC	0.41 (0.31-0.55)
AEC only	0.77 (0.57-1.03)
SAC only	0.84 (0.58-1.20)
none	reference
Male sex	0.97 (0.79-1.19)
Age at index ED visit	0.92 (0.88-0.95)
Age*time^2	1.00 (1.00-1.00)
Pampalon material deprivation index	
1st quintile (most privileged)	reference
2nd or 3rd quintile	0.87 (0.66-1.15)
4th or 5th quintile	0.81 (0.62-1.06)
Pampalon social deprivation index	
1st quintile (most privileged)	reference
2nd or 3rd quintile	0.84 (0.61-1.16)
4th or 5th quintile	0.91 (0.73-1.13)
MORBIDITY IN THE PRECEDING 12 MONTHS	
Atopy	1.53 (1.21-1.94)
1 asthma/asthma-like ED visit	1.20 (0.94-1.52)
≥2 asthma/ asthma-like ED visit	2.21 (1.54-3.16)
1 or more Hospital admissions	1.11 (0.74-1.67)
INDEX ED VISIT CHARACTERISTICS	
Diagnosis	
asthma	0.95 (0.67-1.36)
asthma-like	reference
Season	
winter	1.19 (0.89-1.58)
spring	1.65 (1.14-2.40)
fall	1.18 (0.89-1.56)
summer	reference
Canadian Triage and Acuity Scale	
Triage 1-2 (most urgent)	2.14 (1.18-3.86)

Triage 1-2 *(time)	1.00 (1.00-1.00)
Triage 3	1.29 (0.79-2.12)
Triage 4-5 (less urgent)	reference
Disposition	
Hospital admission	0.47 (0.37-0.60)
Discharge	reference
FOLLOW-UP SEASON	
winter	1.01 (0.75-1.34)
spring	0.63 (0.45-0.88)
fall	1.39 (1.06-1.82)
summer	reference

Appendix VI. Complete Cox proportional hazards model for the main outcome in the subcohort covered by the public prescription drug plan

	n=414
Variable	**Hazard Ratio (95% CI)**
DEMOGRAPHICS	
Intervention exposure	
AEC and SAC	0.30 (0.19-0.47)
AEC only	0.58 (0.37-0.90)
SAC only	0.96 (0.60-1.54)
none	reference
Male sex	0.94 (0.72-1.23)
Age at index ED visit	0.93 (0.89-0.97)
Pampalon material deprivation index	
1st quintile (most privileged)	reference
2nd or 3rd quintile	1.37 (0.88-2.13)
4th or 5th quintile	1.18 (0.78-1.79)
Pampalon social deprivation index	
1st quintile (most privileged)	reference
2nd or 3rd quintile	0.85 (0.57-1.26)
4th or 5th quintile	0.89 (0.67-1.20)
MORBIDITY IN THE PRECEDING 12 MONTHS	
Atopy	1.02 (0.75-1.39)
PPACI in the preceding 6 months	
PPACI 1 (controlled)	reference
PPACI 2 (partly controlled)	0.93 (0.59-1.47)
PPACI 3 (not well controlled)	1.17 (0.88-1.55)
PPACI 4 (very poorly controlled)	1.09 (0.60-1.99)
INDEX ED VISIT CHARACTERISTICS	
Diagnosis	
asthma	0.69 (0.49-0.99)
asthma-like	reference
Season	
winter	1.09 (0.74-1.60)
spring	1.88 (1.17-3.01)
fall	1.62 (1.16-2.24)
summer	reference
Canadian Triage and Acuity Scale	
Triage 1-2 (most urgent)	0.70 (0.12-3.97)
Triage 1-2 *log(time)	1.16 (0.78-1.74)
Triage 3	0.49 (0.26-0.93)

Triage 3 *(time)	1.01 (1.00-1.01)
Triage 4-5 (less urgent)	reference
Disposition	
Hospital admission	0.42 (0.31-0.57)
Discharge	reference
FOLLOW-UP SEASON	
winter	1.38 (0.96-1.98)
spring	0.96 (0.63-1.48)
fall	1.47 (1.02-2.11)
summer	reference

Appendix VII. Distribution of the number of ED visits per patient in the 12 months preceding and the 12 months following the index ED visit

		Intervention exposure			
		AEC and SAC n=563	AEC only n=234	SAC only n=97	None n=339
Number of ED visits in the 12 previous months	No ED visit	440 (78.15%)	192 (82.05%)	81 (83.51%)	272 (80.24%)
	1 ED visit	98 (17.41%)	34 (14.53%)	12(12.37%)	52 (15.34%)
	2 ED visits	25 (4.44%)	8 (3.42%)	4 (4.12%)	15 (4.42%)

		Intervention exposure			
		AEC and SAC n=563	AEC only n=234	SAC only n=97	None n=339
Number of ED visits in the 12 subsequent months	No ED visit	223 (39.61%)	91 (38.89%)	35 (36.08%)	153 (45.13%)
	1 ED visit	146 (25.93%)	65 (27.78%)	32 (32.99%)	90 (26.55%)
	2 ED visits	194 (34.46%)	78 (33.33%)	30 (30.93%)	96 (28.32%)