The Accuracy of Epidemiologic Definitions of Childhood Asthma Using a Clinical Reference Standard

by

Connie Yang

A thesis submitted in conformity with the requirements for the degree of Masters of Medical Science

Institute of Medical Sciences
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Abstract

This study determined the sensitivity and specificity of questionnaires and administrative databases compared to a clinical reference standard for asthma.

208 schoolchildren from a population-based sample participated. They underwent a physician assessment, spirometry, methacholine challenge, exhaled nitric oxide and skin testing. Data was linked to the Ontario Asthma Surveillance Information System.

“Questionnaire diagnosis” was an affirmative response to physician-diagnosed asthma. “Database diagnosis” was 2 outpatient visits or 1 hospitalization within 2 years. “Clinical diagnosis” required a physician assessment and objective findings of asthma.

“Questionnaire diagnosis” of asthma was specific (92.1%) but not sensitive (75.3%) compared to the “clinical diagnosis”. “Database diagnosis” was sensitive (87.5%) but not specific (64.8%). Both sources had an excellent negative predictive value (97-98%) but poor positive predictive value (24-55%).

Epidemiologic methods accurately identify those without asthma but are poor at identifying those with asthma, leading to an overestimation of asthma prevalence and dilution of risk estimates.
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Abbreviations used

ATS – American Thoracic Society
BHR - bronchial hyperreactivity
CTSE - Council of State and Territorial Epidemiologists
FDA – Food and Drug Administration
FEF25-75 – Forced expiratory flow between 25 and 75% of the forced vital capacity
FEV1 – Forced expiratory volumes in 1 second
FVC – Forced Vital Capacity
ICD 10 – International Classification of Diseases version 10
ISAAC – International Study of Asthma and Allergies in Childhood
IUATLD – International Union Against Tuberculosis and Lung Disease
J – Youden`s index (sensitivity + specificity -1 )
MMEF – Maximal mid-expiratory flow (synonym for FEF25-75)
MHSIP – Manitoba Health Services Insurance Plan
NLR – Negative likelihood ratio
NPV – Negative predictive value
T-CHEQ – Toronto Child Health Evaluation Questionnaire
MCH – Methacholine
OASIS – Ontario Asthma Surveillance Information System
PC20 – Provocative concentration causing a 20% decrease in the forced expiratory volume in 1 second
PD20 – Provocative dose causing a 20% decrease in the forced expiratory volume in 1 second
PLR – Positive likelihood ratio
PPV – Positive predictive value
ROC – receiver operator curve
SD – standard deviation
Chapter 1
Introduction

1.1 Definition and pathophysiology of asthma

The constellation of symptoms that define asthma was initially described in the 17\textsuperscript{th} century\textsuperscript{2} by Floyer who described “laborious respirations with lifting of the shoulders and wheezing”. Asthma is now considered a disease that is characterized by persistent or intermittent symptoms of wheezing, cough and shortness of breath\textsuperscript{3}. The symptoms are secondary to airway narrowing from bronchoconstriction, edema, excess mucous and airway hyperresponsiveness and are mediated by inflammation\textsuperscript{4}. Asthma encompasses a wide spectrum of disease severity from mild intermittent bronchoconstriction to airway remodelling secondary to inflammation.

\textit{Figure 1: Pathophysiology of asthma}\textsuperscript{4}

The airways contain smooth muscle, connective tissue, goblet cells and epithelial cells. Adjacent to the airway is the pulmonary vasculature which is lined by endothelial cells. Each of these has a role in the pathogenesis of asthma. Airway smooth muscle contracts in response to stimuli and causes bronchoconstriction, which is the target for beta-agonists and anticholinergic agents. Smooth muscle cells undergo hypertrophy and hyperplasia in response to inflammation. Microvascular leak through endothelial cells causes airway edema which further narrows airways. Goblet cells are more abundant in asthma and produce mucous which can occlude the airways and cause atelectasis. Undifferentiated connective tissue (mesenchyme) and mature cells (fibroblasts and myofibroblasts) produce collagen, proteoglycans, laminin and fibronectin which are deposited beneath the basement membrane in the lamina reticularis. This was thought to correlate with disease duration however it is also seen in children with asthma\textsuperscript{5}, and interestingly also in atopic individuals with asymptomatic bronchial hyperreactivity\textsuperscript{6}. Dysfunctional airway epithelium is
now thought to play a central role in the development of asthma and allergic diseases. The current paradigm suggests that the barrier function provided by the epithelial cell tight junctions is altered due to a failure to repair itself following injury\textsuperscript{7}. Respiratory viruses and allergens are examples of insults that have been shown to alter tight junctions\textsuperscript{7}.

Asthma was initially thought to be a disease of intermittent bronchospasm which is why early treatment consisted solely of bronchodilators. In the 1970s and 80s, understanding of how allergic triggers could induce inflammation led to a greater understanding of how inflammatory cells and cytokines were involved in the pathogenesis of asthma. T-cells are felt to have an important role in the development of asthma as they develop into Th1 or Th2 dominant profiles. Th-2 cells mediate allergic inflammation; they potentiate IgE production and also produce interleukin 4, 5 and 13 which have been found in higher concentrations in asthmatic airways compared to controls\textsuperscript{8}. IgE-induced degranulation of mast cells leads to the release of histamine, and leukotrienes which interact with airway smooth muscle to cause bronchoconstriction. Eosinophils also release leukotrienes and mediators such as major basic protein that damage epithelial cells and cause degranulation of mast cells\textsuperscript{8}. Although asthma is often thought of as eosinophilic inflammation, a different phenotype that seems to feature neutrophilic inflammation has been described\textsuperscript{9} and neutrophils are also thought to play a role in acute exacerbations in children\textsuperscript{10}.

1.2 The Importance of Diagnosing Asthma

From a clinical standpoint, establishing a diagnosis of asthma is important because it can lead to specific treatment which alleviates symptoms, improves quality of life, and possibly prevents long term damage. Environmental factors such as allergens, cigarette smoke or airborne pollution are known to increase asthma symptoms. Educating patients about these potential triggers and ways to avoid them when possible is an important first step in asthma therapy; and tailored environmental changes have been shown to decrease asthma symptoms\textsuperscript{4, 11, 12}. Inhaled corticosteroids currently form the backbone of treatment for persistent asthma and have been shown to decrease exacerbations, symptoms, and improve quality of life\textsuperscript{13}. The non-adherence rate for taking regular asthma medication is estimated to be as high as 50\textsuperscript{14}, and is supported by the observation that many with difficult to treat asthma improve dramatically during trial run-in periods when the only intervention is ensuring compliance\textsuperscript{15}. To improve adherence it is important that patients are
educated about the symptoms of asthma and the need for treatment, which is difficult to do if patients don’t have a formal diagnosis. Asthma treatment is not benign and inhaled corticosteroids are known to transiently decrease growth velocity\textsuperscript{13} and in rare cases to cause adrenal suppression\textsuperscript{16}. Alarming, in a UK Survey, 6 of the 31 patients with an adrenal crisis secondary to inhaled corticosteroids did not even have asthma\textsuperscript{17}. Therefore ruling out a diagnosis of asthma can be equally important as it prevents side-effects from unnecessary medication.

The role of medication in the prevention of long-term airway obstruction in asthma is more controversial. The CAMP trial included 1041 children with mild to moderate asthma and it did not show any difference in post-bronchodilator FEV1 in the corticosteroid group versus the placebo group at the end of the 4 to 6 year treatment period.\textsuperscript{13} However another study did show that treatment with budesonide had a protective effect on lung function following a severe exacerbation in comparison to placebo\textsuperscript{18}.

From the research perspective, a better understanding of the pathophysiologic mechanisms of asthma has led to novel treatments\textsuperscript{19} and in the future, will hopefully lead to primary prevention\textsuperscript{20}. The expression of an asthma phenotype requires a complex interaction between an individual and their environment. Epidemiologic research which is the “distribution and determinants of health and disease in groups”\textsuperscript{21} has attempted to untangle this complex interaction and find factors associated with asthma and mediators of asthma severity. In a recent medline search there were over 10000 articles published about asthma epidemiology from 1948 to the present, with over 60% of those published in the last ten years. This type of research has helped us understand the importance of different allergens, identify potential candidate genes\textsuperscript{22}, and understand risk factors for the persistence of symptoms\textsuperscript{23}. Epidemiologic studies have also provided insights into the natural history\textsuperscript{24, 25} and prognosis of subjects with asthma and it is from these studies that wheezing phenotypes in preschool children and adults were elucidated\textsuperscript{9, 26}. The identification of these subtypes is important as different factors may only increase the risk of certain asthma phenotypes. One example of this is the increased risk of wheezing with prenatal smoke exposure, which increases wheezing during infancy but not later in life.\textsuperscript{27}.

From a societal standpoint, accurately estimating the prevalence of asthma allows us to assess disease burden and plan for resource allocation\textsuperscript{28}. In addition, examining patterns of healthcare use (ie. emergency room versus outpatient clinics, medication usage\textsuperscript{29, 30}), can be a barometer for the quality of care that asthma patients are receiving. This type of research can also determine
targets for educational programs, such as preventing the peak of asthma hospitalizations that occurs in September\textsuperscript{31}.

1.3 Diagnosis of asthma in the clinical setting

“Asthma is like love; we all know what it is but no one really trusts anyone else’s definition”\textsuperscript{32}.

There is no gold standard test for the diagnosis of asthma. Many international asthma guidelines\textsuperscript{3, 4, 33-36} exist which provide recommendations on how a diagnosis of asthma should be made. These guidelines often divide pediatric patients into two age groups: those under the age of five, and those over the age of five. This is done for two reasons: 1) Objective measures of lung function are not clinically available for children under the age of five, and 2) There are many phenotypes of recurrent wheezing in younger children and there is no consensus as to which of these phenotypes should be diagnosed as asthma.

*Children less than five years of age*

The topic of recurrent wheezing in infants and toddlers and its relationship to asthma is a contentious one. The difficulty in this age group is that wheezing, which is the hallmark of asthma, is seen in up to 50% of children by the age of 6\textsuperscript{37}. However, over 50% of those with wheezing before the age of 3 will not have wheezing later in life. Should those transient wheezers be labelled as having asthma? Some guidelines\textsuperscript{38} advocate the terminology “preschool wheezing” as opposed to asthma because of this dilemma. Others continue to use the term asthma and use it to describe those with frequent wheezing with a personal or family history of atopy. They do acknowledge that because viral-induced wheezing is common in this age group, differentiating this from asthma is difficult\textsuperscript{39}. Still others use the term asthma for all children with recurrent wheezing but divide it into atopic asthma which is likely to persist, and non-atopic asthma which is more likely to remit\textsuperscript{3, 26}. Given the difficulties with prognosticating outcomes in early wheezers, some simply divide this group by phenotype into those with “multi-trigger wheeze” and “viral wheeze” although acknowledge that children can move between categories.\textsuperscript{38} The controversy is more than just semantics. These young children do not always respond to typical asthma therapy such as inhaled corticosteroids, which has led to the speculation that there may be a different pathophysiology to these symptoms\textsuperscript{38}. Amongst those who advocate diagnosing asthma in this age group, the diagnosis is based on a history of recurrent wheeze or cough, and improvement of
these symptoms with asthma medication. Given the known association with allergic disease, the diagnosis is more likely if there is a personal or family history of atopy.

*Children greater than five years of age*

In children over the age of five, diagnosing asthma is similar to recommendations for adults. A history of episodic wheeze, shortness of breath, chest tightness or cough associated with evidence of reversible airway obstruction forms the basis of the diagnosis\(^4\). All guidelines recommend spirometry to assess for reversible obstruction, however it is a necessary requirement in only some guidelines\(^4, 35, 40, 41\). Other guidelines only suggest spirometry if there is no improvement after a trial of treatment\(^34\). The diagnosis is also supported by a personal or family history of atopy and an improvement in symptoms with asthma treatment. Other conditions that present with similar symptoms such as reflux or vocal cord dysfunction should also be excluded before a diagnosis is made. Further testing such as bronchial hyperreactivity testing with methacholine, exercise or mannitol is recommended in cases where spirometry is normal, there is no improvement after treatment and there is still diagnostic uncertainty.

1.3.1 The clinical history and physical exam

Wheezing, which is defined as a high-pitched whistling noise that typically occurs in expiration, is the most specific symptom of asthma. It reflects the turbulent sound of air passing through narrowed intrathoracic airways\(^42\). Unfortunately, wheezing is not always audible without a stethoscope and therefore may be underappreciated by patients and their families. In addition, wheezing is a commonly-used term that often has a different meaning between families and healthcare providers. In a study involving 96 children with noisy breathing, wheezing was used by 53% of parents to describe the respiratory sound however after further clarification and demonstration, this number decreased to 36%\(^43\). Another study involving patients referred to a respirology clinic found there was only 45% agreement between parents and physicians regarding the presence of wheeze, with 39% of parents under-reporting wheeze, and 14% over-reporting wheeze\(^44\). Another study found that 60% of parents correctly identified wheezing on a video clip and 8% identified another sound as wheezing\(^45\). Some of this confusion stems from the less than perfect agreement amongst physicians regarding the presence of wheeze. One study used digital recordings of chest sounds in infants and found that the kappa was 0.73 amongst 5 pediatric pulmonologists for the identification of wheeze\(^46\).
Coughing is a symptom that is easier to appreciate however is far less specific for asthma. Coughing can be present along with wheezing and breathlessness but it can also be a precursor to those symptoms\textsuperscript{47}. The term “cough variant asthma” was coined in 1979 and was used to describe six adults who presented with cough and had a positive methacholine challenge, whose symptoms resolved 48 hours after treatment with theophylline and reappeared after the medication was discontinued\textsuperscript{48}. In that case series, two of the six patients went on to develop wheezing within 18 months of completing the study. In 1982, this phenomenon was described in a series of 32 atopic children with chronic cough without wheeze, normal spirometry and a response to bronchodilators. Although these children were reported to have isolated cough, one third of them had prolonged expiration or wheeze on forced expiration suggesting that there was already evidence of classic asthma at that point\textsuperscript{49}. In a two year follow-up of 24 of the children, 18 had developed “overt asthma”\textsuperscript{49}. These studies suggest that isolated cough is a common early presentation of asthma; however in a community study of children with recurrent coughing who were followed for three years, only 7% went on to develop wheezing, which was not different from the 10% of asymptomatic children that developed wheezing\textsuperscript{50}. With the increased awareness of cough-variant asthma, the diagnosis of asthma in those with cough as the only symptom was shown to double from 12% in 1991 to 25% in 1993 in one study\textsuperscript{51}. The history of night cough, or cough brought on by known asthma triggers is suggestive of cough variant asthma. Unfortunately the accuracy of reporting for nocturnal cough by parents in comparison to tape-recorded counts has been shown to be low (kappa 0.3)\textsuperscript{52}. The diagnosis of cough variant asthma relies on the disappearance of cough with asthma treatment, although it is important to verify this by withdrawing the medication and observing if the cough reappears. This is because the placebo effect with cough treatment is high, likely due to the spontaneous resolution of most causes of cough\textsuperscript{53}. In addition, in those with asthma, the frequency of cough does not correlate with measures of lung function or with treatment, leading to the hypothesis that there are different underlying mechanisms for cough and wheeze in asthma\textsuperscript{54}. This helps to explain why positive bronchial hyperreactivity tests do not predict which patients with cough will respond to bronchodilator therapy\textsuperscript{55}.

Another aspect of the history is if the symptoms are triggered by known allergens or irritants. In children, viral illness is the most common trigger but unfortunately even in healthy children viral illnesses are accompanied by respiratory symptoms and it can be difficult to differentiate when these symptoms are pathologic. Another common trigger for symptoms in children is exercise.
Again one of the difficulties is that exercise places a stress on the respiratory system even in health because of the need to increase minute ventilation which is accompanied by increased work of breathing and fatigue. These symptoms can be perceived as pathologic in children and their parents. In a study of 52 children referred for uncontrolled exercise-induced asthma, only 15% were found to have exercise-induced bronchoconstriction whereas 23% were deconditioned and the others had vocal cord dysfunction, habit cough or no final diagnosis\textsuperscript{56}. This study clearly illustrates that a history of exercise-induced symptoms has poor specificity for asthma. This phenomenon also occurs in elite athletes who continually push themselves to the limits of their capabilities. In the aforementioned study, all 8 children who were elite athletes had normal exercise challenges\textsuperscript{56}. Interesting in a study of high performance athletes the discrepancy between symptoms and bronchial hyperreactivity (BHR) was most common in winter athletes, who commonly reported exercise-induced cough despite having no BHR (even after eucapneic hyperventilation)\textsuperscript{57}. This suggests that children who are diagnosed with asthma on the basis of coughing with cold weather exposure may be significantly overdiagnosed.

Another characteristic that is used in the diagnosis of asthma, is the symptomatic relief of symptoms with bronchodilator medication\textsuperscript{3, 4, 34, 58}. Unfortunately as was recently shown, the same improvement in symptoms was reported by patients whether they received a bronchodilator, a placebo inhaler or sham acupuncture for a week, which again highlights the subjective nature of respiratory symptoms and the need for objective testing\textsuperscript{59}.

Asthma often presents with intermittent symptoms, therefore, the physical examination is often normal unless patients are seen during periods of exacerbation. Findings consistent with asthma include wheezing and when more severe decreased air entry, chest hyperinflation and increased work of breathing. Given the increased risk of asthma in those with allergic disease, skin findings consistent with eczema (dry patches of skin, lichenification) or allergic rhinitis (nasal crease, enlarged pale turbinates) should be noted.

Perhaps the most important aspect of the clinical diagnosis of asthma is longitudinal followup. Given the intermittent nature of symptoms, it is very useful for patients to return to their physicians when they are having symptoms so that parental-reported wheeze or increased work of breathing can be confirmed by a physician. In addition, improvement in wheezing with beta-agonists can be documented by auscultation or spirometry.
1.3.2 The role of pulmonary function tests

Given the subjective nature of respiratory symptoms and the difficulty in obtaining an accurate history of respiratory signs and symptoms, objective measures are needed to confirm a diagnosis of asthma.

Spirometry is a simple test that can be performed reliably in children over five years of age\textsuperscript{41}. There are standardized\textsuperscript{60} methods for performing and recording the results to ensure that a reliable test is produced. The forced expiratory volume in the 1\textsuperscript{st} second (FEV\textsubscript{1}) and the forced vital capacity (FVC) are directly measured, and from this other indices such as the maximal mid-expiratory flow (MMEF, also termed the FEF\textsubscript{25-75}\% mean forced expiratory flow between 25 and 75\% of the FVC) can be derived. The derived indices are less robust as they are dependent on the expiratory effort\textsuperscript{60}. Findings consistent with asthma on spirometry include: an FEV\textsubscript{1}/FVC ratio and FEV\textsubscript{1} less than the 5\%ile of the reference standard and a concave flow-volume loop\textsuperscript{61}. FEV\textsubscript{1} is the most reproducible measure and is therefore most often used in clinical studies. Unfortunately, FEV\textsubscript{1} is an insensitive measure as it is normal in 77 to 90\% of children with stable asthma, irregardless of asthma severity\textsuperscript{62, 63}. The FEV\textsubscript{1}/FVC has been found to more sensitive in differentiating between different levels of asthma severity but was still normal in 67\% of children with asthma\textsuperscript{64}. The FEF\textsubscript{25-75} was abnormal in 66\% of children with asthma compared with 41\% and 56\% for FEV\textsubscript{1} and FEV\textsubscript{1}/FVC respectively\textsuperscript{65}. Unfortunately the coefficient of repeatability for the FEF\textsubscript{25-75} is 13\% which is much higher than for the FEV\textsubscript{1} which is only 5\%\textsuperscript{61}. Spirometry is often normal in children with asthma because it is measured at one point in time often when they are stable; and in comparison to adults, children do not have baseline obstruction\textsuperscript{63}.

Peak flow meters are an attractive alternative to spirometry because these simple devices can be used at home and therefore multiple measures over time can be assessed. Unfortunately peak expiratory flow is highly effort and device dependent, and therefore standardized normal values are not helpful and comparisons are instead made to the patient’s personal best peak flow value. Given the decreased reliability of peak flow measurements particularly in untrained subjects, some guidelines do not recommend them for the diagnosis of asthma\textsuperscript{4}, while some guidelines recommend them as an alternative to spirometry\textsuperscript{33, 41}. A peak flow variability of $>20\%$ is used to diagnose asthma based on a previous study which found that subjects without asthma had a mean peak flow variability of 8.3\% with a sample standard deviation of 5.2\%\textsuperscript{66}. Few prospective studies have been done to evaluate the accuracy of peak flow variability in the diagnosis of asthma.
One study found that using a 20% variability led to a sensitivity of 0% although a specificity of 100% \(^6^7\). Changes in peak flows have not been shown to correlate well with changes in symptoms, FEV1 or FEF25-75, which is why it is not widely recommended for asthma action plans\(^6^8\). This is more pronounced in those with air trapping (RV/TLC >30%) and the negative predictive value of a normal peak flow for FEV1 or FEF2575 in this group was only 53% \(^6^9\).

Given the insensitivity of spirometry and peak flow variability for the diagnosis of asthma in children, further diagnostic tests are often needed. One method for improving the sensitivity of spirometry is to attempt to induce bronchoconstriction in the airways and then repeat spirometry, which is the principle behind tests of bronchial hyperreactivity.

### 1.3.3 Measures of bronchial hyperreactivity

Airway hyperreactivity is considered by some to be necessary but not sufficient for the expression of asthma. If one looks at how asthma is defined in treatment studies for older children, objective evidence of reversible obstruction on spirometry or a positive bronchial hyperreactivity test is always used in addition to a symptom history to define the asthma population \(^7^0, 7^1\). In addition, the presence of bronchial hyperreactivity in subjects with asthma symptoms has been found to identify a group that is more likely to have persistent symptoms, require hospitalization, have airway remodeling, and have sleep disturbance or activity limitation secondary to their asthma \(^7^2, 7^3, 7^4\).

Bronchial hyperreactivity can be tested using different stimuli that directly or indirectly stimulate the respiratory tract. Direct stimuli interact with receptors in the airway smooth muscle; whereas, indirect stimuli cause mediators to be released from cells which then interact with the respiratory tract. The outcome variable used for bronchial hyperreactivity testing is the FEV1 because it is the most repeatable of the pulmonary function parameters \(^5^1\). It is measured 30 seconds and 90 seconds after the completion of each dose according to ATS criteria, although the exhalation time can be shortened to 2 seconds compared to the standard 6 seconds \(^7^5\).

When pharmacologic agents (such as methacholine or mannitol) are used, a dose response curve is generated which has the log dose on the x-axis and the FEV1 on the y-axis. The log dose is used because the PC20/PD20 is distributed in a log-normal fashion in the general population \(^7^6\). There are different cutoffs depending on the test used. For methacholine and histamine, a 20% decrease from baseline is considered a positive test (PC20=provocative concentration causing a 20%
decrease, PD20=provocative dose causing a 20% decrease); for mannitol and hypertonic saline a 15% decrease is used and for exercise challenges a 10 to 15% decrease is used. A 20% decrease in FEV1 is often used because the coefficient of repeatability for FEV1 when repeated over weeks is 12% in normal subjects. The PC20 is more easily calculated than the PD20. For exercise tests, a drop of 10% is considered abnormal because the physiologic response to exercise is bronchodilation. The repeatability of the methacholine challenge in stable subjects is +/- 1.5 doubling doses.

1.3.3.1 Indirect versus direct challenges
Substances that are used clinically for direct challenges are methacholine and histamine which have dose-equivalency for causing bronchoconstriction. In North America, methacholine is more widely used and has fewer side effects, such as cough, throat irritation, and headache, flushing and hoarseness. Methacholine (acetyl-beta-methylcholine chlorine) is a dry crystalline powder and is approved by the FDA for human use. It is a synthetic version of acetylcholine, which is a naturally produced neurotransmitter, and it is also broken down by cholinesterase. Therefore, the effects of methacholine are lessened with anticholinergic agents and are prolonged by cholinesterase inhibitors. It’s onset of action is two minutes, and its effects last 75 minutes.

Indirect challenges can be performed using exercise, dry air (via eucapneic hyperventilation), mannitol, and hypertonic saline which cause histamine, prostaglandins, and leukotrienes to be released from mast cells.

1.3.3.2 Methods for performing the methacholine challenge
The two techniques most widely used in North America and Europe for performing a methacholine challenge are the two-minute tidal breathing technique and the five breath dosimeter technique. The Yan technique is not used clinically as it is less reproducible with inexperienced subjects however it will be described briefly as it is often used in epidemiologic studies.

The two-minute tidal technique uses a nebulizer that produces particles with a mass median diameter of 1 to 3.6um with enough flow to maintain an output of 0.13ml/min (+/- 10%). Ten concentrations of methacholine (0.03mg/mL to 16mg/ml) are delivered in doubling doses, although in research studies, maximal doses of 64mg/ml have been used. This method is said to deposit 0.09cc of methacholine below the cords for each dose. This technique can take up to one hour if all doses are administered; therefore, a shortened protocol has been published which
increases the starting dose up to 1mg/mL in patients with an FEV1 ≥ 70%, an FEV1/FVC ≥ 80% and no response to saline. It also allows doses to be skipped if there is a less than 5% decrease in FEV1. This shortened method has been shown in a retrospective study to be safe.

The dosimeter technique uses a nebulizer that delivers 9uL (0.009mL) +/- 10% per 0.6 second actuation. Five doses of methacholine are delivered (concentrations 0.06mg/ml to 16mg/ml) in quadrupling doses. The dose is administered by the dosimeter soon after inhalation begins, and the subjects slowly inhales to total lung capacity and performs a 5 second breath hold before exhaling. This is repeated five times per concentration and is said to deposit 0.03cc of methacholine below the cords for each dose.

These two techniques are said to produce equivalent results in both the ATS and European guidelines on methacholine challenges. This is despite the different volumes of methacholine deposited and the potential for bronchodilation with deep inspiration present in the dosimeter technique. However, further studies have shown that the five breath dosimeter technique is less sensitive for detecting airway hyperreactivity and results in a difference of up to one doubling dose between the methods. This is due to the bronchodilating effect of the deep inhalation as opposed to the differential dose deposition. This was elegantly shown in two experiments that showed that submaximal inhalation using the dosimeter technique and maximal inhalation done during the tidal breathing method produced similar results in those with mild airway hyperreactivity. A further paper altered the volume outputted by the dosimeter such that it was the same as the tidal breathing method and found that the dosimeter method was still less sensitive, which also supports the theory that it is the bronchoprotective effect of full inhalation that leads to the differences in the methods.

The Yan technique is useful for epidemiologic studies because it is more portable. It uses a hand bulb nebulizer which does not require an external gas source to drive the nebulizer, and is also quicker to perform (6 to 7 minutes on average, compared to 30 minutes for dosimeter). The hand bulb is squeezed at the beginning of inhalation and delivers 0.003mL per squeeze. Like the dosimeter method, this technique also requires the subjects to inhale from FRC to TLC with a three second breath-hold. It was shown to yield similar results to the dosimeter method however in other studies a mean difference of 1.14 fold higher doubling dose was found for the Yan method.
compared to the dosimeter. In non-experienced subjects the repeatability was 2.65 doubling doses versus 1.87 doubling doses for the dosimeter method\textsuperscript{91}.

\subsection{Causes of false positive and false negative challenges}

A false positive methacholine challenge occurs when a subject that does not meet the clinical definition for asthma has a positive methacholine challenge, and this leads to low test specificity. Patients with respiratory diseases such as chronic obstructive pulmonary disease in adults\textsuperscript{92}, cystic fibrosis\textsuperscript{93}, and sickle cell disease\textsuperscript{94} also exhibit bronchial hyperreactivity. Non-respiratory diseases such as rhinitis (allergic and non-allergic)\textsuperscript{95,96} can also cause false positive results. Some stimuli, such as recent viral infections and exposure to cigarette smoke, can cause temporary bronchial hyperreactivity\textsuperscript{97,98}. In addition, healthy children with no history of respiratory or allergic disease have been found to have “asymptomatic bronchial hyperreactivity”\textsuperscript{99}. In longitudinal studies, these children are at higher risk for developing symptomatic asthma compared to those without BHR\textsuperscript{99}.

A false negative methacholine challenge occurs when a subject that is thought to have asthma has a negative methacholine challenge, and this leads to low test sensitivity. Bronchodilators (beta-agonists and anticholinergics) decrease bronchial hyperreactivity for their duration of action. It is recommended that short-acting bronchodilators (eg. Salbutamol) are held for 8 hours and long-acting bronchodilators (eg. Salmeterol) are held for 48 hours prior to testing\textsuperscript{98,100}. Guidelines recommend that antihistamines be held for 3 to 4 days prior to testing, although some note that this isn’t necessary for methacholine challenges\textsuperscript{100}. Small studies have shown conflicting results on the effects of antihistamines on methacholine induced bronchial hyperreactivity\textsuperscript{101,102}. Monotherapy with leukotriene receptor antagonists have not been shown to alter bronchial hyperreactivity\textsuperscript{103}, although they have additive protective effects when taken with inhaled corticosteroids\textsuperscript{104}. Anti-inflammatory medications are known to decrease bronchial hyperreactivity although for safety reasons holding them prior to testing is not recommended\textsuperscript{98,100}. The magnitude of the effect depends on the duration of treatment, the dose of medication, and the time since the last dose. A meta-analysis included studies where subjects took inhaled steroids for 2 to 12 weeks consecutively and showed that low to medium dose steroids (<1000ug budesonide/day) decreased the doubling dose by 1.25; whereas, high dose steroids decreased it by 2.16 doubling doses\textsuperscript{105}. 

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Regularly taken inhaled steroids (taken for 8 weeks) have been shown to decrease BHR up to 4 weeks after treatment was discontinued\textsuperscript{106}; in comparison, high single doses of inhaled steroids (fluticasone 1000ug) decreased bronchial hyperreactivity at 14 hours but not at 26 hours\textsuperscript{107}. Bronchial hyperreactivity tests that are done when the subject has not had recent symptoms will also lead to false negative results. As Cockcroft, one of the developers of the methacholine challenge test noted, “A normal methacholine PC20 obtained in an allergic asthmatic out of season or an occupational asthmatic when away from work and asymptomatic does not exclude asthma.”

This was illustrated in a study of 500 university students which included 3.4% with current asthma (symptoms in the last week), 3.8% with past asthma (no symptoms in the last year) and 3.2% with seasonal asthma (symptoms in the last year but not in the last week)\textsuperscript{96}. 100% of those with current asthma, 38% of those with seasonal asthma, and 11% of those with past asthma had a positive histamine challenge. Longitudinal studies illustrate that of those with mild BHR (PC20 4-8mg/ml) 70-90% no longer had BHR when tested 2 to 4 years later; whereas, all subjects with severe BHR (PC20 <0.125) continued to be responsive when re-tested\textsuperscript{108}. Interestingly, asymptomatic adolescents with previous asthma who continue to have BHR are more likely to have a family history of BHR in comparison to those without BHR, which suggests that there may be a genetic component to BHR\textsuperscript{109}. Another cause of having a patient with an asthma phenotype but no bronchial hyperreactivity is that the patient may have eosinophilic bronchitis and not asthma. These patients typically present with chronic cough that is responsive to asthma medication, but they have no evidence of airway obstruction or bronchial hyperreactivity\textsuperscript{110}.

Technical factors can also lead to false negative results. As previously discussed, the repeatability of a methacholine challenge is +/- 1 doubling dose\textsuperscript{75}. Therefore someone with borderline BHR (PC20 8-16mg/ml) could have a negative methacholine challenge upon re-testing. The dosimeter technique is also less sensitive compared to the tidal breathing technique\textsuperscript{84-86}; so again someone with borderline BHR by the tidal breathing method could have a negative methacholine if tested with the dosimeter method.

1.3.4 Accuracy of bronchial hyperreactivity for the diagnosis of asthma

Studies reporting the accuracy of bronchial hyperreactivity tests compared to a clinical diagnosis of asthma report sensitivities from 47%\textsuperscript{111} to 100%\textsuperscript{96} and specificities from 36%\textsuperscript{112} to 93%\textsuperscript{96} (see Appendix 1, page 98). Bronchial hyperreactivity is measured in a continuum and it is therefore
possible to adjust the cutoff to give a high sensitivity and low specificity or vice versa, however the divergent sensitivities and specificities reported are all for a similar range of cutoff values. Given the widely varying results, it is no wonder that some papers claim that “since it is highly sensitive...a negative challenge excludes current asthma with reasonable certainty”\textsuperscript{113} whilst other papers state that “the value of measuring AHR (airway hyper-reactivity) is its relatively high specificity and low sensitivity...that is, there is a high rate of true negatives.”\textsuperscript{114} What are possible explanatory factors for these divergent results?

1) \textit{Spectrum bias and selection of control subjects}

Sensitivity and specificity are properties of a test that are thought to be less variable because they do not vary with disease prevalence as positive and negative predictive values do. Because they are not dependent on prevalence, they are often used to see how well a test will perform across different populations. However a diagnostic test will not perform equally in different settings where there are different spectrums of disease severity because a test may be better at identifying those with more severe disease. For example, studies of BHR performed in clinic settings where asthma patients have more severe disease in comparison to those identified in population studies, show high sensitivity (95\%\textsuperscript{115}, 90.7\%\textsuperscript{116}) and specificity (83\%\textsuperscript{115}, 90.7\%\textsuperscript{116}). These studies also used healthy volunteers with no respiratory or allergy symptoms as their control group, which would also lower the false positive rate (thereby increasing the specificity).

2) \textit{Selection of reference standard}

A true gold standard provides error-free classification of subjects. Such a standard does not exist for asthma and therefore, any diagnostic study is essentially comparing one imperfect test to another imperfect test. The literature becomes very confusing when the test being assessed in one study is then used as the reference standard for another study. Using an imperfect reference standard leads to a biased estimate of accuracy; the magnitude of the bias depends on how inaccurate the reference standard is and if the errors produced by the reference standard and new test are correlated\textsuperscript{117}.

The reference standard used is typically a physician’s diagnosis of asthma as reported on a questionnaire\textsuperscript{80, 96, 112, 118-122} or a physician’s clinical diagnosis after a history and physical exam are completed\textsuperscript{123-127}. The difficulty with using a physician’s clinical opinion as a reference standard is that it may lack inter-rater reliability. In one study where three respirologists or allergists assessed
patients and assigned a diagnosis of asthma or not asthma, there was only moderate agreement (kappa=0.7)\textsuperscript{128}. In addition, a questionnaire-reported diagnosis is influenced by a person’s desire and ability to seek healthcare and by their local practitioners tendency to diagnose asthma in those with respiratory symptoms. This inter-rater variability may explain why there are still very divergent reports of accuracy ranging from sensitivities of 66-83%\textsuperscript{123 125 126} and specificities of 49.1-88% even when the same reference standard is used.

In order to avoid the problem of lack of reliability of a physician’s diagnosis, many studies use symptom-based questionnaires as the reference standard. However, the reported accuracy will vary depending on which questionnaire items are necessary to make the diagnosis of asthma. For example, one questionnaire definition of asthma required at least 3 episodes of wheezing in the last year, shortness of breath with wheezing, symptoms in response to environmental triggers, and improvement with medication use; this study found a sensitivity and specificity of 100% and 89% respectively at a cutoff of 8mg/ml\textsuperscript{118}. Another study using the same criteria found a sensitivity and specificity of 89%\textsuperscript{119}, which illustrates that if similar reference standards are used reproducible results can be obtained. In contrast, a study that used a less stringent definition of wheezing in the last 12 months found a sensitivity of 47% and a specificity of 92%\textsuperscript{121}. As the reference standard becomes more stringent, those classified by that reference standard as having asthma are likely to represent true asthmatics; however, the converse is that those classified as not having asthma represent a mixed bag of those that truly do not have asthma and those that have mild or intermittent symptoms. If a new test was developed that was excellent at identifying subjects with asthma, and it was compared to the aforementioned reference standard, it would appear to have excellent sensitivity but poor specificity (ie. High number of false positives).

Various solutions have been described to contend with the lack of a gold standard in diagnostic studies and include: sensitivity analysis based on the plausible error rates of the reference standard, validating an index test result against a relevant clinical characteristic or outcome, or creating a composite reference standard\textsuperscript{117}. For bronchial hyperreactivity, the latter approach is most often used.

A composite reference standard has been used in a few studies which use a combination of a physician’s clinical diagnosis as well as an objective measure of airway obstruction or bronchial hyperreactivity\textsuperscript{111, 129}. One of these studies was a paper published by Remes who studied 247 children between the ages of 7 and 13 years\textsuperscript{111, 130}. Their reference standard required a physician’s
assessment of asthma and at least one of the following objective measure reflecting airway
obstruction or hyperreactivity 1) acute symptoms with auscultatory wheezing disappearing after
inhaled beta agonist associated with more than 15% increase in peak flow, 2) >20% variability in
home peak flows measured over 4 weeks and >15% increase in peak flows after beta agonist on at
least 3 occasions, 3) baseline obstruction more than 15% improvement in peak flows or FEV1 after
beta agonist, 4) abnormal free running test (more than 10% decrease in FEV1) or a positive
methacholine challenge. Using this reference standard, they found that the methacholine challenge
was 47% sensitive and 97% specific. One potential reason for the low sensitivity is that the cutoff
used was equivalent to a PC20 of 1-2mg/ml, which is lower than 8mg/ml which has been used in
other studies. In addition, although a dosimeter was used to complete the methacholine
challenge, it was unclear if the standardized five breath technique was used, which makes it
difficult to compare these results to other studies.

Another study using a composite reference standard was completed in 2009 by Anderson. As
opposed to a population sample, this study used a sample referred to clinic for asthma symptoms
but no clear diagnosis of asthma at that point. The reference standard used was a physician’s
clinical diagnosis based on a combination of history, physical exam, pulmonary function tests and
an exercise challenge. Although it was not explicitly stated in the study, an objective finding was
likely not required for the final diagnosis, as 38% of those with a final diagnosis of asthma had a
normal exercise test. This study found that for the 115 pediatric subjects, a methacholine
challenge (PC20 16mg/ml) was 66% sensitive and 63% specific. It is difficult to interpret these
results as the validity of the reference standard is difficult to assess, however, it could be argued
that this pragmatic reference standard reflects what is done in clinical practice where a final
diagnosis is based on a gestalt of the patient’s clinical history and their test results.

3) Timing of symptoms

Another aspect of the choice of reference standard is the timing of the symptoms in relation to
when the BHR test was done. As previously discussed, a BHR study is more accurate when the
symptoms have occurred recently. It is thus of no surprise that studies which use a questionnaire
diagnosis of “ever asthma” as a reference standard show poor sensitivity (52%, 53%). This
was illustrated nicely in a study by Cockcroft et al who found that a methacholine challenge was
positive (PC20 <=8mg/ml) in 100% of subjects with symptoms in the last week, 38% of those with seasonal symptoms, and only 11% of those with asthma but no symptoms in the last year\textsuperscript{96}.

4) Age of patients tested

It has been proposed that the same dose of nebulized agonist is delivered to the lungs regardless of the size or age of the child\textsuperscript{131}. This is based on a study involving 26 individuals that illustrated that the amount of nebulized drug inspired was the same irregardless of size or age after the age of six months\textsuperscript{132}. This is because children less than six months of age have inspiratory flows that are less than the nebulizer output and do not entrain any room air; therefore, they receive an undiluted dose of nebulized drug. Because drug doses used for challenge tests are not altered based on size, this would mean that smaller children are receiving more agonist and would be expected to have more bronchial hyperreactivity in comparison to an adult using the same dose of drug. This is particularly true in infants who receive an undiluted amount of agonist, and some have suggested that this is the explanation for why asymptomatic infants seem to have such high rates of bronchial hyperreactivity\textsuperscript{133}. This may also be why a study involving a cohort of six year old children showed a 60% false positive rate\textsuperscript{112} which is quite high in comparison to the 13 to 35% false positive rate reported in other studies involving a wide range of older children\textsuperscript{80, 123, 127}.

Appendix 1 (page 98) summarizes the pediatric studies that have evaluated the accuracy of the methacholine challenge for diagnosing asthma. Although the results are variable for the reasons discussed above, for the diagnosis of current asthma, a cutoff of 8-16mg/ml has good sensitivity for asthma (68-100%).

1.4 Diagnosing asthma in epidemiologic studies

Epidemiologic studies often require large sample sizes to be representative of the populations that they are sampling. In addition, a high rate of participation is desired to reduce participation bias. In order to achieve these goals, questionnaires are often used to categorize subjects with asthma as they are cost-efficient and easy for participants to complete. It is important to know how accurate these questionnaires are in comparison to a clinical diagnosis in order to determine how applicable the results of epidemiologic studies are to clinical practice.

1.4.1 Epidemiologic study designs
Epidemiologic studies on asthma are undertaken to: estimate disease frequency, assess disease burden, determine prognosis, and identify risk factors associated with the disease to allow for preventative measures to be developed.

Disease frequency is expressed as prevalence (fraction of the population with asthma at a given time) or incidence (number of new cases occurring in a disease-free population over a given period of time). Cross-sectional studies are used to estimate prevalence; whereas, cohort studies are used to estimate incidence. The most important factor in prevalence studies is that the sample be representative of the population. Therefore it is recommended that large sample sizes (≥3000) are used and simple non-invasive measures of asthma be used to optimize response rates. In Canada, estimates of prevalence and incidence are obtained through administrative databases as well as population-based surveys (eg. National Longitudinal Survey of Children and Youth).

Although sensitivity and specificity should both be optimized, for surveillance purposes sensitivity is more important. When comparing the prevalence of asthma between different populations, Youden’s index \((J=\text{sensitivity}+\text{specificity}-1)\) has been suggested as the best measure of test validity. This is because Youden’s index determines how much an estimated prevalence difference is attenuated based on the sensitivity and specificity of the test used (see Figure 2).

Figure 2: Youden’s Index

\[
P_1 = \text{prevalence in population 1} \\
P_2 = \text{prevalence in population 2} \\
(P_1-P_2)(\text{sensitivity} + \text{specificity} -1) = (P_1-P_2)(\text{Youden’s index})
\]

The true difference in prevalence \((P_1-P_2)\) is attenuated in proportion to Youden’s index.

Eg. Sensitivity = 0.8, Specificity = 0.8, Youden’s index = 0.6, True difference in prevalence is 20% Observed difference in prevalence using the test is \((0.6)(20\%) = 12\%\)

Another measure of test accuracy is the area under the receiver operator curve (ROC). Like Youden’s index it combines information about sensitivity and specificity to determine the test’s overall accuracy. However, the area under the curve assesses overall accuracy at various cut-off points; whereas, Youden’s index describes the accuracy at a specific cut-off point. Because questionnaires and database algorithms have dichotomous outcomes, receiver operator curves are not often used to describe their accuracy.
Potential risk factors for asthma can be identified using cross-sectional, case-control or cohort studies. Cross-sectional studies can measure prevalence and exposures in different populations, or can measure prevalence and exposures over time in the same population to find factors that explain the prevalence differences. To allow for comparisons, it is important that an instrument is repeatable and valid in different populations and over time. Objective measures are well-suited for this because they are not subject to regional or longitudinal differences in diagnostic tendencies or terminology. Unfortunately there is no completely accurate objective measure for asthma; although, of those currently available, measures of bronchial hyperreactivity are arguably the most sensitive. Data from case-control and cross-sectional studies are used to calculate odds ratios; whereas, data from cohort studies can be used to calculate relative risks. For these studies, which calculate prevalence ratios, the best test is one that provides a high positive predictive value which is more dependent on the specificity than the sensitivity, although varies significantly with prevalence 145, 146.

As the above paragraphs describe, choosing the best test for a study depends on the purpose of the study. For studies of prevalence, highly sensitive tests are preferred to ensure that all subjects with disease are captured. For studies that aim to identify risk factors associated with asthma, a highly specific test is preferred to ensure that the case group is not diluted with healthy subjects.

Misdiagnosis of subjects with respect to disease occurs because no diagnostic test is perfect. Misclassification of disease status or exposure status is referred to as information bias 147. The effect of the bias on the risk estimate depends on two factors 1) if the misclassification is differential, and 2) if the misclassification is independent 147-149. With respect to errors in asthma diagnosis, it is non-differential if the test for the disease is equally accurate (ie. the same sensitivity and specificity) in the exposed and unexposed groups. For example, if the exposure is a family history of atopy and the disease is asthma measured by airway biopsy, then the misclassification is non-differential because the accuracy of a biopsy diagnosis of asthma should be the same whether the subjects have a family history of atopy or not. However, if the diagnosis of asthma is based on exhaled nitric oxide (which is only elevated in those with eosinophilic inflammation 150) then the misclassification may be differential because exhaled NO may be a more accurate test in those with a family history of atopy versus those who do not. Misclassification is independent if the factors leading to an inaccurate diagnosis of the disease are unrelated to the factors leading to an inaccurate estimation of the exposure. Most misclassification is independent but an example of
dependent misclassification is if the exposure is contact with a volatile organic compounds measured by perception of a chemical odour and the disease is asthma, diagnosed by a self-reported history of wheeze or cough. In this case an increased perception of symptoms (respiratory and olfactory) could lead to a misclassification of both the disease and the exposure.

Figure 3: Types of Misclassification

| Disease | | | | |
|---------|---------|---------|--------|
| Test for disease | Positive | a | b |
| Negative | c | d |

| Exposure | | | | |
|---------|---------|---------|--------|
| Test for exposure | Present | A | B |
| Absent | C | D |

1) Differential: the sensitivity (a/(a+c)) and specificity (d/(b+d)) are the same in the exposed (A+C) and unexposed groups (B+D)

2) Independent: the factors that increase false positive (b) and false negative (c) test results for the disease are unrelated to the factors that increase false positive (B) and false negative (C) test results for exposure

Having an inaccurate test for asthma leads to a biased estimate of risk (relative risk or odds ratio). The direction and magnitude of this bias depends on if the misclassification is nondifferential and/or independent. Non-differential and independent misclassification causes the risk estimate to move towards the null, which is important in studies which do not show an effect of the exposure. If the misclassification is differential or dependent then the effect of the bias is difficult to predict and it could either under or overestimate risk.

1.4.2 The evolution of asthma questionnaires and the International Study of Asthma and Allergies in Childhood (ISAAC)

Questionnaires about asthma have items that inquire about a diagnosis of asthma and/or symptoms of asthma. Diagnosis-based questionnaires have the advantage of being more specific than symptom-based questionnaires, given that respiratory symptoms have many causes other than asthma. However, a questionnaire based on a prior diagnosis is influenced by factors such as: a patient’s access to healthcare, if a patient is troubled enough by their symptoms to see a physician, a practitioner’s knowledge of asthma and their tendency to diagnose respiratory symptoms as asthma. These factors are likely to vary widely between different countries which makes valid
comparisons difficult. Also, in healthcare research if a difference in disease severity or mortality is noted, it would be difficult to ascertain if this was secondary to underdiagnosis and undertreatment if the screening method required people to already have a diagnosis of asthma.

For these reasons, questionnaires that focused on symptoms were developed. As wheezing is central to the diagnosis of asthma, it is the key diagnostic question in most questionnaires. As discussed in the section on clinical diagnosis (1.3.1), wheezing is a colloquial term that has many meanings. In order to decrease confusion surrounding the term wheezing, videos demonstrating wheeze have been developed to be used in conjunction with written questionnaires\textsuperscript{152, 153}. Although these video questionnaires are more specific than the written questionnaires, they are less sensitive leading to a lower Youden’s index\textsuperscript{154}. Another issue with using wheeze to define asthma is that although it is more specific than cough for the diagnosis of asthma\textsuperscript{155} there are still many conditions other than asthma that present with wheezing.

Clearly, neither diagnosis-based nor symptom-based questionnaires are perfect however to facilitate comparisons, it was necessary to create and validate a questionnaire that could be used to measure asthma prevalence in different centers.

The International Study of Asthma and Allergies in Childhood (ISAAC) is a multi-phase study that was started in 1991 to study differences in asthma prevalence and severity between populations\textsuperscript{156}. Uniform methods for recruiting subjects and administering questionnaires and videos were developed to allow for valid comparisons between centers. Phase 1 and 3 were cross-sectional studies that estimated the prevalence of asthma symptoms and were conducted on average 7 years apart to detect differences in asthma prevalence. In addition, they determined environmental factors that were associated with a higher prevalence of asthma. Phase 2 involved fewer centers and sought to gather objective data on asthma (including bronchial hyperreactivity) and to further investigate the associations determined in phase 1.

The questionnaire used in the ISAAC study contained a core set of questions which focused on wheezing and also had one question about cough and one about a diagnosis of asthma. The core question that was used to assess asthma prevalence was “Has your child ever had wheezing or whistling in the chest?” This question was adapted from the International Union against Tuberculosis and Lung Disease (IUATLD) questionnaire, which was found to be repeatable and
was validated in adults against bronchial hyperreactivity in several countries. This study found
that the wheeze question had a higher Youden’s index compared with the ever asthma question for
predicting bronchial hyperreactivity. As acknowledged by the authors, BHR alone is not the
gold standard for asthma, however it was chosen because in an international study it was important
to have a reference standard that was not subject to cultural influences and one that could be
reproduced in future studies. For the phase II studies which examine risk factors for asthma, the
ever asthma question is used to define the asthma population since a higher specificity is needed in
these studies.

1.4.3 Accuracy of the questionnaire for the diagnosis of asthma

For the results of a study to be relevant to a specific population, it is necessary to bridge the gap
between an “epidemiologic” diagnosis of asthma and a “clinical” diagnosis of asthma. In other
words, it is important to validate the questionnaire diagnosis against a physician’s assessment
which ideally includes objective measures of asthma.

Appendix 2 (page 100) includes studies in children which have validated a questionnaire diagnosis
of asthma against a physician’s diagnosis.

The study by Hederos et al used a chart review as their reference standard. They found that a
question about physician’s diagnosed asthma had a specificity of 97.5% and a sensitivity of 76.9%
(J=0.74), whereas wheezing in the past 12 months had a better sensitivity (86.3%) but worse
specificity (84.1%). This study included children from 1-6 years old, and it is surprising how
sensitive and specific the question about wheezing was in this age group given the high prevalence
of viral wheezing in this age group. One reason could be that this study selected for more severely
affected children since those with mild wheezing and no respiratory distress may not have visited
their physician and certainly would not have been admitted to the hospital. Although it was stated
in the methods that a diagnosis of asthma in Sweden is based 1) three episodes of wheezing prior
to age 2, 2) a first wheezing episode after age 2, or 3) the first episode of wheezing in an atopic
child, it could not be ensured that physician’s followed these diagnostic guidelines. In this same
article, they mentioned that a nested case-control validation study was done using this cohort.
Compared to a “physician’s diagnosis by examination”, the questionnaire was 70% sensitive and
97.8% specific. Unfortunately details of that study were not given and that information has not
been published.
A much-cited study by Jenkins et al\textsuperscript{163} involving 168 children ages 13 to 14 years also used a physician’s diagnosis of asthma as the reference standard. Current wheeze was defined by a positive response to the questions “Have you ever had wheezing or whistling in the chest at any time in the past?” and “have you had wheezing or whistling in the chest in the past 12 months?” Current wheeze identified on questionnaire was validated against a physician’s diagnosis of current asthma which was defined as a “history of wheeze suggestive of a clinical diagnosis of asthma within the past 12 months.” This study found that the sensitivity and specificity of the questionnaire was 0.85 and 0.81 respectively (J=0.66). They also found that if one used the questionnaire plus a positive response to BHR as the operational definition of asthma, it led to an increase in specificity but a significant decline in sensitivity (0.94 and 0.47 respectively) with a subsequent decline in Youden’s index to 0.41. This study did not use any objective measures in their reference standard of asthma.

This problem was remedied in the study by Remes which included 247, 7 to 12 year old children\textsuperscript{130}. This study had a reference standard that included a clinical diagnosis of asthma as well as at least one objective finding consistent with asthma. The criteria needed for a clinical diagnosis were clearly identified as at least two episodes of 1) shortness of breath or wheeze, or 2) cough triggered by exercise, allergen exposure, or infection. The objective criteria required for the diagnosis was 1) acute asthma symptoms or wheezing which disappeared after inhaled beta-agonist, 2) acute asthma symptoms and >15% increase in peak flow after inhaled beta agonist, 3) 4 week home peak flow measurements with >20% variability and >15% increase on three occasions after beta-agonist, 4) baseline obstruction improving after beta-agonist and with a 15% improvement in peak flow or FEV\textsubscript{1}, 5) >10% drop in peak flow or FEV\textsubscript{1} after free running test, or 6) positive methacholine challenge (PD20 <400ug ~ PC20 between 1-2mg/ml). They clarified the methods used for the exercise and methacholine challenge in a subsequent paper\textsuperscript{111} however it was unclear if objective criteria 1 through 4 were formally assessed as part of a study or if they relied on parental report or chart review. In addition, this study did not use an ISAAC based questionnaire making it difficult to compare the results with the Jenkins study. The Remes study found that the question regarding a wheezy chest apart from colds in the past 12 months had a sensitivity of 78% and a specificity of 97%. This question was more specific but had a similar sensitivity compared to the results of the Jenkins study. This is not surprising given the caveat that the wheezing occurred apart from colds. The study also found that a question about physician
diagnosed asthma had a similar sensitivity and specificity (82% and 99% respectively) compared to the question about wheezing (results adjusted for sampling scheme).

1.4.4 Accuracy of administrative database algorithms for identifying asthma

Administrative databases have been used to assess asthma prevalence\textsuperscript{164} medication use\textsuperscript{165}, and quality of care\textsuperscript{166, 167}; however, few studies have assessed the accuracy of database definitions of asthma (Appendix 3, page 102).

One study conducted in the United States looked at the accuracy of the International Classification of Diseases (ICD) code for asthma in the Rochester Epidemiology Project database which includes all inpatient and outpatient data from the children in the community\textsuperscript{168}. This study involved a convenience sample of children that had previously participated in a study looking at factors associated with parents seeking healthcare. It used a chart review as the reference standard and found that the database had a 24% sensitivity and 98% specificity. The low sensitivity may be due to the young age of the participants (mean age 2 years old) where it is more difficult to make a definitive diagnosis of asthma.

A Danish study examined the use of pharmacy data to identify those with asthma\textsuperscript{169}. The pharmacy data was collected from the regional Health Service Register and from the Odense Pharmacoepidemiologic Database, and all children that had a prescription for an asthma medication in the last year were included in the study. The reference standard was a diagnosis of asthma from the National Patient Registry which contains all inpatient and outpatient hospital visits. For those not in the registry, a questionnaire was sent to the patient’s general practitioner to determine the asthma status. This study found that a prescription for asthma medication in the last 12 months was 96% sensitive but only 46% specific. A more stringent criteria of at least one prescription other than a one-time prescription for a beta-agonist was 83% sensitive and 73% specific.

Another definition for asthma was proposed by the Council of State and Territorial Epidemiologists (CSTE) in the United States. A case definition of 1 emergency room, outpatient or inpatient claim with asthma as the primary or secondary diagnosis in the last year was validated in a Medicaid database\textsuperscript{170}. The reference standard used was physician-diagnosed asthma based on
responses from the Easy Breathing Questionnaire™ and medical records. The subjects were all children who were seen at one of the 6 primary care clinics and were enrolled in the Easy Breathing management program, which is an educational program for primary care physicians to better manage asthma. This study found that the CTSE definition had a sensitivity of 61% and a specificity of 98%. When the CTSE definition was expanded to include 2 prescriptions for asthma medication, the sensitivity increased to 90% with a similar specificity of 95%. The expanded definition was then validated in a managed care organization database (Conneticare) and was found to have a sensitivity of 80% and a specificity of 93%. One of the issues with that study is that patients were excluded if they did not have a clear diagnosis, or documentation of their asthma severity and for the Medicaid database, only 53% of eligible subjects were included. This may explain the high sensitivity and specificity of the database definition in this study compared to others.

Because of the universal healthcare system in Canada, there are provincial and national health administrative databases that contain information on the populace. Recent studies have validated health claims database algorithms of asthma in pediatric and adult patients in Ontario. There is no provincial pharmacy database in Ontario; therefore, validated algorithms do not contain data on prescription medication. The case definition of at least 2 asthma physician visits within 2 consecutive years and/or 1 or more asthma hospitalization was found to be 89% sensitive and 72% specific for the diagnosis of asthma in pediatric patients compared to chart abstraction reviewed by a panel of experts. The same definition was found to be 84% sensitivity and 77% specific in adults and it is currently the algorithm used to identify patients for the Ontario Asthma Surveillance Information System Database (OASIS).

Two other studies have validated administrative data for pediatric asthma in Canada. Both studies involved the administrative data from Manitoba. One study attempted to identify those with persistent asthma using data from the Manitoba Health Services Insurance Plan (MHSIP). The administrative database definition was one physician encounter for asthma or an asthma-like diagnosis (bronchitis or bronchiolitis) in the calendar year. The reference standard was children who had at least one prescription for an asthma drug (inhaled corticosteroid, cromone, beta-agonist) identified on the provincial drug database. This definition had a sensitivity of 74% and specificity of 91% for the reference standard.
One issue with the above studies is that chart reviews or other databases are used as the reference standard. This may lead to incorporation bias because the physician that completes the chart or writes a prescription then provides a diagnosis for the administrative database. Ideally an investigator would establish the diagnosis of asthma blinded to any data that was used in the administrative database. This was done in a second study from Manitoba that combined prescription drug data and physician visits to create multiple algorithms\(^{174}\). The reference standard was a pediatric allergist’s clinical diagnosis of asthma in the same year. This study found that the algorithm of one hospitalization, or two physician visits, or four prescription medications had a sensitivity of 47% and a specificity of 92%. An algorithm that required one hospitalization, or one physician visit or two prescription medications had a higher sensitivity of 77% with no decrease in the specificity.
Chapter 2
Objectives

The primary objectives of this study are to 1) validate a parental-proxy questionnaire diagnosis and 2) to validate a health claims database diagnosis of physician-diagnosed asthma in a population-based sample of Canadian children, using a gold-standard that utilizes objective measures of lung function.

A secondary objective was to determine the diagnostic cut-off value for pulmonary function test parameters that optimized the sensitivity and specificity compared to the gold-standard.
Chapter 3
Research Hypothesis

The questionnaire and health claims diagnoses will be more accurate at identifying those without asthma than those with asthma. The questionnaire diagnosis will be specific but not sensitive compared to a clinical diagnosis, and will be more specific than a health claims diagnosis. There will be more overdiagnosis than underdiagnosis of asthma, and the majority of those with undiagnosed asthma will have reported respiratory symptoms on the questionnaire.

Pulmonary function test parameters (FEV1, FEV1/FVC, FEF25-75\%) will be very specific but insensitive for the diagnosis of asthma.
Chapter 4
Methods

4.1 Research Design
This validation study was a nested cross-sectional case-control study.

4.2 The Sampling Frame
This study used data collected from a subsample of patients from the Toronto Child Health Evaluation Questionnaire (T-CHEQ) study. Phase I of the TCHEQ was a cross sectional study that took place from January to March of 2006. That study randomly sampled 230 of the 600 Toronto schools (sampling 23, 349 of the potential 50,000 grade 1 and 2 students). A 20 minute questionnaire regarding respiratory and allergic symptoms was given to each of the students to be taken home and voluntarily filled out by their parents. The survey was returned to the classroom by the students and picked up by the research assistants. A second distribution of the questionnaire was conducted 1-2 weeks after this to enhance the response rate. The overall response rate from both distributions was 25% (5619 returned questionnaires of the 23 349 distributed) however the characteristics of the study participants with respect to income adequacy, education, and household size were similar to those of the general population in the Toronto area according to National census data\textsuperscript{175}.

Phase II involved a subset of the children that participated in Phase 1 and was a case-control study conducted from June to September of 2006. It randomly sampled 1500 patients (750 controls, 750 asthma cases) who had lived in Toronto and had been in the respondent’s care since birth. These patients participated in more detailed evaluations of their environmental exposures. It was necessary to only include children who had lived in Toronto from birth because part of the environmental assessment was a calculation of their lifetime pollution exposure based on their lifetime address history, and detailed pollution data was only available for the Toronto area.

This validation study used a subsample of 200 randomly selected patients who participated in Phase II of the study. The random selection was done via SAS which uses a probability-based simple random selection process such that each subject has an equal probability of being sampled.
The questionnaire diagnoses was obtained from the questionnaire completed when the child and parent were seen for their study visit.

The administrative database diagnosis was obtained from the OASIS (Ontario Asthma Surveillance Information System) database. The OASIS database contains information from two Ontario health care administrative databases. The Canadian Institute for Health Information (CIHI) discharge abstract database for inpatient services and the Ontario Health Insurance Plan (OHIP) database for ambulatory and emergency services. A unique personal identifier (the scrambled Health Card Number) included in each database permits the linkage of a child’s records across all databases and time while preserving patient confidentiality. Both of these databases contain diagnostic codes based on the International Classification of Disease (ICD)-9 or 10. A claim for asthma was identified by the ICD-9 code 493 for claims up to March 31, 2002 and ICD-10 codes J45 and J46 identified asthma in subsequent years.

The CIHI database currently allows up to 25 diagnostic codes (prior to 2002, 16 diagnostic codes were allowed) and if any of these was for asthma, the hospitalization was included. Providing discharge information to the CIHI database is mandatory for all Canadian hospitals (with the exception of Quebec). The accuracy of the CIHI database is assessed annually with re-abstraction studies that use information from patient charts as the reference standard. These studies have found that the discharge database has 80% sensitivity for diagnoses that were found in the chart and that there was 87% agreement for the ICD-10 diagnostic code assigned. Although these abstraction studies have not specifically evaluated the accuracy for asthma in the database, other diseases such as stroke, acute myocardial infarction, and birth trauma have been evaluated. At the time of analysis, this data had been updated to March 2011; therefore all hospitalizations that occurred in our study patients in the year before their clinic visit would be captured.

The OHIP database contains information submitted by all fee-for-service physicians in the province and allows one diagnostic code per visit. Only one claim per physician per day per patient was allowed. The OHIP database was found to be 91.4% sensitive and 82.9% specific compared to expert chart review for pediatric asthma. This data had been updated to March 2011 at the time of the analysis.
4.3 Inclusion and Exclusion Criteria

Inclusion criteria:
1. Participated in TCHEQ phase II study and agreed to future research and telephone contact.
2. Still live within driving distance of Toronto
3. Age 9-12 at time of recruitment into this study
4. Able and cooperative enough to participate in investigations
5. Free of upper respiratory tract infections for three weeks prior to participation

Exclusion criteria:
1. Did not consent to future research as part of T-CHEQ study
2. Born <37 weeks prematurely
3. Have a chronic health condition other than asthma

4.4 Setting
All visits and testing was performed at the Hospital for Sick Children between December 2008 and October 2010.

4.5 Recruitment
All patients who participated in Phase II of the TCHEQ study and who agreed to future research and telephone contact (95% of the original cohort) were included in the sampling frame. A letter describing the study was sent to the parents of potential subjects. Two to three weeks after the letter was sent, research staff contacted the parents via telephone. The purpose of the study, and the study procedure was described in more detail and the patient’s eligibility was assessed. Patients who agreed to participate and were eligible were booked for a clinic appointment. All subjects that participated were asked during the clinic visit if they agreed to provide their healthcard number for linkage with provincial administrative databases. After the clinic appointment, the parents were given vouchers for public transportation or parking, and the children were given a gift certificate valuing $25. In addition, the study physician explained the results of all of the tests performed and provided the parents with a report outlining the findings. Recruitment continued until 100 cases and 100 controls were assessed.
4.6 The questionnaire diagnosis

Subjects and their parents were seen at the start of the clinic visit by the study coordinator who obtained consent. A questionnaire, which was a shortened version of the questionnaire that they had completed in 2006, was administered by the coordinator. The coordinators were instructed not to clarify any of the questions, and simply told the parents to answer the questions to the best of their understanding.

4.6.1 Lifetime asthma

Lifetime asthma was defined by a positive response to the following questions 1) “Has your child ever had asthma?” and 2) “Was this diagnosed by a physician?”. Those that had asthma that was not diagnosed by a physician were excluded from the analysis.

All control subjects had a negative response to the question 1) “Has your child ever had asthma?” They were further divided into those with respiratory symptoms and those without. Those with respiratory symptoms had a positive response to one or more of the following questions: 1) “Has your child ever had wheezing or whistling in the chest?”; 2) “In the past 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection?”; 3) “In the past 12 months, has your child used any prescribed medicines, pills, puffers or other medication for wheezing or asthma” or 4) “In the past 12 months, has your child’s chest sounded wheezy during or after exercise?”

4.6.2 Current asthma

Current asthma cases met the criteria for lifetime asthma and answered yes to one of the following: 1) “Has your child had wheezing or whistling in the chest in the past 12 months?” or 2) “In the past 12 months, has your child used any prescribed medicines, pills, puffers or other medication for wheezing or asthma?”

Controls had a negative response to “Has your child ever had asthma?” and were divided into those with current respiratory symptoms and those without. Those with current symptoms answered yes to at least one of the following “Has your child ever had wheezing or whistling in the chest in the past 12 months?”, “In the past 12 months, has your child’s chest sounded wheezy during or after exercise?”, “In the past 12 months, has your child had a dry cough at night, apart
from cough associated with a cold or chest infection?”, “In the past 12 months, has your child used any prescribed medicines, pills, puffers or other medication for wheezing or asthma?” Controls with no symptoms answered no to all of the above questions.

4.7 The administrative database diagnosis

A dataset was constructed which contained information from those subjects that consented to have their data linked to the administrative database. All identifying information was removed from the dataset and it was sent via a secure portal to an analyst at the Institute for Clinical Evaluative Sciences. This dataset was then linked to the Ontario Asthma Surveillance Information System (OASIS) database via the unique healthcard numbers.

4.7.1 Lifetime Asthma

Lifetime asthma cases were defined by a previously validated algorithm as follows: at least one hospitalization for asthma at any time during the child’s life or two separate ambulatory or emergency room visits for asthma within a two year time frame\textsuperscript{171}. This algorithm was previously found to have optimal diagnostic parameters using an expert consensus diagnosis from chart abstraction\textsuperscript{171, 179}.

4.7.2 Current Asthma

Current asthma cases were defined as those that met the criteria for lifetime asthma and had: at least one outpatient visit (ambulatory or emergency room) or hospitalization for asthma in the last year (defined as the year preceding the subject’s clinic visit date). A sensitivity analysis was done extending the lookback period to two years prior to their clinic visit date.

4.8 The reference standard

4.8.1 Clinical history and physical exam

All subjects were assessed by a pediatric respirologist (CY, SD) or pediatric allergist (ES) who were blinded to the questionnaire diagnosis and saw the subjects prior to any objective testing. The subjects were given a clinical diagnosis of asthma, possible asthma or not asthma based on a standardized history and physical exam. The assessors discussed the data collection form to ensure that the data was collected and interpreted consistently.
A history consistent with lifetime asthma required a) recurrent episodes of wheezing with or without difficulty breathing or b) recurrent episodes of dry cough with difficulty breathing, and c) these episodes responded to standard asthma management (systemic or inhaled corticosteroids or bronchodilator treatment). Physical exam findings consistent with asthma included wheezing or a hyperinflated chest.

Possible lifetime asthma was diagnosed if a) the only symptom was dry cough without a history of wheeze or respiratory distress, b) there was an unconvincing history of wheeze or c) the respiratory symptoms were not recurrent, or c) there was an unclear response to asthma medication.

In order to dichotomize the asthma outcome into asthma or not asthma, the history and physical exam data for those with possible clinical asthma were independently re-assessed by two of the study physicians. If there was agreement between the two physicians, that diagnosis was taken as the final clinical diagnosis. If there was disagreement between the two diagnoses, the data was then assessed by the third physician and the diagnoses that was agreed upon by any of the two physicians was taken as the final clinical diagnosis. In the case where all three physicians disagreed on the diagnosis, the case was discussed between them until a consensus was reached.

Subjects were classified as having current asthma if they met the criteria for lifetime asthma and had respiratory symptoms in the last 12 months.

4.8.2. Objective testing

After being assessed by the physician, all subjects had the following tests performed:

- Allergy skin testing
- Exhaled nitric oxide test
- Spirometry
- Methacholine challenge.

All tests were completed by trained pulmonary function technicians (EA, JD, AW, DW) who had on average 10 years of experience. Subjects were asked to hold all asthma medication for 48 hours and all antihistamines for 5 days.

Allergy skin testing was performed using a multi-test device placed on the volar surface of the forearms (Multi-Test ® II, Lincoln Diagnostics Inc, Illinois). The following allergens were tested: dust mite/Dermatophagoides Farinae, dust mite/Dermatophagoides Pteronyssinus, dog, cat, horse, mouse, cockroach, feather, tree mix, grass mix, ragweed, aspergillus, hormodendum,
Alternaria. A positive (histamine) and negative (saline) control was used for quality assurance. A test was positive if the resulting wheal was $\geq$3mm larger than the saline control. Subjects were considered atopic if they had $\geq$ 1 positive skin test. The skin tests from the subjects with negative histamine controls were excluded from the analysis.

**Exhaled nitric oxide** was measured online using a chemiluminescent gas analyzer (NIOX-Flex™, Aerocrine, Sweden or the CLD 88 sp™, Eco Physics, Switzerland) which are calibrated with test gases of known concentration (200ppb for the NIOX-Flex™, 10ppm for the CLD 88sp™) at a minimum of every 2 weeks. The measurements were completed according to ATS criteria with flow at 0.05L/S which was maintained using biofeedback. Subjects inhaled air that contained less than 5ppb of nitric oxide and exhaled against resistance for 4 seconds until a 2 second plateau was reached. The test was repeated until 3 plateaus that agreed at the 10% level or 2 plateaus agreed at the 5% level were reached.

**Spirometry** was done according to ATS criteria using a mass flow sensor (VMAX™, Carefusion, United States). The FEV1, FVC and FEF25-75 were recorded for tests that were acceptable and reproducible. The data was interpreted using reference values from Stanojevic et al.

**The methacholine challenge** was done using the 2-minute tidal breathing technique with an English Wright nebulizer. The first inhalation was done with normal saline and the concentrations then increased incrementally from 0.03mg/ml to 16mg/mL. A shortened protocol (described below) which is a conservative version of the one recommended for adults was used. Subjects with no previous history of asthma symptoms, an FEV1/FVC over 80%, an FEV1 over 70% and over 2L, less than a 10% fall in FEV1 after saline inhalation and on no medication or on occasional bronchodilators were tested with the shortened protocol. For those on no medication the starting dose was 0.25mg/ml and for those on bronchodilators the starting dose was 0.06mg/ml. If there was less than a 5% fall in FEV1 from baseline and no clinical symptoms of bronchoconstriction then the next dose was omitted. After the 1mg/ml concentration, no further doses were omitted.

For subjects with an FEV1 less than 65% of predicted, the methacholine challenge was not performed and 400ug of salbutamol (via meter-dose inhaler and aerochamber) was given to assess for reversibility. The bronchodilator response was expressed as the percent change from baseline for FEV1 (eg. [Postbronchodilator FEV1 – Prebronchodilator FEV1] / Prebronchodilator FEV1).
Objective test measures consistent with asthma:

1) Methacholine challenge with a PC20 less than or equal to 16mg/ml
2) In patients with baseline obstruction (FEV1/FVC and FEV1 less than the lower limit of normal for their age) that were unable to complete a methacholine challenge, a 12% increase in FEV1 from absolute baseline value.

4.8.3 The algorithm for the reference standard
A diagnosis of asthma required both a clinical diagnosis of asthma and one objective finding consistent with asthma (see figure 4).

Figure 4: The algorithm for the reference standard

4.8.4 Assessing agreement between assessors
The physician’s data collection form from all of the subjects with an initial clinical diagnosis of possible asthma and from 48 randomly selected subjects were re-assessed by another study physician to determine the agreement in clinical diagnosis between physicians.

4.9 Statistical Analysis
All data was analyzed using SAS version 9.2. A chi-square test with Yates correction was used to compare differences in baseline proportions between groups and a t-test was used to compare differences in means. For comparison of multiple proportions, if the overall chi-square test was significant a multiple comparisons test for proportions was conducted to determine which pairs were significantly different. The kappa was calculated to assess the agreement between the two physicians’ clinical diagnosis.

4.9.1 Sample size calculation
The sample size has been calculated using an estimated questionnaire sensitivity of 0.85 and a specificity of 0.81 obtained from the literature. The following formula for estimation of sample size for binomial proportions was used:
\[
N = \frac{Z^2 \times P (1-P)}{\Delta^2}
\]

Where \(N\) = sample size, \(z = 1.96\) for 95% confidence, \(P\) = proportion, \(\Delta\) = desired precision.

To obtain a precision of 0.05 with 95% confidence for sensitivity the required sample size is 196 and the required sample size for specificity would be 236. Using a sample size of 200, we will obtain a precision of 0.049 for sensitivity and a precision of 0.055 for specificity for the questionnaire. The sensitivity and specificity of the database definition are 89% and 72% respectively. With a sample size of 200, we will obtain a precision of 0.043 for sensitivity and 0.062 for specificity for the database definition.

4.9.2 Sensitivity, Specificity, Positive and Negative Predictive Values, Positive and Negative Likelihood Ratios

The calculations for the sensitivity, specificity and predictive values of the questionnaire compared to the reference standard were adjusted for the sampling scheme to avoid verification bias. This was done because the subjects with a questionnaire diagnosis of asthma and control subjects with respiratory symptoms were more likely to be sampled for this validation study compared to those with no diagnosis of asthma. The adjustment was done according to the method originally described by Begg et al\textsuperscript{184,185} given that the subjects were not chosen based on their true disease state (ie. the conditional independence assumption was met). To calculate the sensitivity, specificity and predictive values from the second table, the control subjects with and without respiratory symptoms were combined into one group and calculations were done as described in Figure 5. The 95% confidence interval for the corrected sensitivity and specificity were calculated using the method described by Begg\textsuperscript{185}, and the confidence interval for the predictive values was calculated from the binomial proportion as these are unbiased estimates\textsuperscript{186}. 

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### Raw data from verification study

<table>
<thead>
<tr>
<th>Questionnaire result</th>
<th>All patients from original cohort</th>
<th>Verified Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Asthma</td>
</tr>
<tr>
<td>Asthma</td>
<td>n₁</td>
<td>a</td>
</tr>
<tr>
<td>Control with respiratory symptoms</td>
<td>n₂</td>
<td>c</td>
</tr>
<tr>
<td>Control with no respiratory symptoms</td>
<td>n₃</td>
<td>e</td>
</tr>
</tbody>
</table>

### Data corrected for verification bias

<table>
<thead>
<tr>
<th>Questionnaire result</th>
<th>Empirical probability of verification</th>
<th>Corrected for verification bias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asthma</td>
<td>No asthma</td>
</tr>
<tr>
<td>Asthma</td>
<td>p₁ = (a + b) / n₁</td>
<td>a¹ = a / p₁</td>
</tr>
<tr>
<td>Control with respiratory symptoms</td>
<td>p₂ = (c + d) / n₂</td>
<td>c¹ = c / p₂</td>
</tr>
<tr>
<td>Control with no respiratory symptoms</td>
<td>p₃ = (e + f) / n₃</td>
<td>e¹ = e / p₃</td>
</tr>
</tbody>
</table>

To calculate the accuracy of the administrative database definition against the reference standard diagnosis, a simple 2x2 table was created. Sensitivity, specificity, positive and negative likelihood ratios were calculated from the table (see Figure 5). The prevalence of asthma was taken from the original cohort to determine the positive and negative predictive values of the database. 95% confidence intervals were calculated for all proportions using a Gaussian approximation.

Similar calculations were carried out to assess the accuracy of pulmonary function test parameters (FEV1/FVC, FEV1 and FEF25-75) compared to the reference standard. For pulmonary function data, any value less than or equal to the 5th percentile of predicted was considered abnormal. In addition, ROC curves were plotted for FEV1/FVC, FEV1 and FEF25-75 to find the percentile that optimized sensitivity and specificity.

Sensitivity analysis was done excluding control subjects with respiratory symptoms, excluding those with a potential cause for having a false negative methacholine challenge, excluding cases with no respiratory symptoms in the last 12 months, and using a lower methacholine cutoff for the reference standard (8mg/ml versus 16mg/ml). A subanalysis was also done to determine if the
sensitivity and specificity of the questionnaire or database differed by gender, atopic status, socioeconomic status, weight and race.

The agreement (kappa) was calculated between the questionnaire or database diagnosis and the reference standard\textsuperscript{187}. The kappa was also calculated to assess the agreement between physicians.

\textit{Figure 5: Calculations for sensitivity, specificity, likelihood ratios, predictive values and Youden’s index}

<table>
<thead>
<tr>
<th>Reference standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>Questionnaire / Database diagnosis</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Sensitivity = \( a / (a + c) \)

Specificity = \( d / (b + d) \)

Youden’s index = \( J = \text{sensitivity} + \text{specificity} - 1 \)

Positive likelihood ratio = \( a / (a + c) / b / (b + d) = \text{sensitivity} / (1 - \text{specificity}) \)

Negative likelihood ratio = \( c / (a + c) / d / (b + d) = (1 - \text{sensitivity}) / \text{specificity} \)

Negative predictive value = \( \text{specificity} (1 - \text{prevalence}) / (1 - \text{sensitivity})(\text{prevalence}) + (\text{specificity})(1 - \text{prevalence}) \)

Positive predictive value = \( \text{prevalence} (\text{sensitivity}) / (\text{prevalence})(\text{sensitivity}) + (1 - \text{specificity})(1 - \text{prevalence}) \)

\textbf{4.10 Ethics approval}

This study was approved by The Research Ethics Board of the Hospital for Sick Children in Toronto. To utilize administrative data from the Institute of Clinical Evaluative Sciences, a privacy impact assessment form was completed and ethics approval was obtained from Sunnybrook Health Sciences Centre.
Chapter 5
Results

5.1 Response rate and subject participation

We attempted to contact 599 subjects by telephone. We had an incorrect telephone number for 76 (13%), 29 were ineligible (5%), 89 we were unable to reach by telephone despite leaving messages (15%), 75 consented but recruitment was complete prior to booking their appointment (13%), 8 subjects were booked but then didn’t arrive for their appointment (1%), 114 did not consent to the study (19%) and 208 consented and participated in the study (35%). Of those that were contacted, the consent rate was 70% (283/405) and the completion rate was 63% (208/330). Of those that participated in the study 183 (88%) gave permission to use their healthcard number to link their data to the provincial database.

5.2 Characteristics of participants compared to the original study participants

There were 5619 subjects in the original study and of these 208 participated in this study. There were more males amongst the participants (58 vs. 49%), and participants were more likely to be in the highest income bracket, to have a university education, and less likely to be exposed to tobacco smoke compared to non-participants (Table 1). Participants had more visits to a pediatrician in the last year compared to non-participants, but no difference in the number of visits to a general practitioner. The higher proportion of males was secondary to oversampling those with lifetime asthma as there were more males than females with asthma in the original study (69% males, 41% females in original study; 65% males, 35% females in this study). Oversampling the lifetime asthma group did not explain the differences in income adequacy, education level, type of dwelling or smoke exposure in our study. Income adequacy was highly correlated with education level and type of dwelling (r=0.41, r=0.51 respectively) but not tobacco exposure (r=0.09).
Table 1: Baseline characteristics of participants compared to non-participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Participants N=208</th>
<th>Non Participants N=5411</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex (n=5573)</td>
<td>121 (58%)</td>
<td>2651 (49%)</td>
</tr>
<tr>
<td>Income adequacy (n=5241)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest (n=935)</td>
<td>6 (3%)</td>
<td>929 (18%)</td>
</tr>
<tr>
<td>Lower middle (n=1160)</td>
<td>26 (13%)</td>
<td>1134 (23%)</td>
</tr>
<tr>
<td>Upper middle (n=1201)</td>
<td>36 (18%)</td>
<td>1165 (23%)</td>
</tr>
<tr>
<td>Highest (n=1945)</td>
<td>133 (66%)</td>
<td>1812 (40%)</td>
</tr>
<tr>
<td>Highest level of education¹ (n=5421)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary/secondary only (n=1074)</td>
<td>22 (11%)</td>
<td>1052 (20%)</td>
</tr>
<tr>
<td>College education only (n=1841)</td>
<td>61 (30%)</td>
<td>1780 (34%)</td>
</tr>
<tr>
<td>University (n=2506)</td>
<td>122 (60%)</td>
<td>2384 (46%)</td>
</tr>
<tr>
<td>Household size (n=5542)</td>
<td>4.4 ± 1.3</td>
<td>4.3 ± 1.3</td>
</tr>
<tr>
<td>Mean 2</td>
<td>3 (1%)</td>
<td>163 (3%)</td>
</tr>
<tr>
<td>Mean 3</td>
<td>25 (12%)</td>
<td>958 (18%)</td>
</tr>
<tr>
<td>Mean 4</td>
<td>103 (50%)</td>
<td>2332 (44%)</td>
</tr>
<tr>
<td>Mean &gt;=5</td>
<td>75 (36%)</td>
<td>1883 (35%)</td>
</tr>
<tr>
<td>Environmental tobacco smoke (n=5515)</td>
<td>12/207 (6%)</td>
<td>618 (12%)</td>
</tr>
<tr>
<td>Mean ± SD number of visits to Family Physician in last year (n=5100)</td>
<td>2.6 ± 6.8</td>
<td>2.1 ± 4.4</td>
</tr>
<tr>
<td>Mean ± SD number visits to paediatrician in last year (n=5084)</td>
<td>2.3 ± 7.6</td>
<td>1.4 ± 3.7</td>
</tr>
<tr>
<td>Mean Hospitalizations in last year n=5574</td>
<td>10 (5%)</td>
<td>209 (4%)</td>
</tr>
</tbody>
</table>

¹ Highest level of education of person that completed the questionnaire

Of those with physician-diagnosed asthma in the original study (n=847), there was no difference in the severity of the asthma symptoms in the participants compared to non-participants. There were more subjects with self-reported eczema but not hayfever or rhinitis amongst the participants with asthma (Table 2).
Table 2: Characteristics of asthma for those with self-reported physician-diagnosed asthma: participants compared to non-participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Participants N=98</th>
<th>Non Participants N=749</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of wheezing attacks in the last 12 months (n=837)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>43 (44%)</td>
<td>347 (47%)</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>8 (1%)</td>
</tr>
<tr>
<td>2</td>
<td>33 (34%)</td>
<td>262 (35%)</td>
</tr>
<tr>
<td>3</td>
<td>17 (17%)</td>
<td>94 (13%)</td>
</tr>
<tr>
<td>4</td>
<td>5 (5%)</td>
<td>28 (4%)</td>
</tr>
<tr>
<td>Sleep disturbance due to wheezing in past 12 months (n=836)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>63 (65%)</td>
<td>496 (67%)</td>
</tr>
<tr>
<td>&lt;1 night/week</td>
<td>23 (24%)</td>
<td>180 (24%)</td>
</tr>
<tr>
<td>&gt;= 1 night/week</td>
<td>11 (11%)</td>
<td>63 (9%)</td>
</tr>
<tr>
<td>Wheezing severe enough to limit speech in last 12 months (n=835)</td>
<td>12 (13%)</td>
<td>68 (9%)</td>
</tr>
<tr>
<td>Hospital admissions for respiratory problems in the last year (n=843)</td>
<td>5 (5%)</td>
<td>38 (5%)</td>
</tr>
<tr>
<td>Medication use for asthma in last year (n=818)</td>
<td>71 (73%)</td>
<td>511 (71%)</td>
</tr>
<tr>
<td>History of sneezing, or a runny, or blocked nose without a cold or flu ever n=843</td>
<td>53 (54%)</td>
<td>351 (47%)</td>
</tr>
<tr>
<td>History of hayfever ever n=839</td>
<td>29 (30%)</td>
<td>171 (23%)</td>
</tr>
<tr>
<td>History of eczema n=827</td>
<td>52 (53%)</td>
<td>297 (41%)</td>
</tr>
</tbody>
</table>
5.3 Overview of Patient flow

5.3.1 Patient flow for determining the final “questionnaire” diagnosis for lifetime asthma

208 subjects completed questionnaire

101 controls

107 self reported lifetime asthma

5 with lifetime asthma but not physician diagnosed

102 self reported lifetime MD-diagnosed asthma

4 unable to do methacholine
2 took medication in last 24hr

49 with no history of respiratory symptoms

52 with lifetime history of respiratory symptoms

96 lifetime asthma

N=197
Main analysis

12 with no symptoms in last 12 months

49 asymptomatic controls

52 with lifetime history of respiratory symptoms

40 symptomatic controls

74 with symptoms in last 12 months

N=163
Analysis excluding outgrown

49 asymptomatic controls

52 with lifetime history of respiratory symptoms

40 symptomatic controls

74 with symptoms in last 12 months

N=145
Analysis excluding symptomatic controls

49 asymptomatic controls

52 with lifetime history of respiratory symptoms

40 symptomatic controls

74 with symptoms in last 12 months

N=145
Analysis excluding symptomatic controls

49 asymptomatic controls

52 with lifetime history of respiratory symptoms

40 symptomatic controls

74 with symptoms in last 12 months

N=145
Analysis excluding symptomatic controls

49 asymptomatic controls

52 with lifetime history of respiratory symptoms

40 symptomatic controls

74 with symptoms in last 12 months

N=145
Analysis excluding symptomatic controls

49 asymptomatic controls

52 with lifetime history of respiratory symptoms

40 symptomatic controls

74 with symptoms in last 12 months

N=145
Analysis excluding symptomatic controls

49 asymptomatic controls

52 with lifetime history of respiratory symptoms

40 symptomatic controls

74 with symptoms in last 12 months

N=145
Analysis excluding symptomatic controls

49 asymptomatic controls

52 with lifetime history of respiratory symptoms

40 symptomatic controls

74 with symptoms in last 12 months

N=145
Analysis excluding symptomatic controls

49 asymptomatic controls

52 with lifetime history of respiratory symptoms

40 symptomatic controls

74 with symptoms in last 12 months

N=145
Analysis excluding symptomatic controls

49 asymptomatic controls

52 with lifetime history of respiratory symptoms

40 symptomatic controls

74 with symptoms in last 12 months

N=145
Analysis excluding symptomatic controls

49 asymptomatic controls
5.3.2 Patient flow for determining the final “questionnaire” diagnosis for current asthma

208 subjects completed questionnaire

101 controls

49 with no history of respiratory symptoms

26 reported no respiratory symptoms in last year

75 asymptomatic controls

52 with lifetime history of respiratory symptoms

26 reported respiratory symptoms in last year

26 symptomatic controls

102 with physician-diagnosed asthma

101 with physician-diagnosed asthma

107 self reported lifetime asthma

5 with lifetime asthma but not physician diagnosed

102 with physician-diagnosed asthma

28 with no reported symptoms on questionnaire in last 12 months

2 took medication in last 24 hours

26 symptomatic controls

28 with no reported symptoms on questionnaire in last 12 months

2 unable to do Mch

26 symptomatic controls

69 current asthma

2 took medication in last 24 hours

69 current asthma

2 unable to do Mch

75 asymptomatic controls

73 with current asthma

28 with no reported symptoms on questionnaire in last 12 months

N=170
Main analysis

N=144
Analysis excluding symptomatic controls
5.3.3 Patient flow for determining the final “administrative” diagnosis for lifetime asthma

208 subjects completed questionnaire

25 did not consent to have records linked

183 consented to have records linked

87 with no asthma according to administrative database

96 with lifetime asthma according to administrative database

3 unable to do methacholine
2 took medication in last 24hr

87 no asthma

91 lifetime asthma

N=178
Main analysis

87 no asthma

66 lifetime asthma with symptoms in last 12m

N=151
Analysis excluding outgrown

27 with no symptoms in last 12 months
5.3.4 Patient flow for determining the final “administrative” diagnosis for current asthma

- 208 subjects completed questionnaire
  - 25 did not consent to have records linked
  - 183 consented to have records linked
    - 152 with no current asthma according to administrative database definition
      - 3 unable to do
      - 149 no asthma
    - 31 with current asthma according to administrative database
      - 2 took LABA in last 24hr & had negative Mch
      - 29 current asthma
      - N=178
      - Main analysis
5.4 Baseline characteristics by self-reported lifetime physician-diagnosed asthma status

The subjects with self-reported asthma did not differ significantly from those with no asthma with respect to age, gender, race, weight, socioeconomic status or smoke exposure (Table 3). As expected, those with self-reported asthma were more likely to be atopic or have a family history of atopy, and were more likely to report respiratory symptoms or medication use (Table 3).

Table 3: Baseline characteristics categorized by self-reported lifetime physician-diagnosed asthma

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>n</th>
<th>Self Reported Asthma (n=102)</th>
<th>Controls (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age yrs (range)</td>
<td>203</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Male Sex</td>
<td>203</td>
<td>66 (65%)</td>
<td>52 (51%)</td>
</tr>
<tr>
<td>Race</td>
<td>194</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td></td>
<td>76 (79%)</td>
<td>86 (88%)</td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td>13 (14%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td>4 (4%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Arab</td>
<td></td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Mixed</td>
<td></td>
<td>2 (2%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Weight</td>
<td>203</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight or normal weight</td>
<td></td>
<td>70 (69%)</td>
<td>73 (72%)</td>
</tr>
<tr>
<td>Overweight or obese</td>
<td></td>
<td>32 (31%)</td>
<td>28 (28%)</td>
</tr>
<tr>
<td>Income adequacy</td>
<td>196</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest</td>
<td></td>
<td>4 (4%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Lower middle</td>
<td></td>
<td>13 (13%)</td>
<td>13 (13%)</td>
</tr>
<tr>
<td>Upper middle</td>
<td></td>
<td>22 (22%)</td>
<td>13 (13%)</td>
</tr>
<tr>
<td>Highest</td>
<td></td>
<td>60 (61%)</td>
<td>69 (71%)</td>
</tr>
<tr>
<td>Exposure to environmental tobacco</td>
<td>203</td>
<td>2 (2%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>smoke (%) n=203</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopy</td>
<td>198</td>
<td>72 (73%)</td>
<td>56 (56%)</td>
</tr>
<tr>
<td>ISAAC Atopy</td>
<td>198</td>
<td>68 (69%)</td>
<td>55 (55%)</td>
</tr>
<tr>
<td>Parental history of asthma</td>
<td>203</td>
<td>46 (45%)</td>
<td>28 (28%)</td>
</tr>
<tr>
<td>Self-Reported symptoms &amp; medication use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheeze</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime</td>
<td>202</td>
<td>95 (94%)</td>
<td>43 (43%)</td>
</tr>
<tr>
<td>In last 12 months</td>
<td>202</td>
<td>58 (57%)</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>Chronic cough</td>
<td>203</td>
<td>41 (42%)</td>
<td>18 (18%)</td>
</tr>
<tr>
<td>Use of medication</td>
<td>203</td>
<td>67 (66%)</td>
<td>7 (7%)</td>
</tr>
</tbody>
</table>

Percent are column percents
1 Self identified race
2 According to BMI percentiles: >95%ile obese, 85-95%ile overweight, 5-85%ile healthy, <5%ile underweight
3 Derived variable defined by Statistics Canada as total household income adjusted for the number of persons in the household. Lowest income: <$15 000 1-2 or <$20 000 3-4 or <$30 000 5-6, Lower middle income: $15 000 to $29 999 1-2 or $20 000 to $39 999 3-4 or $30 000 to $59 999 5-6, Upper middle income: $30 000 to $59 999 1-2 or $40 000 to $79 999 3-4; Highest income ≥ $60 000 1 or ≥ $80 000 ≥ 2
4 Atopy defined as ≥1 positive skin test (≥3mm above saline control)
5 Atopy defined as ≥1 positive skin test (≥3mm above saline control) using dustmite DP, dustmite DF, grass mix, tree mix, alternaria, cat
6 Positive answer to “Has your child ever had wheezing or whistling in the chest at any time in the past?”
7 Positive answer to “Has your child had wheezing or whistling in the chest in the past 12 months?”
8 Positive answer to “In the past 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection?”
9 Positive answer to “In the past 12 months, has your child used any prescribed medicines, pills, puffers or other medication for wheezing or asthma?”
5.5 Characteristics of subjects categorized by asthma reference standard

The characteristics of the subjects were assessed by their reference standard asthma diagnosis. Those with outgrown asthma had a diagnosis of lifetime asthma but did not have respiratory symptoms in the last 12 months (Table 4).

There was over-reporting of wheezing and under-reporting of cough on questionnaire compared to the physician’s assessment.

There was no difference in demographic data between the groups except that there more males with outgrown asthma compared to the current asthma or no asthma groups. As expected those with current asthma were more likely to be atopic compared to those with outgrown and no asthma; however there was no difference in atopy between the outgrown asthma and no asthma groups. The reported rate of medication use was similar on questionnaire and on physician’s assessment, and interestingly 23% and 11% of those with outgrown and no asthma had taken some type of asthma medication in the last year.

Those with current asthma were well controlled in the last year as evidenced by the low number requiring systemic steroids, hospitalization or emergency room visits. There was however 17% of those with current asthma that classified themselves as poorly controlled according to their responses on the Children’s Asthma Control Test.

Those with current asthma had higher exhaled nitric oxide levels, lower FEV1, FEF25-75 and FEV1/FVC ratios and had more positive methacholine challenges in the PC20 1-4mg/ml range. Those with outgrown asthma and no asthma did not differ with respect to exhaled nitric oxide, pulmonary function tests or methacholine results.
<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Current asthma (n=47)</th>
<th>Outgrown asthma (n=35)</th>
<th>Not asthma (n=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age yrs (range)</td>
<td>202</td>
<td>10 (9-12)</td>
<td>10 (9-12)</td>
<td>10 (9-12)</td>
</tr>
<tr>
<td>Male Sex</td>
<td>202</td>
<td>27 (57%)</td>
<td>25 (71%)</td>
<td>64 (53%)</td>
</tr>
<tr>
<td>Race</td>
<td>192</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>29 (66%)</td>
<td>29 (88%)</td>
<td>101 (88%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>7 (16%)</td>
<td>4 (12%)</td>
<td>8 (7%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>3 (7%)</td>
<td>0</td>
<td>3 (3%)</td>
<td></td>
</tr>
<tr>
<td>Arab</td>
<td>1 (2%)</td>
<td>0</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>4 (9%)</td>
<td>0</td>
<td>2 (2%)</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>202</td>
<td>37 (79%)</td>
<td>23 (66%)</td>
<td>84 (70%)</td>
</tr>
<tr>
<td>Underweight or Normal</td>
<td>10 (21%)</td>
<td>12 (34%)</td>
<td>36 (30%)</td>
<td></td>
</tr>
<tr>
<td>Overweight or Obese</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Income adequacy</td>
<td>196</td>
<td>2 (4%)</td>
<td>1 (3%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Lowest</td>
<td>45 (9%)</td>
<td>4 (9%)</td>
<td>18 (16%)</td>
<td></td>
</tr>
<tr>
<td>Lower middle</td>
<td>9 (20%)</td>
<td>3 (9%)</td>
<td>22 (19%)</td>
<td></td>
</tr>
<tr>
<td>Upper middle</td>
<td>31 (67%)</td>
<td>26 (79%)</td>
<td>74 (64%)</td>
<td></td>
</tr>
<tr>
<td>Highest</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure to environmental tobacco smoke</td>
<td>202</td>
<td>1 (2%)</td>
<td>1 (3%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Atopy</td>
<td>197</td>
<td>41 (89%)</td>
<td>20 (63%)</td>
<td>67 (56%)</td>
</tr>
<tr>
<td>ISAAC Atopy</td>
<td>197</td>
<td>38 (83%)</td>
<td>20 (63%)</td>
<td>65 (55%)</td>
</tr>
<tr>
<td>Atopy Sum</td>
<td>197</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5 (10%)</td>
<td>12 (28%)</td>
<td>52 (44%)</td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>15 (33%)</td>
<td>11 (34%)</td>
<td>37 (31%)</td>
<td></td>
</tr>
<tr>
<td>4-8</td>
<td>23 (50%)</td>
<td>7 (22%)</td>
<td>25 (21%)</td>
<td></td>
</tr>
<tr>
<td>&gt;=9</td>
<td>3 (7%)</td>
<td>2 (6%)</td>
<td>5 (4%)</td>
<td></td>
</tr>
<tr>
<td>Parental history of asthma</td>
<td>202</td>
<td>20 (43%)</td>
<td>11 (31%)</td>
<td>42 (35%)</td>
</tr>
<tr>
<td>C-ACT score ≤ 19 †</td>
<td>93</td>
<td>7 (17%)</td>
<td>1 (5%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Median (range)</td>
<td></td>
<td>23 (16-27)</td>
<td>26 (12-27)</td>
<td>24 (14-27)</td>
</tr>
<tr>
<td>Wheeze (physician assessment)</td>
<td>202</td>
<td>46 (98%)</td>
<td>35 (100%)</td>
<td>44 (37%)</td>
</tr>
<tr>
<td>Lifetime</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In last 12 months</td>
<td>201</td>
<td>41 (87%)</td>
<td>1 (3%)</td>
<td>19 (16%)</td>
</tr>
<tr>
<td>Wheeze (self-reported on questionnaire)</td>
<td>201</td>
<td>47 (100%)</td>
<td>33 (97%)</td>
<td>57 (48%)</td>
</tr>
<tr>
<td>Lifetime</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last 12m</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic cough (physician assessment)</td>
<td>202</td>
<td>43 (91%)</td>
<td>27 (77%)</td>
<td>43 (36%)</td>
</tr>
<tr>
<td>Lifetime</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last 12m</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough (self-reported on questionnaire)</td>
<td>201</td>
<td>39 (83%)</td>
<td>11 (31%)</td>
<td>32 (27%)</td>
</tr>
<tr>
<td>Last 12m</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty breathing ever (physician assessment)</td>
<td>202</td>
<td>41 (87%)</td>
<td>20 (57%)</td>
<td>29 (24%)</td>
</tr>
<tr>
<td>Asthma medication in last12m</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-reported on questionnaire</td>
<td>202</td>
<td>41 (87%)</td>
<td>4 (11%)</td>
<td>27 (23%)</td>
</tr>
<tr>
<td>Assessed by physician</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled corticosteroid (ICS)</td>
<td></td>
<td>31 (66%)</td>
<td>1 (3%)</td>
<td>18 (15%)</td>
</tr>
<tr>
<td>ICS + Long acting beta agonist</td>
<td></td>
<td>6 (13%)</td>
<td>1 (3%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Leukotriene receptor antagonist</td>
<td></td>
<td>2 (4%)</td>
<td>0</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Short acting beta agonist</td>
<td></td>
<td>34 (72%)</td>
<td>3 (9%)</td>
<td>22 (22%)</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>Current asthma (n=47)</td>
<td>Outgrown asthma (n=35)</td>
<td>Not asthma (n=120)</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----</td>
<td>-----------------------</td>
<td>------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td><strong>Systemic steroids in lifetime</strong></td>
<td>202</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>24 (53%)</td>
<td>22 (71%)</td>
<td>99 (88%)</td>
</tr>
<tr>
<td>1-4</td>
<td></td>
<td>17 (38%)</td>
<td>8 (26%)</td>
<td>11 (10%)</td>
</tr>
<tr>
<td>5-10</td>
<td></td>
<td>1 (2%)</td>
<td>1 (3%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>&gt;10</td>
<td></td>
<td>3 (6%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><strong>Systemic Steroids in last 12m</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>43 (94%)</td>
<td>35 (100%)</td>
<td>112 (99%)</td>
</tr>
<tr>
<td>1-2</td>
<td></td>
<td>2 (4%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>1 (2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Hospitalizations for respiratory reasons</strong></td>
<td>201</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>34 (72%)</td>
<td>29 (83%)</td>
<td>106 (89%)</td>
</tr>
<tr>
<td>1-5</td>
<td></td>
<td>13 (28%)</td>
<td>6 (17%)</td>
<td>13 (11%)</td>
</tr>
<tr>
<td>Last 12 months</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Emergency room visits for resp reasons</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime</td>
<td></td>
<td>19 (40%)</td>
<td>16 (46%)</td>
<td>27 (23%)</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>24 (51%)</td>
<td>19 (54%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>1-5</td>
<td></td>
<td>2 (4%)</td>
<td>0</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>&gt;5</td>
<td></td>
<td>2 (4%)</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Last 12 months</td>
<td></td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Median exhaled Nitric Oxide (range)</strong></td>
<td>167</td>
<td>30 (4-97)</td>
<td>9.7 (3-75)</td>
<td>11 (2-68)</td>
</tr>
<tr>
<td><strong>Positive bronchodilator response (≥12%)</strong></td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Methacholine PC20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;16mg/ml</td>
<td></td>
<td>0</td>
<td>22 (63%)</td>
<td>89 (74%)</td>
</tr>
<tr>
<td>8 to ≤ 16mg/ml</td>
<td></td>
<td>7 (16%)</td>
<td>2 (6%)</td>
<td>10 (8%)</td>
</tr>
<tr>
<td>4 to ≤ 8mg/ml</td>
<td></td>
<td>7 (16%)</td>
<td>5 (14%)</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>≤ 4mg/ml</td>
<td></td>
<td>31 (69%)</td>
<td>6 (17%)</td>
<td>14 (12%)</td>
</tr>
<tr>
<td>Mean FEV1/FVC %ile (SD)²</td>
<td>202</td>
<td>21 (24)</td>
<td>31 (20)</td>
<td>32 (22)</td>
</tr>
<tr>
<td>Mean FEV1 %ile (SD)</td>
<td></td>
<td>26 (26)</td>
<td>45 (27)</td>
<td>50 (27)</td>
</tr>
<tr>
<td>Mean FVC %ile (SD)</td>
<td></td>
<td>45 (32)</td>
<td>56 (29)</td>
<td>57 (27)</td>
</tr>
<tr>
<td>Mean FEF25-75 %ile (SD)</td>
<td></td>
<td>16 (20)</td>
<td>31 (23)</td>
<td>39 (25)</td>
</tr>
</tbody>
</table>

1 Children’s Asthma Control Test score: scores less than 19 indicate poor control, data only available for those that self-reported asthma on the questionnaire
2 Using Stanojevic et al reference data

5.6 Correlation between physician’s clinical diagnosis and results of methacholine challenge

There was only fair agreement with the physician’s clinical diagnosis and the methacholine challenge using a cutoff of 16mg/ml (k=0.22 for lifetime asthma, k= 0.28 for current asthma).

This did not change significantly when a cutoff of 8mg/ml (k=0.23 for lifetime asthma, 0.29 for current asthma) or 4mg/ml (k=0.19 for lifetime asthma, 0.30 for current asthma) was used.

The tables below illustrate the results of the methacholine according to the physician’s initial clinical assessment. Those with “Possible Lifetime Asthma” and “Possible No Lifetime Asthma” were initially diagnosed with possible asthma by the first physician, and when the consensus
diagnosis was obtained were later classified as having “Lifetime Asthma” and “No Lifetime Asthma” respectively.

45% of those with a final clinical diagnosis of lifetime asthma and 67% of those with a final diagnosis of no asthma had a negative methacholine challenge (PC20 ≥16mg/ml) (Table 5). Of the 45% with a final clinical diagnosis of asthma but a negative methacholine challenge, 44% (21) did not have symptoms in the last 12 months. In those with a clinical diagnosis of current asthma and no asthma, 37% and 66% respectively had a negative methacholine challenge (Table 6).

Tables 5: Results of methacholine challenge by physician’s clinical lifetime diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Physician’s Clinical Assessment</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asthma Lifetime</td>
<td>Possible ¹</td>
<td>No lifetime asthma</td>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>PC20 ≤ 4mg/ml</td>
<td>28</td>
<td>9</td>
<td>7</td>
<td>7</td>
<td>51</td>
</tr>
<tr>
<td>4mg/ml &gt; PC20 ≤ 8mg/ml</td>
<td>11</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>8mg/ml &gt; PC20 ≤ 16mg/ml</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>PC20 &gt; 16mg/ml</td>
<td>27</td>
<td>21</td>
<td>8</td>
<td>55</td>
<td>111</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>71</td>
<td>35</td>
<td>16</td>
<td>78</td>
<td>200</td>
</tr>
</tbody>
</table>

Excludes 2 patients with bronchodilator response and no methacholine challenge, 4 that couldn’t do methacholine, and 2 that took LABA on day of testing with negative methacholine
¹ Patients initially diagnosed with possible asthma (symptom of cough with no wheeze or respiratory distress, vague history of wheeze, respiratory symptoms not recurrent or unclear response to asthma medication), charts reassessed by two physicians to arrive at final diagnosis

Tables 6: Results of methacholine challenge by physician’s clinical current diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Physician’s Clinical Assessment</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Current Asthma</td>
<td>Possible ¹</td>
<td>No Current Asthma</td>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>PC20 ≤ 4mg/ml</td>
<td>24</td>
<td>7</td>
<td>9</td>
<td>11</td>
<td>51</td>
</tr>
<tr>
<td>4mg/ml &gt; PC20 ≤ 8mg/ml</td>
<td>7</td>
<td>0</td>
<td>3</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>8mg/ml &gt; PC20 ≤ 16mg/ml</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>PC20 &gt; 16mg/ml</td>
<td>11</td>
<td>15</td>
<td>15</td>
<td>70</td>
<td>111</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>46</td>
<td>25</td>
<td>28</td>
<td>101</td>
<td>200</td>
</tr>
</tbody>
</table>

Excludes 2 patients with bronchodilator response and no methacholine challenge, 4 that couldn’t do methacholine, and 2 that took LABA on day of testing with negative methacholine
¹ Patients initially diagnosed with possible asthma (symptom of cough with no wheeze or respiratory distress, vague history of wheeze, respiratory symptoms not recurrent or unclear response to asthma medication), charts reassessed by two physicians to arrive at final diagnosis

48 subjects had a final clinical diagnosis of lifetime asthma but had a negative methacholine challenge. 26 had potential causes for a false negative methacholine challenge: 22 did not have symptoms in the last 12 months, 1 was on regular inhaled steroids within two weeks of testing, and 3 were tested in a season when they didn’t have symptoms. A much higher proportion of subjects
with a clinical diagnosis of possible asthma compared with definite asthma had a negative methacholine challenge (60% vs. 24%).

44 (34%) of those with no clinical diagnosis of current asthma had a positive methacholine challenge. 12 of these had borderline methacholine challenges (8-16mg/ml) and 13 had a history of previous asthma symptoms and may therefore have had some remaining bronchial hyperreactivity.

5.7 Correlation between questionnaire and results of methacholine challenge

There was again only mild agreement between the questionnaire and the methacholine challenge at a cutoff of 16mg/ml (kappa=0.28 for lifetime asthma, k=0.3 for current asthma). This did not significantly change when a cutoff of 8mg/ml (kappa=0.31 for lifetime asthma, k=0.36 for current asthma) or 4mg/ml was used (k=0.26 for lifetime, k=0.31 for current).

Of those that had a questionnaire diagnosis of lifetime asthma and no asthma, 41% and 70% had a negative methacholine challenge (Table 7). Of those that had a questionnaire diagnosis of current asthma and not current asthma, 36% and 68% had a negative methacholine challenge (Table 8).

Table 7: Results of methacholine challenge by questionnaire lifetime diagnosis

<table>
<thead>
<tr>
<th>PC20</th>
<th>Asthma Lifetime</th>
<th>Control with respiratory symptoms</th>
<th>Control with no respiratory symptoms</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 4mg/ml</td>
<td>36</td>
<td>7</td>
<td>5</td>
<td>51</td>
</tr>
<tr>
<td>&gt; 4mg/ml</td>
<td>11</td>
<td>4</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>&gt; 8mg/ml</td>
<td>8</td>
<td>5</td>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>&gt; 16mg/ml</td>
<td>39</td>
<td>36</td>
<td>35</td>
<td>113</td>
</tr>
<tr>
<td>Total</td>
<td>94</td>
<td>52</td>
<td>49</td>
<td>195</td>
</tr>
</tbody>
</table>

Excludes 2 patients with bronchodilator response and no methacholine challenge, 4 that couldn’t do methacholine, 2 that took LABA on day of testing with negative methacholine

Table 8: Results of methacholine challenge by questionnaire current diagnosis

<table>
<thead>
<tr>
<th>PC20</th>
<th>Asthma Current</th>
<th>Control with respiratory symptoms</th>
<th>Control with no respiratory symptoms</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 4mg/ml</td>
<td>30</td>
<td>3</td>
<td>9</td>
<td>42</td>
</tr>
<tr>
<td>&gt; 4mg/ml</td>
<td>9</td>
<td>2</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>&gt; 8mg/ml</td>
<td>5</td>
<td>3</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>&gt; 16mg/ml</td>
<td>23</td>
<td>18</td>
<td>53</td>
<td>94</td>
</tr>
<tr>
<td>Total</td>
<td>67</td>
<td>26</td>
<td>75</td>
<td>168</td>
</tr>
</tbody>
</table>

Excludes those patients with a previous history of asthma but no current symptoms (n=27)
5.8 Accuracy of questionnaire for lifetime asthma

Table 9: Number of subjects with and without lifetime asthma in original study compared to in this study

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>All patients from original study</th>
<th>Patients included in this study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asthma</td>
<td>No asthma</td>
</tr>
<tr>
<td>Asthma</td>
<td>847</td>
<td>53</td>
</tr>
<tr>
<td>Control with respiratory symptoms</td>
<td>1592</td>
<td>5</td>
</tr>
<tr>
<td>Control with no respiratory symptoms</td>
<td>3000</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 10: Corrected number of subjects with and without lifetime asthma accounting for probability of verification*

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Empirical probability of verification</th>
<th>Corrected for verification bias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asthma</td>
<td>No asthma</td>
</tr>
<tr>
<td>Asthma</td>
<td>0.11</td>
<td>467</td>
</tr>
<tr>
<td>Control with respiratory symptoms</td>
<td>0.03</td>
<td>153</td>
</tr>
<tr>
<td>Control with no respiratory symptoms</td>
<td>0.016</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 11: 2x2 table used to calculate sensitivity and specificity of questionnaire for lifetime asthma

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Asthma</th>
<th>Not Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>467</td>
<td>379</td>
</tr>
<tr>
<td>Not Asthma</td>
<td>153</td>
<td>4439</td>
</tr>
<tr>
<td></td>
<td>620</td>
<td>4818</td>
</tr>
<tr>
<td></td>
<td>846</td>
<td>4592</td>
</tr>
<tr>
<td></td>
<td>5438</td>
<td></td>
</tr>
</tbody>
</table>

*See page 38 for further details

The initial sensitivity and specificity for the questionnaire diagnosis of lifetime asthma compared to the reference standard were 91% and 69% for the unadjusted data; however when adjusted for verification bias, the sensitivity and specificity were 75% and 92% respectively (Table 11). This led to a positive and negative predictive value of 55 and 97%. Given that only 5 subjects had a questionnaire diagnosis of asthma that was not physician-diagnosed, it is not surprising that using this definition did not change the sensitivity and specificity (data not shown). Of these five subjects, 3 had a final diagnosis of no asthma and 2 had a diagnosis of asthma. As expected, using a definition of ever wheeze led to a higher sensitivity and a lower specificity (100%, 81% respectively) and subsequently to a higher negative predictive value and a lower positive predictive value. Using a PC20 of 8mg/ml as the cutoff for the asthma diagnosis did not significantly change the sensitivity or specificity (76%, 91% respectively) (Table 12).
The questionnaire diagnosis was also compared to the physician’s clinical diagnosis. This led to a non-significant improvement in specificity and a decrease in sensitivity (Table 12). This is likely because many subjects that were given a clinical diagnosis of lifetime had a negative methacholine challenge.

The subanalysis was done stratifying the subjects by gender, weight, socioeconomic status, atopic status and race however some of the resulting cell sizes contained less than 5 subjects and meaningful conclusions could not be drawn (data not shown).

Table 12: Accuracy of questionnaire compared to the reference standard for lifetime asthma

<table>
<thead>
<tr>
<th>Definition</th>
<th>Reference standard *</th>
<th>n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>PLR</th>
<th>NLR</th>
<th>J</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD dx lifetime asthma</td>
<td>Clinical dx + Mch 16</td>
<td>197</td>
<td>75%</td>
<td>92%</td>
<td>55%</td>
<td>96%</td>
<td>9.6</td>
<td>0.27</td>
<td>0.67</td>
</tr>
<tr>
<td>Ever wheeze</td>
<td>Clinical dx + Mch 16</td>
<td>201</td>
<td>100%</td>
<td>81%</td>
<td>43%</td>
<td>100%</td>
<td>5.3</td>
<td>0</td>
<td>0.81</td>
</tr>
<tr>
<td>MD dx lifetime asthma</td>
<td>Clinical dx + Mch 8</td>
<td>197</td>
<td>76%</td>
<td>90%</td>
<td>46%</td>
<td>97</td>
<td>8.4</td>
<td>0.26</td>
<td>0.67</td>
</tr>
<tr>
<td>Ever wheeze</td>
<td>Clinical dx + Mch 8</td>
<td>201</td>
<td>100%</td>
<td>79%</td>
<td>37%</td>
<td>100%</td>
<td>3.6</td>
<td>0.30</td>
<td>0.79</td>
</tr>
<tr>
<td>MD dx lifetime asthma</td>
<td>Clinical dx</td>
<td>203</td>
<td>52%</td>
<td>97%</td>
<td>86%</td>
<td>85%</td>
<td>18.1</td>
<td>0.49</td>
<td>0.49</td>
</tr>
<tr>
<td>Ever wheeze</td>
<td>Clinical dx</td>
<td>207</td>
<td>87%</td>
<td>90%</td>
<td>76%</td>
<td>95%</td>
<td>9.4</td>
<td>0.14</td>
<td>0.77</td>
</tr>
</tbody>
</table>

All reported data adjusted for verification bias as described in methods
PPV = positive predictive value, NPV = negative predictive value, PLR = positive likelihood ratio, NLR = negative likelihood ratio, J=Youden’s index
1 excluded 5 subjects with non-MD dx asthma
2 excluded 1 subject that didn’t answer question on wheezing
3Reference
Clinical dx + Mch 16 = clinical dx with either 12% bronchodilator response or PC20 ≤ 16mg/ml
Clinical dx + Mch 8 = clinical dx with either 12% bronchodilator response or PC20 ≤ 8mg/ml

5.8.1 Analysis excluding those that did not report symptoms in the last 12 months
A false negative methacholine challenge can be seen in subjects that have not had recent symptoms; thereby decreasing the specificity of the test. Therefore an analysis was done excluding all subjects that did not report respiratory symptoms in the last 12 months during the physician assessment (n=35). Excluding these patients did not significantly change the sensitivity or specificity (81% and 92% respectively) (Table 13).
Table 13: Accuracy of questionnaire compared to the reference standard for lifetime asthma excluding those without symptoms in the last 12 months

<table>
<thead>
<tr>
<th>Definition</th>
<th>Reference standard</th>
<th>n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>PLR</th>
<th>NLR</th>
<th>J</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD dx lifetime asthma</td>
<td>Clinical dx + Mch 16</td>
<td>163</td>
<td>81%</td>
<td>92%</td>
<td>58%</td>
<td>97%</td>
<td>10.6</td>
<td>0.20</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>56-93</td>
<td>90-94</td>
<td>47-69</td>
<td>94-100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever wheeze</td>
<td>Clinical dx + Mch 16</td>
<td>167</td>
<td>100%</td>
<td>81%</td>
<td>45%</td>
<td>100%</td>
<td>5.4</td>
<td>0</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>78-84</td>
<td>78-84</td>
<td>36-55</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.8.2 Analysis excluding controls with respiratory symptoms

One factor affecting the accuracy of the questionnaire is that control subjects with respiratory symptoms may have undiagnosed asthma. These subjects were therefore excluded to determine if the accuracy of the test improved. Of the 52 subjects with respiratory symptoms and no asthma, 5 (10%) had asthma as assessed by the reference standard. By excluding these subjects, the sensitivity improved (75% to 100%) with only a small decrease in specificity (92% to 88%). This led to an improvement in the negative predictive value but did not significantly change the positive predictive value (Table 14).

Table 14: Accuracy of questionnaire compared to the reference standard for lifetime asthma excluding control subjects with respiratory symptoms

<table>
<thead>
<tr>
<th>Questionnaire definition</th>
<th>Reference standard</th>
<th>N</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>PLR</th>
<th>NLR</th>
<th>J</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD dx lifetime asthma</td>
<td>Clinical dx + Mch 16</td>
<td>145</td>
<td>100%</td>
<td>88%</td>
<td>55%</td>
<td>100%</td>
<td>8.9</td>
<td>0</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>85-90</td>
<td>45-65</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever wheeze</td>
<td>Clinical dx + Mch 16</td>
<td>149</td>
<td>100%</td>
<td>85%</td>
<td>58%</td>
<td>100%</td>
<td>6.8</td>
<td>0</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>82-88</td>
<td>49-68</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5.9 Accuracy of questionnaire for current asthma

Table 15: Number of subjects with and without current asthma in original study compared to this study

<table>
<thead>
<tr>
<th>Questionnaire result</th>
<th>All patients</th>
<th>Verified Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asthma</td>
<td>No asthma</td>
</tr>
<tr>
<td>Asthma</td>
<td>619</td>
<td>41</td>
</tr>
<tr>
<td>Control with respiratory symptoms</td>
<td>1249</td>
<td>2</td>
</tr>
<tr>
<td>Control with no respiratory symptoms</td>
<td>3326</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 16: Corrected number of subjects with and without current asthma accounting for probability of verification

<table>
<thead>
<tr>
<th>Questionnaire result</th>
<th>Empirical probability of verification</th>
<th>Corrected for verification bias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Asthma</td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>Control with respiratory symptoms</td>
<td></td>
<td>0.021</td>
</tr>
<tr>
<td>Control with no respiratory symptoms</td>
<td></td>
<td>0.023</td>
</tr>
</tbody>
</table>

Table 17: 2x2 table used to calculate sensitivity and specificity of questionnaire for current asthma

<table>
<thead>
<tr>
<th>Reference standard</th>
<th>Asthma</th>
<th>Not Asthma</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questionnaire</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>368</td>
<td>251</td>
<td>619</td>
</tr>
<tr>
<td>No asthma</td>
<td>140</td>
<td>4435</td>
<td>4575</td>
</tr>
</tbody>
</table>

*See page 38 for further details

The sensitivity prior to correction for the verification bias was 93% and the specificity was 78%. After correction the sensitivity was 72% and the specificity was 95% leading to a positive predictive value of 60% and a negative predictive value of 97%, which was very similar to the accuracy of the questionnaire for lifetime asthma. Again the accuracy did not change if a PC20 cutoff of less than 8mg/ml was used to define asthma (sensitivity 78%, specificity 94%, PPV 52%, NPV 98%) (Table 18). There were five subjects that had a clinical diagnosis of asthma with a plausible reason for having a false negative methacholine: 1 was on regular inhaled steroids within two weeks of testing, and four were tested outside of their symptomatic season. The sensitivity and specificity did not change when these five subjects were excluded (sensitivity 72.3%, specificity 94.6%).

Alternate definitions for a questionnaire diagnosis of current asthma were assessed. Again, because only two subjects with current asthma did not have physician-diagnosed asthma the
sensitivity and specificity did not change when a definition of diagnosed asthma (versus physician-diagnosed asthma) was used. The definition of wheeze in the last twelve months was only 69% sensitive and 94% specific compared to the reference standard (Table 18). The sensitivity was significantly lower compared to the definition of ever wheeze for lifetime asthma (69% vs. 100%); however, this large difference is due to five patients that did not have wheezing in the last 12 months but had a diagnosis of asthma. When the data was corrected for verification bias, these five patients exerted a large effect on the sensitivity. This also explains why the sensitivity of the current wheeze question was lower than the physician diagnosis definition.

When the questionnaire was compared to the physician’s diagnosis, the sensitivity decreased from 72% to 52% and the specificity did not significantly change (Table 18). This occurred because there were 7 control subjects that were difficult to diagnose clinically. These subjects were initially diagnosed as possible asthma and were eventually given a clinical diagnosis of asthma, thereby decreasing the sensitivity of the questionnaire in comparison to the physician’s clinical diagnosis. However five out of seven of these subjects had a negative methacholine and were given a final diagnosis of not asthma. This highlights the misclassification that occurs when only a physician’s clinical diagnosis is used as the reference standard. The subanalysis was done stratifying the subjects by gender, weight, socioeconomic status, atopic status and race however some of the resulting cell sizes contained less than 5 subjects and meaningful conclusions could not be drawn (data not shown).
Table 18: Accuracy of questionnaire compared to the reference standard for current asthma

<table>
<thead>
<tr>
<th>Definition</th>
<th>n</th>
<th>Reference standard</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>PLR</th>
<th>NLR</th>
<th>J</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD dx current asthma</td>
<td>170</td>
<td>Clinical dx + Mch 16</td>
<td>72%</td>
<td>95%</td>
<td>59%</td>
<td>97%</td>
<td>13.4</td>
<td>0.29</td>
<td>0.67</td>
</tr>
<tr>
<td>Wheeze in last 12m</td>
<td>175</td>
<td>Clinical dx + Mch 16</td>
<td>69%</td>
<td>94%</td>
<td>62%</td>
<td>96%</td>
<td>11.2</td>
<td>0.33</td>
<td>0.63</td>
</tr>
<tr>
<td>Medication use in last 12m</td>
<td>176</td>
<td>Clinical dx + Mch 16</td>
<td>87%</td>
<td>82%</td>
<td>57%</td>
<td>96%</td>
<td>4.9</td>
<td>0.15</td>
<td>0.7</td>
</tr>
<tr>
<td>MD Dx lifetime asthma + wheeze, wheeze after PA, cough, OR meds in last 12m</td>
<td>170</td>
<td>Clinical dx + Mch 16</td>
<td>73%</td>
<td>95%</td>
<td>59%</td>
<td>97%</td>
<td>13.4</td>
<td>0.28</td>
<td>0.68</td>
</tr>
<tr>
<td>MD dx lifetime asthma + wheeze in last 12m</td>
<td>170</td>
<td>Clinical dx + Mch 16</td>
<td>56%</td>
<td>97%</td>
<td>70%</td>
<td>95%</td>
<td>20</td>
<td>0.45</td>
<td>0.53</td>
</tr>
<tr>
<td>Wheeze or medication use</td>
<td>176</td>
<td>Clinical dx + Mch 16</td>
<td>95%</td>
<td>90%</td>
<td>52%</td>
<td>99%</td>
<td>8.9</td>
<td>0.09</td>
<td>0.82</td>
</tr>
<tr>
<td>MD dx current asthma(^1)</td>
<td>170</td>
<td>Clinical dx + Mch 8</td>
<td>77%</td>
<td>94%</td>
<td>52%</td>
<td>98%</td>
<td>12.5</td>
<td>0.24</td>
<td>0.72</td>
</tr>
<tr>
<td>Wheeze in last 12m</td>
<td>175</td>
<td>Clinical dx + Mch 8</td>
<td>71%</td>
<td>93%</td>
<td>54%</td>
<td>96</td>
<td>9.7</td>
<td>0.31</td>
<td>0.64</td>
</tr>
<tr>
<td>MD dx current asthma</td>
<td>174</td>
<td>Clinical dx</td>
<td>52%</td>
<td>98%</td>
<td>90%</td>
<td>84%</td>
<td>21.8</td>
<td>0.49</td>
<td>0.50</td>
</tr>
<tr>
<td>Wheeze in last 12m</td>
<td>179</td>
<td>Clinical dx</td>
<td>59%</td>
<td>98%</td>
<td>90%</td>
<td>90%</td>
<td>33.2</td>
<td>0.41</td>
<td>0.58</td>
</tr>
</tbody>
</table>

5.9.1 Analysis excluding control subjects with respiratory symptoms

26 of the control subjects reported having respiratory symptoms in the last 12 months. 24 were later categorized as not having asthma and 2 were found to have asthma. When these subjects were excluded, the sensitivity significantly increased to 89% with a non-significant decrease in specificity (Table 19).

Table 19: Accuracy of questionnaire compared to the reference standard for current asthma excluding control subjects with respiratory symptoms

<table>
<thead>
<tr>
<th>Definition</th>
<th>N</th>
<th>Reference standard</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>PLR</th>
<th>NLR</th>
<th>J</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD dx current asthma</td>
<td>144</td>
<td>clinical dx + Mch 16</td>
<td>89%</td>
<td>93%</td>
<td>60%</td>
<td>97%</td>
<td>12.6</td>
<td>0.12</td>
<td>0.82</td>
</tr>
<tr>
<td>Wheeze in 12m</td>
<td>149</td>
<td>clinical dx + Mch 16</td>
<td>68%</td>
<td>95%</td>
<td>69%</td>
<td>95%</td>
<td>13.4</td>
<td>0.33</td>
<td>0.63</td>
</tr>
</tbody>
</table>
5.10 Accuracy of administrative database for lifetime asthma

The sensitivity and specificity of the database definition compared to the reference standard were 88% and 65% respectively (Table 20). This is similar to the accuracy of the questionnaire before those numbers were corrected for verification bias. There was no significant difference when a reference standard using a methacholine cutoff of 8mg/ml was used. When a reference standard of the physician’s clinical diagnosis was used, the sensitivity decreased and the specificity increased. Part of the reason this occurred was because when a clinical diagnosis of asthma was used, more subjects were classified as having asthma thereby increasing the denominator of the sensitivity calculation. The subanalysis was done stratifying the subjects by gender, weight, socioeconomic status, atopic status and race however some of the resulting cell sizes contained less than 5 subjects and meaningful conclusions could not be drawn (data not shown).

Table 20: Accuracy of the administrative database for lifetime asthma

<table>
<thead>
<tr>
<th>Definition</th>
<th>Reference standard</th>
<th>n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV*</th>
<th>NPV*</th>
<th>PLR</th>
<th>NLR</th>
<th>J</th>
</tr>
</thead>
<tbody>
<tr>
<td>Database lifetime definition</td>
<td>Clinical dx + Mch 16</td>
<td>178</td>
<td>88%</td>
<td>65%</td>
<td>24%</td>
<td>98%</td>
<td>2.5</td>
<td>0.19</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>78-97</td>
<td>56-74</td>
<td>15-33</td>
<td>94-100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Database lifetime definition</td>
<td>Clinical dx + Mch 8</td>
<td>178</td>
<td>92%</td>
<td>63%</td>
<td>24%</td>
<td>98%</td>
<td>2.5</td>
<td>0.13</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>83-100</td>
<td>54-72</td>
<td>14-33</td>
<td>95-100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Database lifetime definition</td>
<td>Clinical dx</td>
<td>183</td>
<td>80%</td>
<td>84%</td>
<td>37%</td>
<td>97%</td>
<td>4.8</td>
<td>0.24</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>72-88</td>
<td>75-92</td>
<td>27-48</td>
<td>93-100</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Hospitalization or 2 outpatient visits for asthma in 2 consecutive years
*Predictive values were calculated using the corrected prevalence of 11.4% for lifetime asthma from the original study

5.10.1 Analysis excluding those with no current symptoms

The accuracy of a methacholine challenge is decreased in those with no current symptoms, which may lead to those with outgrown asthma being misclassified based on a false negative methacholine challenge. Therefore those with no symptoms in the last 12 months were excluded (n=31) and this did not significantly change the sensitivity or specificity (Table 21).
Table 21: Accuracy of the administrative database for lifetime asthma excluding subjects with no current symptoms

<table>
<thead>
<tr>
<th>Definition</th>
<th>Reference standard</th>
<th>n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV*</th>
<th>NPV*</th>
<th>PLR</th>
<th>NLR</th>
<th>J</th>
</tr>
</thead>
<tbody>
<tr>
<td>Database lifetime definition¹</td>
<td>Clinical dx + Mch 16</td>
<td>178</td>
<td>91% 81-100</td>
<td>71% 62-80</td>
<td>28% 17-39</td>
<td>98% 95-100</td>
<td>0.31</td>
<td>1.3</td>
<td>0.62</td>
</tr>
<tr>
<td>Database lifetime definition¹</td>
<td>Clinical dx + Mch 8</td>
<td>178</td>
<td>95% 86-100</td>
<td>68% 59-77</td>
<td>27% 16-38</td>
<td>99% 96-100</td>
<td>2.97</td>
<td>0.08</td>
<td>0.63</td>
</tr>
<tr>
<td>Database lifetime definition¹</td>
<td>Clinical dx</td>
<td>183</td>
<td>85% 76-94</td>
<td>84% 75-92</td>
<td>39% 27-51</td>
<td>98% 94-100</td>
<td>5.15</td>
<td>0.18</td>
<td>0.68</td>
</tr>
</tbody>
</table>

¹ 1 hospitalization or 2 outpatient visits for asthma in 2 consecutive years
* predictive values were calculated using the corrected prevalence of 11.4% for lifetime asthma from the original study

5.11 Accuracy of administrative database for current asthma

The administrative database had excellent specificity but poor sensitivity compared to the reference standard (90% and 36% respectively) (Table 22). When a two-year lookback period was used instead of the one-year lookback period, the sensitivity increased to 52% with a decrease in the specificity to 81%. The subanalysis was done stratifying the subjects by gender, weight, socioeconomic status, atopic status and race however some of the resulting cell sizes contained less than 5 subjects and meaningful conclusions could not be drawn (data not shown).

Table 22: Accuracy of the administrative database for current asthma

<table>
<thead>
<tr>
<th>Definition</th>
<th>Reference standard</th>
<th>n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV*</th>
<th>NPV*</th>
<th>PLR</th>
<th>NLR</th>
<th>Kappa</th>
<th>J</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year look back¹</td>
<td>Clinical dx and Mch 16</td>
<td>178</td>
<td>36% 21-52</td>
<td>90% 85-96</td>
<td>29% 11-47</td>
<td>93% 89-97</td>
<td>3.7</td>
<td>0.70</td>
<td>0.30</td>
<td>0.27</td>
</tr>
<tr>
<td>1 year look back¹</td>
<td>Clinical dx and Mch 8</td>
<td>178</td>
<td>35% 18-52</td>
<td>89% 83-94</td>
<td>25% 8-43</td>
<td>93% 88-97</td>
<td>3.10</td>
<td>0.73</td>
<td>0.26</td>
<td>0.24</td>
</tr>
<tr>
<td>1 year look back¹</td>
<td>Clinical dx</td>
<td>183</td>
<td>33% 17-50</td>
<td>94% 89-98</td>
<td>36% 17-56</td>
<td>93% 88-97</td>
<td>5.3</td>
<td>0.71</td>
<td>0.3</td>
<td>0.27</td>
</tr>
<tr>
<td>2 year look back²</td>
<td>Clinical dx and Mch 16</td>
<td>178</td>
<td>52% 36-68</td>
<td>81% 74-88</td>
<td>23% 10-36</td>
<td>94% 90-98</td>
<td>2.8</td>
<td>0.59</td>
<td>0.33</td>
<td>0.34</td>
</tr>
<tr>
<td>2 year look back²</td>
<td>Clinical dx and Mch 8</td>
<td>178</td>
<td>54% 37-72</td>
<td>80% 73-87</td>
<td>23% 10-36</td>
<td>94% 90-98</td>
<td>2.7</td>
<td>0.57</td>
<td>0.31</td>
<td>0.34</td>
</tr>
<tr>
<td>2 year look back²</td>
<td>Clinical dx</td>
<td>183</td>
<td>49% 36-61</td>
<td>86% 79-93</td>
<td>27% 13-39</td>
<td>94% 89-98</td>
<td>3.4</td>
<td>0.6</td>
<td>0.36</td>
<td>0.34</td>
</tr>
</tbody>
</table>

¹ Criteria for lifetime asthma met AND 1 hospitalization or outpatient visit in year preceding study assessment
² Criteria for lifetime asthma met AND 1 hospitalization or outpatient visit in 2 years preceding study assessment
* predictive values were calculated using the corrected prevalence of 9.8% for current asthma from the original study
5.12 Accuracy of pulmonary function tests in the diagnosis of asthma

From the spirometry data, the forced expiratory volume in 1 second (FEV1), the FEV1/FVC ratio, and the forced expiratory flow between 25 and 75% of the FVC (FEF25-75, also known as the maximal midexpiratory flows MMEF) were compared to the reference standard for current asthma. For this analysis, those with outgrown asthma were excluded. Receiver operator curves were created for each pulmonary function variable to determine the optimal cutoff point (area on the curve closest to the top left corner).

Figure 6: Receiver operator curves for pulmonary function parameters

Table 23: Accuracy of pulmonary function parameters compared to the current asthma reference standard

<table>
<thead>
<tr>
<th></th>
<th>FEV1/FVC</th>
<th>FEV1</th>
<th>FEF25-75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard cutoff</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>5%ile (85% predicted)</td>
<td>5%ile (80% predicted)</td>
<td>5%ile (63% predicted)</td>
</tr>
<tr>
<td>Specificity</td>
<td>34%</td>
<td>28%</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td>97%</td>
<td>98%</td>
<td>96%</td>
</tr>
<tr>
<td>Optimal cutoff</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area under the curve</td>
<td>0.69 (0.59-0.79)</td>
<td>0.75 (0.66-0.83)</td>
<td>0.79 (0.70-0.87)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>55%</td>
<td>51%</td>
<td>66%</td>
</tr>
<tr>
<td>Specificity</td>
<td>80%</td>
<td>90%</td>
<td>80%</td>
</tr>
</tbody>
</table>
The most accurate test for asthma is the FEF25-75 regardless of which cutoff is used. Using the recommended 5%ile cutoff leads to a high specificity but a low sensitivity for all indices. The cutpoint that optimized sensitivity and specificity was around the 15%ile which increased the sensitivity to 66% for FEF25-75, 55% for the FEV1/FVC and 51% for the FEV1.

5.13 Agreement between physicians
The inter-rater agreement for the clinical diagnosis was assessed. There was better agreement for lifetime asthma (agreement 73-91%, kappa 0.46-0.81) then for current asthma (agreement 64% to 82%, kappa 0.35-0.55).

These kappas were skewed by the increased number of subjects with possible asthma (n=51 for lifetime asthma, n=53 for current asthma) compared to the number of subjects with definite asthma or not asthma (n=16) that were chosen for comparison. The kappa for those with definite asthma or not asthma ranged from 0.81 to 1 (88-100% agreement) versus a kappa of 0-0.78 for those with possible asthma.

5.14 Adverse events
No adverse events were experienced secondary to participating in the study.
Chapter 6
Discussion

The diagnosis of asthma has been plagued by a lack of agreement over how asthma is defined. There is often concern amongst clinicians that the definition of asthma in epidemiologic studies is so far removed from a clinical definition that the results of these studies are not applicable to those patients seen in practice. In particular, studies that use questionnaires about wheezing to draw implications about asthma prevalence and associations have been criticized for being imprecise\textsuperscript{189, 190}. Even when questionnaires inquire about a diagnosis of asthma, there is concern about what diagnostic criteria were used to establish the diagnosis. This goal of this study was therefore to determine the accuracy of questions widely used in epidemiologic studies using a clinical reference standard.

6.1 Questionnaires in Epidemiologic Research

6.1.1 Physician Diagnosed Asthma
The sensitivity and specificity of the physician-diagnosed asthma question was 75\% and 92\% for lifetime asthma and 72\% and 95\% for current asthma. The effect of correcting for verification bias was to decrease the sensitivity and increase the specificity. This is because the majority of the subjects in the original study did not report having asthma and the questionnaire was very accurate for those without asthma (high number of true negatives and low number of false negatives). Although in this validation study there were a low number of false negatives, these subjects exerted a large effect on the corrected sensitivity. The questionnaire was not as accurate at identifying those with asthma (low number of true positives and high number of false positives) however there were relatively few subjects with reported asthma (11\% reported current asthma, 16\% reported lifetime asthma) therefore the number of false positives did not exert a great effect on the specificity. These findings are reflected in the high negative predictive value and low positive predictive value of the questionnaire.

The Remes study, discussed in depth in the introduction section (page 23) is the only other validation study that used a combination of a clinical assessment and objective markers of asthma; it found a sensitivity of 82\% and a specificity of 99\% for physician diagnosed lifetime asthma, and a sensitivity of 88\% and a specificity of 97\% for current asthma\textsuperscript{111}. Their sensitivity for current asthma is likely higher than our reported 72\% because their definition of current asthma was a
physician diagnosis of asthma ever or wheeze in the last 12 months; whereas, our definition required a physician diagnosis of asthma and wheeze or medication use in the last 12 months.

Validation studies that used a clinician’s diagnosis as the reference standard reported sensitivities between 63-70% and specificities between 98-99% for physician diagnosed lifetime asthma\textsuperscript{191,192}. Our study also looked at the accuracy of the questionnaire compared to a clinician’s diagnosis and found a similar specificity of 98% but a slightly lower sensitivity of 52%. This is due to the fact that those with respiratory symptoms but no diagnosis of asthma were purposely oversampled in this study, and this group represented the vast majority of those with undiagnosed asthma. Indeed when this group was excluded from the lifetime analysis, the sensitivity increased to 100% and the specificity remained high at 96%.

6.1.2 Wheezing
As one would expect, using a definition of ever wheeze led to a higher sensitivity (100%) and lower specificity (81%) compared to the physician-diagnosed asthma question. The low specificity of ever wheeze largely reflects the children with transient wheezing who did not have a clear response to asthma medication. Only one other study evaluated the ever wheeze definition and it found a similar sensitivity of 95% and specificity of 78\%\textsuperscript{192}.

Interestingly the current wheeze question had a similar sensitivity and specificity (69\% and 94\% respectively) compared to our questionnaire diagnosis of current asthma (physician diagnosed asthma and wheeze or medication use in the last 12 months) (72\% and 95\%). This may reflect the fact that older children with wheezing are more likely to be given a diagnosis of asthma compared to younger children. Other studies that examined the accuracy of current wheezing using a clinician’s diagnosis of asthma as the reference standard found sensitivities of 86\% and 85\% and specificities of 84\% and 81\%\textsuperscript{163,192}. Our study had a lower sensitivity (60\%) and higher specificity (98\%) when using a clinician’s diagnosis as the reference standard. Some of the differences in the reported accuracy are likely related to the variability in diagnostic criteria between different studies. For example, the study by Jenkins et al\textsuperscript{163} used a clinical definition of “a history of wheeze suggestive of a clinical diagnosis of asthma” and found that the wheezing question led to very few false negatives (1.5\%); whereas our study used a broader definition to include symptoms other than wheeze and found that the current wheeze question had a false negative rate of 10\%. 

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Excluding subjects that have no diagnosis of asthma but report respiratory symptoms led to an improvement in the sensitivity of the questionnaire without a significant decrease in the specificity. Although the rate of asthma underdiagnosis was low in this study (5% for lifetime asthma, 3% for current asthma), this rate was much higher in the group with respiratory symptoms but no asthma diagnosis (10% for lifetime asthma, 8% for current asthma).

6.2. Administrative databases in asthma research

The database definition of lifetime asthma was found to have good sensitivity and reasonable specificity for the diagnosis of asthma (88% and 65% respectively), which led to an excellent negative predictive value but a poor positive predictive value. This supports previous findings from a chart abstraction study that found that the administrative database definition was 89% sensitive and 72% specific\textsuperscript{171}.

The definition for current asthma had very poor sensitivity but good specificity (36% and 90% respectively) which again led to a poor positive predictive value but a good negative predictive value (29% and 93% respectively). When the current asthma definition was expanded to include any hospitalizations or physician visits in the previous two years, the sensitivity increased to 52% but the specificity decreased to 81% which led to a non-significant change in the positive and negative predictive values. This data agrees with another study done in Manitoba which validated an administrative definition of asthma and found that using two years of data led to the highest correlation between the database and questionnaire diagnosis. That study also found that using more than two years of data did not lead to an improvement in the correlation\textsuperscript{193}. The poor sensitivity of the database definition is likely multifactorial: the children in this study had mild asthma and did report any recent emergency room visits or hospitalizations, acute exacerbations did not require a visit to the physician or the visit was coded for something other than asthma (eg. Viral illness), or the children did not have acute exacerbations and asthma medication was prescribed during an annual visit.

There is unfortunately no prescription drug database available in Ontario and having this information would likely have improved the sensitivity of the database based on findings from other studies. One study done in Quebec looked at the utility of adding prescription drug information to an administrative database algorithm\textsuperscript{194}. An algorithm based on medical service information alone had a sensitivity of 54% and a specificity of 83%. When data about controller and reliever medication was added to the algorithm the sensitivity and specificity increased to 70%.
and 94% respectively. In their regression analysis, the strongest predictor for the presence of asthma was the prescription for controller medication with an odds ratio of 22.0. The second strongest predictor was the prescription for a rescuer medication with an odds ratio of 11.6. This data may not be generalizable to Ontario given that prescription drug coverage through either a private or public plan is mandatory in Quebec which is not the case in Ontario. Another study from Winnipeg\textsuperscript{174} showed that the algorithm of one hospitalization, two physician visits or four prescriptions for asthma medication had a sensitivity of 47% and a specificity of 92%, which is similar to our findings of a sensitivity of 36% and a specificity of 90%. That study found that decreasing the requirement to two prescriptions for asthma medication increased the sensitivity to 77% with no change in the specificity. Although that study reported positive predictive values of over 90% for their database algorithms, this is due to the high prevalence (over 60%) of asthma in their cohort. The positive predictive values would be much lower in population based studies where the asthma prevalence is closer to 10%; although this is not clarified in studies that use these algorithms\textsuperscript{195}.

6.3 Impact of misclassification on epidemiologic studies

6.3.1 Studies of prevalence
Relying on questionnaires or administrative databases to ascertain asthma prevalence will inevitably lead to some misclassification of patients. However, given that accurate prevalence estimates require large sample sizes to represent the population, these data sources are ideally suited for prevalence studies. This study shows that questionnaires and administrative databases have an excellent negative predictive value but a much lower positive predictive value. Using the questionnaire, the reported prevalence of physician diagnosed lifetime asthma in our original study was 15.5%; however using the PPV and NPV from our validation study, the calculated corrected prevalence would be 11.4%. Similarly the prevalence of current asthma which was 11.4% in the original study, is corrected to 9.8% using the results of our validation study. It is possible to calculate these prevalence rates directly from the questionnaire data as the correction for the verification bias estimates the prevalence in the original study. Given the high negative predictive value and low positive predictive value, one might expect a much greater difference between the reported versus validated prevalence rates. However the example below, which uses
the asthma prevalence from the National Longitudinal Survey of Children and Youth (NLSCY), illustrates why this is not the case.

Our original study was shown to have a similar asthma prevalence compared to the NLSCY\textsuperscript{175}. The administrative database had a lower positive predictive value but a similar negative predictive value compared to the questionnaire; which suggests that using the database would lead to higher estimates of asthma prevalence. This may help explain the higher prevalence of asthma seen in studies which use this administrative database (21.5% prevalence in children < 14 years old)\textsuperscript{1} compared to the National Longitudinal Survey data (13.4% in children <11 years old)\textsuperscript{196} which uses a questionnaire to ascertain asthma prevalence. The administrative data was not corrected for verification bias; therefore, it is not possible to use the data to directly estimate the prevalence. However it is possible to use the predictive values to calculate an estimate of the lifetime prevalence. Using this method the administrative database gives a lifetime asthma prevalence of 7.0% (see calculation below).

\begin{verbatim}
Data from National Longitudinal Survey of Children and Youth (NLSCY)
40 200 of 241 300 (16.7%) reported a lifetime diagnosis of asthma

Data from validation study for lifetime asthma
positive predictive value (PPV)= 55.2%
negative predictive value (NPV)= 96.7%

Corrected asthma prevalence = [(Number with asthma)(PPV) + (Number without asthma)(1-NPV)] / total
Corrected asthma prevalence = [(40 200)(0.552) + (201100)(0.033)] / 241300 = 12.5%
\end{verbatim}

2001 Prevalence data from OASIS database\textsuperscript{1}
362988 of 1 600 850 (22.7%)

Data from validation study for lifetime asthma
positive predictive value (PPV)= 24%
negative predictive value (NPV)= 98%

Corrected asthma prevalence = [(Number with asthma)(PPV) + (Number without asthma)(1-NPV)] / total
Corrected asthma prevalence = [(362988)(0.24) + (1237862)(0.02)] / 1 600 850 = 7.0%

This data suggests that current methods of assessing childhood asthma prevalence may overestimate the true prevalence.
If one is using the questionnaire to compare asthma prevalence in different populations, the attenuation in the reported prevalence difference is best represented by Youden’s index (J). This study illustrates that for lifetime asthma the ever wheeze question had a higher Youden’s index compared to the ever asthma question (0.81 versus 0.67). For current asthma prevalence, Youden’s index was similar for the current wheeze question compared to our algorithm for current asthma (physician diagnosed asthma with either wheeze or medication use in the last 12 months). The definition that maximized Youden’s index (J=0.82) for current asthma required either wheeze or medication use in the last 12 months. Although the Youden’s index is higher for this definition, it may lead to differential misclassification if used in international studies, where access to medication may vary widely between centers.

6.3.2 Effect on studies of risk estimate

The effect of misclassification is more problematic in estimates of risk compared to prevalence studies. This study confirms that diagnosis-based questions are better than symptom-based questions for accurately evaluating risk estimates given the higher positive predictive value of these questions. The positive predictive value was 55% for lifetime asthma and 59% for current asthma, which means that if a questionnaire was used to define the asthma group almost half of the group would not have asthma. If the misclassification was undifferential and independent (see section 1.4.1) then this would lead to a decrease in the estimated risk towards the null. On the other hand, the negative predictive value of the questionnaire was high irrespective of which question was used. The effect of using different definitions of asthma on the observed odds ratio was illustrated using the data from the European Community Respiratory Health Study I. This paper looked at the odds ratio for atopy and found that using a definition of wheeze produced an odds ratio of 1.84, while a definition of wheeze and bronchial hyperreactivity led to an odds ratio of 4.13.

There is ongoing debate about how asthma should be defined in epidemiologic studies exploring the causes of asthma. The two previous studies that have validated the questionnaire in the pediatric population both came to the conclusion that a questionnaire alone should be used to define the asthma population. These studies found that adding BHR to the results of the questionnaire decreased the sensitivity to the degree that many with asthma would be excluded if this definition were used. However, one study used a clinician’s diagnosis as the gold standard.
and given that the questionnaire and the clinical diagnosis are both based on symptoms, it is not surprising that adding BHR to a symptom questionnaire led to a lower sensitivity. The topic of what constitutes an appropriate reference standard for asthma validation studies will be discussed further in section 6.6.3. The second study used a reference standard which did include objective measures, however the cutoff used for the methacholine challenge was very low (equivalent to a PC20 of 1-4mg/ml) and given this stringent cutoff, it is not unexpected that the sensitivity of the questionnaire and BHR definition was only 38%\(^{111}\). The low sensitivity and high specificity of a definition that combines symptoms with BHR, makes it an inappropriate measure of prevalence however this does not negate its utility in risk estimates. Although predictive values are heavily affected by population prevalence, if one considers that asthma prevalence is less than 20%,\(^{134}\) definitions with high specificity and moderate sensitivity will have better positive predictive values compared to definitions that have high sensitivity and moderate specificity (see appendix 4, page 104). For this reason, it has been advocated that a definition of symptomatic bronchial hyperreactivity be used to identify asthma patients in studies that estimate risk\(^{72,145,197}\).

The results from this study suggest that a questionnaire alone can be used to accurately identify subjects without asthma; however, to decrease misclassification in the asthma group further testing, such as a methacholine challenge, should be done to confirm the diagnosis. If questionnaires alone are used to define the asthma group, the degree of misclassification should be taken into consideration when calculating sample sizes.

### 6.4 Biases in the assessment of diagnostic test accuracy

There are multiple types of bias that can potentially occur when evaluating a diagnostic test. These include biases of disease spectrum, diagnostic review (the test result affects the interpretation of data that is used to make the gold standard diagnosis), test review (the diagnosis affects the interpretation of the test), incorporation bias (the test being evaluated is used to establish the gold standard diagnosis) and verification bias (a disproportionate number of subjects with a positive test undergo further testing to establish the goldstandard diagnosis)\(^{198}\). This study was carefully constructed to avoid these types of biases. The gold standard diagnosis was made after the test (either the questionnaire or administrative database diagnosis) was completed thereby avoiding test review bias. In addition, the physicians were blinded to the results of the questionnaire and administrative database diagnosis thereby avoiding diagnostic review bias. Given that these tests
are to be used in population-based studies, the spectrum of disease in our subjects was appropriate. The reference standard was established without using the data from the questionnaire or database, thereby avoiding incorporation bias. However, this is the reason that the accuracy of the methacholine challenge could not be assessed (see section 6.5).

Verification bias is an issue that is intrinsic to nested case-control studies that evaluate diagnostic test accuracy, as cases are typically oversampled from the general study based on the result of the test under study. This leads to an overestimation of the sensitivity and underestimation of the specificity compared to what would be seen in the original study. Because the decision to verify a subject’s disease status is predictable, it is possible to correct for this bias (using the terminology of Begg\textsuperscript{184}, the conditional independence assumption has been met). This statistical correction was used in the calculation of the sensitivity and specificity of the questionnaire, given that subjects were chosen based on their questionnaire response. As expected, the sensitivity significantly decreased and the specificity increased when the correction was applied. Using the example of the questionnaire diagnosis for lifetime asthma, the sensitivity and specificity were 91\% and 69\% using the uncorrected data and 75\% and 92\% for the corrected data. This method of correction is suggested by some epidemiologists\textsuperscript{145} and was used in this study to allow for comparison with other papers which used this method of correction\textsuperscript{111,163}. The Begg method may be an oversimplication which tends to overestimate specificity and underestimate sensitivity\textsuperscript{199}. An alternative technique which uses multiple imputations to determine the values for the non-verified subjects has been proposed as a more accurate way to correct the bias, however it has not been used in previous asthma validation studies\textsuperscript{199,200}.

The issue of the statistical correction for verification bias is further highlighted in this study because two data sources were assessed (the questionnaire and the administrative database). Because the subjects were chosen based on their response to the questionnaire and not based on their database diagnosis, the correction for verification bias was only applied to the questionnaire data. In fact, the raw data for the questionnaire diagnosis for lifetime asthma was very similar to the data for the administrative database diagnosis for lifetime asthma. However if one looks at the corrected sensitivity and specificity for the questionnaire, it suggests that the questionnaire diagnosis is much more specific than the database diagnosis. Although this finding is somewhat intuitive, it is not supported by the raw data. The Begg method for correcting for verification bias may lead to an inflation of the specificity and a deflation of the sensitivity compared to the
Therefore it is possible that using the multiple imputation method to correct the questionnaire data may have led to similar estimates of sensitivity and specificity compared to the administrative database. However, this comparative analysis is beyond the scope of this thesis.

6.5 What tests are useful in the diagnosis of asthma?

This study was not designed to assess the accuracy of the methacholine challenge as that would result in incorporation bias. However, it is possible to explore the accuracy of the methacholine challenge compared to a clinician’s diagnosis studies. The high rate of negative methacholine challenges (45%) in those with a clinical diagnosis of lifetime asthma could be attributed to the large number of subjects with outgrown asthma who had a negative methacholine challenge (44% with a clinical diagnosis of outgrown asthma had a PC20≥16mg/ml). For those with a clinical diagnosis of current asthma, 37% had a PC20 greater than 16mg/ml and 46% had a PC20 greater than 8mg/ml. This is comparable to other studies using a physician’s clinical diagnosis as the reference standard, which have found a false negative rate ranging from 30-34%\textsuperscript{124,129} using a cutoff of 16mg/ml, and a false negative rate from 30-50%\textsuperscript{96,123,127,80,120,122} using a cutoff of 8mg/ml. Studies that have used a higher cutoff of 25mg/ml have found false negative rates of only 17%\textsuperscript{125}; whereas, studies that have used a lower cutoff of 1-2mg/ml have found higher false negative rates of 53%\textsuperscript{111}. The rate is much higher than those found in clinic-based studies where only 5 to 8%\textsuperscript{115,116} of those with asthma have a negative methacholine challenge. This may be because asthma subjects found in asthma clinics tend to have more severe and clearly defined disease, compared to those sampled randomly from the population. Indeed, our study found that only 24% of those with definite asthma diagnosed by the study physician had a negative methacholine challenge compared to 60% of subjects that were initially diagnosed with possible asthma. The use of asthma medication is often cited as a cause for false negative methacholine challenges. During this study, all medications were held 48 hours prior to the methacholine challenge which is enough time for the effects of beta-agonists to dissipate. Inhaled corticosteroids can affect bronchial hyperreactivity by up to 1-2 doubling doses if the medication is taken regularly (eg. Daily for 8 weeks) or is taken at high doses (eg. Fluticasone 1000ug)\textsuperscript{105,106}. In this study, only 8 subjects fulfilled either of these criteria and of these 7 had objective evidence of
asthma (6 with a positive methacholine challenge, 1 with a bronchodilator response). One of these subjects had a PC20 of 11.6 and would have been classified as not having asthma if the standard PC20 cutoff of 8mg/ml was used. The persistence of bronchial hyperreactivity in patients taking regular inhaled corticosteroids has also been described in asthma treatment trials\textsuperscript{201}. This is not surprising given that children with persistent symptoms requiring regular inhaled corticosteroids typically have a lower PC20 and although the medication increases this by up to two doubling doses, they would still be expected to exhibit some bronchial hyperreactivity. A previous study concluded that the accuracy of the methacholine challenge was affected by gender and atopy status and was particularly poor in non-atopic males\textsuperscript{123}, however our study did not find that this group was over-represented in those with a clinical diagnosis of asthma but a negative methacholine challenge.

Thirty-four percent of those with no clinical diagnosis of current asthma had a methacholine challenge less than 16mg/ml and this number decreased to 25% if a cutoff of 8mg/ml was used. This is similar to other studies that have reported rates of 10% to 22% using a cutoff of 16mg/ml\textsuperscript{118-120, 122, 124, 127, 129}; however it is much lower than the 52-72% reported in some studies that have also used a cutoff of 8mg/ml\textsuperscript{112, 123, 126}. This number may be higher than other studies because of the number of subjects with outgrown asthma that were included in the control group. In our study, 13 of the 44 subjects with a PC20 ≤ 16mg/ml and no diagnosis of asthma had a previous history consistent with asthma but did not have current symptoms. In the studies with high rates of false positive methacholines\textsuperscript{112, 123, 126}, there was no clarification if those with a previous history of asthma but no symptoms in the last 12 months were excluded. In addition, one of the studies used a cohort of children at high risk for asthma and even in the group with no asthma, 75% had a family history of asthma\textsuperscript{126}. Given that there is likely some genetic determinant for bronchial hyperreactivity\textsuperscript{109}, this may explain the 73% of children with asymptomatic bronchial hyperreactivity (PC20 ≤ 8mg/ml) in that study. Another study used a cohort of 6 year old children and the 64% false positive rate using a cutoff of 4mg/ml may be due to the increased relative dose of methacholine delivered and the higher rates of asymptomatic bronchial hyperreactivity found in younger children\textsuperscript{131, 132}.

This study also examined the utility of pulmonary function tests in the diagnosis of current asthma. In addition to looking at the suggested cutoff of the fifth percentile to define abnormal pulmonary function to calculate accuracy, we also created receiver operator curves to determine the optimal
cutoff points. The fifth percentile is the recommended cutoff because given a normal distribution of results, a value less than the fifth percentile is statistically abnormal (ie. greater than 2 standard deviations from the normal), however this may not be a clinically significant cutoff point.

This study confirms findings from other studies that show that using less than the 5%ile to define abnormal lung function has a low sensitivity for asthma. The sensitivity was highest for the FEF25-75 at 51% and lowest for the FEV1 at 28%. However, at this cutoff pulmonary function tests were very specific for the diagnosis of asthma. The 13-16th percentile was the cutoff point that optimized sensitivity and specificity for each of the indices. At this cutoff the sensitivity for asthma increased to 66% for the FEF25-75 and 51% for the FEV1. Even with the improved sensitivity, these tests are still not accurate enough to identify those with asthma for epidemiologic studies. In the clinical setting where the asthma prevalence is much higher than in a population-based sample, using the fifth percentile cutoff is useful for diagnosing someone with asthma if they have an abnormal test. On the other hand, using the cutoff that optimizes both sensitivity and specificity leads to moderate positive and negative predictive values, which is not useful for confidently ruling in or out a diagnosis of asthma. Given that pulmonary function tests are often normal in those with stable asthma, the way to utilize pulmonary function tests in a clinical setting would be to do a pulmonary function test at the first visit, knowing that a normal test will not rule out the diagnosis but that an abnormal test will help to confirm the diagnosis. In those with a normal test, a repeat spirometry when the patient is symptomatic will improve the accuracy of the test because it can determine if the patient’s symptoms are due to airway obstruction. Although it could be argued that given the low sensitivity of pulmonary function testing, it is not useful to perform in patients with stable asthma, multiple studies have shown that both patients and physicians are poor at determining the severity of obstruction. In this study 34%, 28%, 51% of those with current asthma had an FEV1/FVC ratio, FEV1, FEF2575 less than the 5th percentile. This was found even in those subjects who classified themselves as well-controlled on the Child Asthma Control Test.

6.6 Strengths of the study

6.6.1 Spectrum of disease representative of community sample

The subjects with asthma in this study were representative of the case mix expected in the community. There was no difference in the severity of symptoms in the group of subjects with
asthma that participated in this study, compared to the original study. The majority were classified as having mild intermittent symptoms, according to the GINA guidelines\textsuperscript{205} and the most symptomatic were classified as having moderate persistent symptoms and this group constituted only 9\% of those with current asthma. This supports other papers that suggest that the increase in asthma prevalence is due to those with mild symptoms\textsuperscript{206}. Given that the hospitalization rate for asthma in Ontario in this age group is only 1.9/100, it is not surprising that there were no recent hospitalizations in the 47 subjects with confirmed current asthma.

6.6.2 Ability to assess agreement between physicians
Another strength of the study was that three different physicians took part in determining the clinical diagnosis. This allowed us to compare the level of agreement between physicians. It has previously been published that the level of agreement between physicians for the diagnosis of asthma in adults is high\textsuperscript{128}, however there are reasons why the level of agreement may be lower in children. Children often cannot self-report symptoms therefore a parental proxy must be used. Because one is relying on an observer’s history, the details are subject to interpretation and inquiring about shortness of breath or difficulty breathing can be especially subjective. It has been shown in a previous study that children often perceive their symptoms differently than what is reported by parents\textsuperscript{207}. The variability in physician opinion seen in this study is likely a true reflection of what occurs in the clinical and research settings. In fact, the effect was likely diluted in this study given that all three physicians were from the same center and used the Canadian Asthma Guidelines\textsuperscript{41} to determine the clinical diagnosis. This highlights the potential danger in using a clinical diagnosis as the reference standard for validation studies. It cannot be ensured that a consistent group of subjects is identified given the variability in the reference standard.

6.6.3 Objective testing included in reference standard
The requirement to have objective evidence to confirm the diagnosis of asthma would be considered a strength of the study by some, and a weakness by others. The detractors of including objective testing in the definition of asthma argue that it will lead to the exclusion of subjects that have an asthma phenotype but lack objective evidence of the disease at the time of testing. Given that the repeatability of a methacholine challenge is +/- 1 doubling dose, it is possible that those with no bronchial hyperreactivity might have mild bronchial hyperreactivity if re-tested, which is why the high cutoff of 16mg/ml was used in this study. As discussed in the
introduction (section 1.3.3), subjects with bronchial hyperreactivity are more likely to have persistent symptoms that affect activity and sleep and to be hospitalized and have airway remodelling, compared with subjects that have only symptoms. Whether those with asthma symptoms but no objective findings should be categorized as having very mild asthma or not asthma, may be an issue of semantics if this group of patients has not been shown to respond to asthma therapy (given that they would not meet inclusion criteria for therapeutic studies) and do not experience significant complications of the disease.

The reference standard used in this study required both a physician’s clinical diagnosis as well as objective evidence of reversible obstruction or bronchial hyperreactivity, which is the standard suggested in clinical asthma guidelines\textsuperscript{4,33,41}. Others have suggested that a clinical diagnosis alone should be the reference standard, given that tests of bronchial hyperreactivity are not perfectly sensitive or specific for asthma\textsuperscript{123,163}.

This study illustrates that there can be significant inter-rater variability in diagnosing asthma. The agreement was assessed between each of the three physicians and the kappa ranged from 0.35 to 0.81, which is lower than has previously been reported\textsuperscript{128}. This is due to the oversampling of those with self-reported asthma and those with respiratory symptoms but no previous diagnosis of asthma. Thirty percent of the subjects in these two groups presented a diagnostic dilemma and were initially classified as having possible asthma. The data from these subjects was re-evaluated to establish a final clinical diagnosis; however, there was only fair agreement (kappa 0 to 0.78) between two physicians and often the final diagnosis required the clinical opinion of the third physician. The major challenge in making a definitive clinical diagnosis in an epidemiologic cross-sectional study is that the vast majority of those with asthma have mild intermittent symptoms. Of those that were given a final diagnosis of asthma, none had hospitalizations or emergency room visits in the last year, only four required systemic steroids in the last year, and the majority were on intermittent therapy. In this group of patients, the details regarding their respiratory symptoms and their response to asthma treatment were often not clear. The challenges in making a clinical diagnosis of asthma in an epidemiologic study are likely not unique to this study, although the clinical certainty of the assessor is not discussed in other studies that use this as their reference standard.

If the conditions that cause false negative methacholine challenges (recent medication use, tested out of season to their symptoms, no recent symptoms) are accounted for, previous studies indicate
that a methacholine challenge is highly sensitive and would indeed rule out a diagnosis of asthma. These conditions were more difficult to satisfy when validating lifetime asthma as 17% of subjects did not report symptoms in the last 12 months. For this reason an analysis was done excluding those without current symptoms and this led to a non-significant increase in the sensitivity and no change in the specificity. For those with current asthma, a sensitivity analysis was done excluding the five subjects with a possible cause for a false negative methacholine challenge and this did not significantly alter the accuracy of the questionnaire.

In this study, the results of the methacholine challenge did not affect the final diagnosis of those with a clinical diagnosis of not asthma. Although this group of patients with asymptomatic bronchial hyperreactivity has been shown to be at increased risk for the future development of asthma, given their lack of current symptoms, they should not be classified as having asthma.

6.6.4 Avoidance of Diagnostic Review Bias
As discussed in section 6.4, the physicians were blinded to the questionnaire and administrative database diagnosis. This ensured that the diagnostic tests under review did not affect the final reference standard assigned to each subject.

6.7 Limitations of the study
6.7.1 Requiring objective evidence of asthma when assessing for lifetime asthma
It is known that the sensitivity of the methacholine challenge decreases in subjects that do not have current symptoms, and in this study likely accounted for some of the discrepancy between the clinical diagnosis of lifetime asthma and the methacholine results. It would therefore seem counterintuitive to require objective evidence of asthma in the reference standard for lifetime asthma. The rationale for this was that the majority of those with lifetime reported asthma had experienced current symptoms and the methacholine challenge was therefore still considered a valid test in this group. However, an analysis was done which excluded the subjects that had not experienced symptoms in the last year and it did not significantly change the accuracy. This occurred because there was an almost equal number of subjects without current symptoms in the control and asthma groups. This may not be true in future studies, and the accuracy of a methacholine challenge in those without current symptoms should be carefully considered.
6.7.2 Generalizability

The children in this study were randomly selected from a population-based sample. Although the original T-CHEQ study only had a 25% participation rate, those children were shown to be similar to the Canadian population with respect to demographic factors\textsuperscript{175}; therefore, the low participation rate is unlikely to lead to bias. This study had a 35% participation rate and when comparing the participants to the original study subjects, the major difference was that the children that participated were from a higher socioeconomic strata compared to non-participants. This may have been because the children and their families were asked to come to the hospital in the evening to participate in the study, and although compensation was given for travel expenses, it was difficult for some families to arrange childcare for their other children and for parents who worked in the evenings to participate. Previous studies from the United States\textsuperscript{208} have shown that those from lower socioeconomic classes are more likely to be underdiagnosed with asthma, however this may be related to access to healthcare and similar studies have not been done within the Canadian context. A study done in Canada has shown that those with asthma in a lower socioeconomic strata have higher health care utilization and hospitalizations which may contribute to the low rate of hospitalizations in the study\textsuperscript{209}.

The participants in this study do not necessarily reflect the ethnic and cultural diversity seen in Canada. This was due to two factors: the participants had to be born in Toronto to be a part of the previous study, and they had to speak English to participate in the physician interview. Unfortunately, given the diversity of the population in Toronto, translators were not available for the clinic visits. Including this subset of the population may have decreased the accuracy of the questionnaire given the different perception of respiratory symptoms and of asthma in different cultures.

This study found that the question regarding asthma diagnosis was as accurate as a question regarding physician-diagnosed asthma. The low number (n=5) of subjects that had asthma that was not physician diagnosed may be a consequence of the universal health care system and this may not be generalizable to populations with different systems of healthcare.

The accuracy of the administrative database definitions are not applicable to all administrative databases. In Ontario, there is mandatory reporting for the hospital discharge data and the accuracy of the OHIP data has been previously validated for pediatric asthma\textsuperscript{179}, which makes these data sources quite robust. The accuracy of these databases may change over time if more
physicians are paid through alternative funding plans as opposed to fee-for-service arrangements, as the incentive for providing accurate and complete billing data will decrease. These alternate funding plans are already in place in many academic centers across Ontario, however typically only the more severe asthma patients, which are a small percentage of those with asthma, are cared for in these academic facilities. Other changes that may affect the accuracy of the data include changes to the billing codes. In 2005 a billing code (E078A) was added which allowed providers to bill an extra 50% for visits involving children with chronic diseases such as asthma. It is reassuring that the validation study involving data from 1992 to 2001 had similar results to our validation study which used data from 1999 to 2011.

The children in this study were all 8 to 12 years old and these results may not be generalizable outside of this age range. As previously discussed, the diagnosis of asthma in children under the age of five is difficult and terms such as “wheezy bronchitis” or “reactive airway disease” are often used to describe younger children with recurrent wheezing. Therefore, the question regarding a diagnosis of asthma may be less sensitive in this age range. This was illustrated in a large study of children aged 1-5 that found that 20% of children with recurrent weekly respiratory symptoms did not have a diagnosis of asthma. The other age group where the questionnaire may not be as accurate would be in adolescents. Multiple studies have shown that this group is at risk for underdiagnosis; which again means that the physician-diagnosed asthma question may be less sensitive.

6.7.3 Cross-sectional nature of the study

This was a cross-sectional study and therefore longitudinal followup of the subjects was not possible. Ideally, the group with a clinical diagnosis of asthma but a negative methacholine challenge would be followed up to determine if they had evidence of reversible obstruction or bronchial hyperreactivity at a later date. Previous data suggests that up to 30% of those with respiratory symptoms and normal pulmonary function tests will later have evidence of reversible obstruction. A longitudinal study done in adults showed that in those with a diagnosis of asthma but a negative methacholine challenge, 34% took some type of asthma medication in the 7 month followup; although only 1% required steroid therapy. If this data was extrapolated to our study, and 30% of those with a clinical diagnosis of asthma but a negative methacholine challenge in fact had asthma, the sensitivity of the questionnaire for lifetime asthma would have decreased from to 75.3% to 63.4%, the specificity would have increased from 92.1% to 93.1%, the negative
predictive would still be high at 93.3% although the positive predictive value would increase from 55.2% to 62.7% (data not shown). Similar results were found for current asthma if a 30% misclassification rate was applied to those with a clinical diagnosis of asthma but a negative methacholine.
Chapter 7
Conclusions

The benefit of using questionnaires and administrative databases for epidemiologic research is that they provide representative population samples in a cost-effective manner. The drawback is that they have a low positive predictive value in comparison to a clinical diagnosis of asthma.

In Canada, estimates of asthma prevalence are obtained from both questionnaire and administrative databases. The lower positive predictive value of the administrative database compared to the questionnaire explains why the estimates of prevalence from these databases is higher compared to estimates from questionnaires (21.5% versus 13.4%). When the predictive values from this study were used to adjust the reported prevalence rates, estimates of 8.0 and 10.7% were calculated for the administrative database and questionnaire data, respectively. Although these data sources do overestimate asthma prevalence, this study illustrates that childhood asthma is still a common condition with prevalence rates similar to those of childhood obesity.

This study also sheds some light on the resource utilization of children with respiratory symptoms. The administrative database identifies asthma cases by visits to a physician, emergency room or hospital. The administrative database identified 29 children with asthma; however, only 55% of these met the gold standard definition of asthma. Clearly the other 45% of children identified in the database had respiratory symptoms suggestive of asthma however they may not benefit from asthma treatment. Conversely 44 children were diagnosed with asthma by the gold standard and only 36% of these were identified in the administrative database. Although it is encouraging that none of the children with asthma had a recent hospitalization, it is surprising that 64% of those with asthma identified by the goldstandard had not seen a physician for their asthma in the last year. This study illustrates that there is both over and underdiagnosis of asthma in children, and the first step in improving the quality of care for these children would be to use objective measures to confirm a diagnosis of asthma. Although pulmonary function tests were found to be insensitive for the diagnosis of asthma in this population-based sample, 30-50% of those with asthma had abnormal tests depending on what parameter was evaluated. Further studies should be done to evaluate the accuracy of these tests in the primary care setting where children are seen when they are symptomatic.
Questionnaires are the primary data source for asthma studies evaluating risk. The high negative predictive value of these questionnaires suggests that they are accurate in identifying control subjects. To further improve the selection of control subjects, those that report respiratory symptoms on the questionnaire should be excluded, as the negative predictive value of the questionnaire was 100% when this was done. The identification of asthma subjects using a questionnaire is more problematic given the lower positive predictive value. This misclassification leads to a dilution of the asthma group with subjects who have respiratory symptoms but not necessarily asthma. This has implications for studies that attempt to elucidate the genetic or environmental causes of asthma, as the effect size will be diminished if the misclassification is non-differential. For these studies, confirming a questionnaire diagnosis of asthma using a methacholine challenge may increase the accuracy of the estimated risk. Alternatively, developing questionnaires that have a higher positive predictive value for asthma would be beneficial. This misclassification is less problematic in population studies that identify irritant environmental factors (such as tobacco smoke or pollution) that have a negative effect on respiratory health, since there is still a significant public health consequence whether the symptoms are due to asthma or not.

Administrative datasets and questionnaires will always have a place in epidemiologic studies given their cost-effectiveness and ease of administration. However, it is important to consider the limitations of these data sources when designing future studies.
Chapter 8
Future directions

The understanding of the underlying pathophysiology of asthma has evolved over the past decades however diagnostic tests for asthma have had a slower evolution. An ideal test would identify patients based on the underlying abnormality that causes the reversible airways obstruction. This presupposes that there is one underlying mechanism that is responsible for the manifestations of asthma. The concept of asthma as a single disease is being replaced by the paradigm that asthma is a collection of phenotypes which may respond to different treatments and have different prognoses. This paradigm shift is occurring in research involving preschool wheezers, where some have advocated abandoning the term “asthma” altogether. Indeed a recent study exploring the association between paracetamol use and asthma failed to find a significant odds ratio in children with late onset wheezing, in comparison to those with early onset or persistent wheezing\textsuperscript{214}, which highlights the importance of considering asthma phenotypes in epidemiologic research. The existence of different asthma phenotypes has also helped to explain why some tests such as exhaled nitric oxide have not proven to be overly useful for diagnosing asthma. In theory, exhaled nitric oxide was the ideal test for asthma as it is a biomarker for lower airway inflammation, which is thought to be the underlying mechanism for all types of asthma. However, further research has shown that since it most closely correlates with eosinophilic inflammation, it is only useful for those with atopic asthma\textsuperscript{150}.

Asthma epidemiologists have the difficult task of untangling which environmental factors lead to the development of asthma in the susceptible individual. Adding to this complexity is the possibility that different asthma phenotypes may be influenced by different environmental factors. This may explain why even large studies are unable to conclusively identify risk factors for this common disease. Currently questionnaires alone are used to identify subjects with asthma in most epidemiologic studies; however this selects a very heterogeneous group of subjects. Perhaps stronger associations would be found in epidemiologic studies if a more homogenous group of subjects with well-defined asthma were chosen. As in clinical studies, this could be accomplished by requiring objective testing to confirm a diagnosis of asthma. As the importance of various cytokines (eg. IL-5, IL-13) are better understood, diagnostic tests that are able to phenotype those with asthma are being developed. Epidemiologic studies are interested in the determinants of disease; the idea of asthma as an assortment of phenotypes is developing. In the future, the
epidemiologic study of asthma may follow suit and endeavor to identify factors that contribute to each of these phenotypes.
References


120. Pattemore PK, Asher MI, Harrison AC, Mitchell EA, Rea HH, Stewart AW. The interrelationship among bronchial hyperresponsiveness, the diagnosis of asthma, and asthma symptoms. American Review of Respiratory Disease 1990;142:549-54.


188. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159-74.

189. Scott M, Kurukulaaratchy RJ, Arshad SH. Definitions are important and not all wheeze is asthma. Thorax 2011;66:633.


**Appendices**

**Appendix 1: Table of pediatric studies assessing the accuracy of the methacholine/histamine challenge**

<table>
<thead>
<tr>
<th>Population tested</th>
<th>N</th>
<th>Ages (years)</th>
<th>Test</th>
<th>Gold standard</th>
<th>PC20/PD20 (approx PC20 equivalent)*</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spiropoulos</td>
<td>70</td>
<td>4-16</td>
<td>Dosimeter (max: 25mg/ml)</td>
<td>Questionnaire History of chronic cough clinically responsive to bronchodilators</td>
<td>100 breath units (10mg/ml)</td>
<td>70</td>
<td>61</td>
<td>Population of asthmatics not well defined</td>
</tr>
<tr>
<td>Pattermore</td>
<td>2045</td>
<td>7-10</td>
<td>Yan</td>
<td>Questionnaire (Ever asthma)</td>
<td>7.8umol (8mg/ml)</td>
<td>52</td>
<td>90</td>
<td>Low sensitivity even for those with current sx</td>
</tr>
<tr>
<td>Forastiere</td>
<td>1777</td>
<td>7-11</td>
<td>Tidal breathing (max: 64mg/ml)</td>
<td>Questionnaire (Ever asthma diagnosed by a physician)</td>
<td>8mg/ml</td>
<td>50</td>
<td>78</td>
<td>Did not specify if asthma was current</td>
</tr>
<tr>
<td>Salome</td>
<td>2363</td>
<td>8-11</td>
<td>Yan</td>
<td>Questionnaire (Ever asthma diagnosed by a physician)</td>
<td>7.8umol (~16mg/ml)</td>
<td>53²</td>
<td>87²</td>
<td>Over half of those with a questionnaire diagnosis of asthma did not have symptoms in the last 12 months</td>
</tr>
<tr>
<td>Cockcroft</td>
<td>500</td>
<td>20-29</td>
<td>Tidal breathing (max: 8mg/ml)</td>
<td>Questionnaire (MD dx asthma and recurrent wheezing)</td>
<td>8mg/ml</td>
<td>100</td>
<td>93</td>
<td>Clarified relationship between timing of symptoms and accuracy of methacholine</td>
</tr>
<tr>
<td>Joseph-Bowen</td>
<td>537</td>
<td>6</td>
<td>Yan</td>
<td>Questionnaire (Md dx and current sx of wheeze or night cough without URTI and on meds in last 12m)</td>
<td>3.9mg/ml</td>
<td>86</td>
<td>36</td>
<td>Low specificity may be due to younger age of cohort</td>
</tr>
<tr>
<td>Backer</td>
<td>495</td>
<td>7-16yo</td>
<td>Tidal breathing (max: 8mg/ml)</td>
<td>Algorithm from questionnaire</td>
<td>8mg/ml</td>
<td>100</td>
<td>89</td>
<td>Very specific questionnaire algorithm used for reference</td>
</tr>
<tr>
<td>Hopp</td>
<td>156</td>
<td>5-21yo</td>
<td>Dosimeter (max: 60mg/ml)</td>
<td>Algorithm from questionnaire</td>
<td>100 breath units (10mg/ml)</td>
<td>89</td>
<td>89</td>
<td>Very specific questionnaire algorithm used for reference</td>
</tr>
</tbody>
</table>
## Appendix 1 cont’d

<table>
<thead>
<tr>
<th>Population tested</th>
<th>N</th>
<th>Ages (years)</th>
<th>Test</th>
<th>Gold standard</th>
<th>PC20/PD20 (approx PC20 equivalent)*</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Godfrey</td>
<td>232 with asthma</td>
<td>5-18</td>
<td>Tidal breathing (max: 32mg/ml)</td>
<td>Database diagnosis of asthma diagnosed by physician</td>
<td>8umol (6-8mg/ml)</td>
<td>96</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Sears</td>
<td>766</td>
<td>9</td>
<td>Dosimeter (Max: 25mg/ml)</td>
<td>Physician history of recurrent wheezing</td>
<td>25mg/ml</td>
<td>83</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Galdes-Sebaldt</td>
<td>33</td>
<td>7-16</td>
<td>Dosimeter (max: 25mg/ml)</td>
<td>Physician history of episodes of reversible obstruction</td>
<td>25mg/ml</td>
<td>95</td>
<td>83</td>
<td>Unclear if reversible obstruction documented with spirometry</td>
</tr>
<tr>
<td>Lee</td>
<td>270</td>
<td>7</td>
<td>Dosimeter</td>
<td>Physician assessment and family reported response to bronchodilators</td>
<td>16g/l&lt;sup&gt;1&lt;/sup&gt;</td>
<td>67</td>
<td>67</td>
<td>Bronchodilator response not measured objectively</td>
</tr>
<tr>
<td>Carlsten</td>
<td>348</td>
<td>7</td>
<td>Tidal breathing</td>
<td>Physician dx based on history</td>
<td>8mg/ml</td>
<td>92</td>
<td>27</td>
<td>Low specificity may be due to high family history of atopy</td>
</tr>
<tr>
<td>Liem</td>
<td>412</td>
<td>8</td>
<td>Tidal breathing</td>
<td>Physician assessment</td>
<td>8</td>
<td>70</td>
<td>48</td>
<td>No objective evidence of asthma</td>
</tr>
<tr>
<td>Andersen</td>
<td>96</td>
<td>6-18</td>
<td>Dosimeter</td>
<td>Clinical assessment based on hx, physical exam, PFT, exercise challenge</td>
<td>16mg/ml</td>
<td>66</td>
<td>63</td>
<td>Unclear what objective criteria were needed for final diagnosis</td>
</tr>
<tr>
<td>Remes</td>
<td>247</td>
<td>7-12</td>
<td>Dosimeter (unclear if this was the five breath method)</td>
<td>Physician assessment of SOB w/ wheeze or prolonged cough with one objective measure</td>
<td>PD20 400ug (~2-4mg/ml)</td>
<td>47</td>
<td>97</td>
<td>Used low PC20 cutoff</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unclear if standardized method used for methacholine challenge</td>
</tr>
</tbody>
</table>

<sup>*equivalency as per Juniper et al. 81</sup>

<sup>1Histamine acid phosphate used instead of histamine diphosphate</sup>

<sup>2Calculated from data provided in study</sup>
Appendix 2: Table of pediatric studies assessing the accuracy of questionnaires for asthma

<table>
<thead>
<tr>
<th>Study</th>
<th>Gold standard</th>
<th>Question</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Youden's index</th>
<th>(+) Advantages</th>
<th>(-) Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lukrafka (Ages 12-19yo)</td>
<td>“Have you ever been told by a physician that you have asthma or bronchitis?”</td>
<td>Ever wheeze Wheeze in last 12m</td>
<td>81</td>
<td>75</td>
<td>0.56</td>
<td>(+) oversampled population that is prone to misclassification</td>
<td>(-) used questionnaire as reference standard (-) used bronchitis in the reference standard</td>
</tr>
<tr>
<td>Hederos (Ages 1-6yo)</td>
<td>Physician’s diagnosis of asthma obtained from hospital or pediatrician’s charts</td>
<td>Asthma dx by doctor Wheezing in past 12m Wheezing ever</td>
<td>77</td>
<td>98</td>
<td>0.74</td>
<td>(+) includes younger age group (+) large sample size</td>
<td>(-) incomplete information from charts (-) biased sample of those who accessed health care (-) possible misclassification of mild asthmatics (no healthcare visits in the last year)</td>
</tr>
<tr>
<td>Hasselgren (unpublished, personal communication from Hederos paper)</td>
<td>Clinician assessment</td>
<td>MD diagnosed asthma</td>
<td>70</td>
<td>98</td>
<td>0.68</td>
<td>(-) unpublished, details not available</td>
<td></td>
</tr>
<tr>
<td>Jenkins (13-14yo)</td>
<td>Physician diagnosis of history of wheeze suggestive of asthma within the past 12 months</td>
<td>Wheezing or whistling in chest at any time in the past AND wheezing or whistling in chest in the last 12 months</td>
<td>85</td>
<td>81</td>
<td>0.66</td>
<td>(+) included clinical assessment (-) no objective measures used</td>
<td></td>
</tr>
<tr>
<td>Steen-Johnsen (7-13yo)</td>
<td>History of &gt;=3 episodes of obstructive symptoms (with at least one in the last year) and/or reversible obstruction on peak flow or spirometry</td>
<td>“Has the child ever suffered from asthma?” or “Does the child wheeze, cough, or have attacks of breathlessness (asthma) after exposure to extrinsic factors (Grass, animals, food, infection, weather)?”</td>
<td>63(^1)</td>
<td>99(^1)</td>
<td>0.62</td>
<td>(+) included objective measures (-) objective measures not required in reference standard and it was unclear how many with asthma had objective findings</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 2 cont’d

<table>
<thead>
<tr>
<th>Study</th>
<th>Gold standard</th>
<th>Question</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Youden’s index</th>
<th>(+) Advantages</th>
<th>(-) Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remes</td>
<td>Physician history and objective tests</td>
<td>MD dx asthma ever</td>
<td>82</td>
<td>99</td>
<td>0.81</td>
<td>(+) clinical assessment and multiple objective measures used</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MD diagnosed asthma ever OR attacks of wheezing or breathlessness in last 12m</td>
<td>88</td>
<td>97</td>
<td>0.85</td>
<td>(+) followed up patients with symptoms but normal testing to assess for underdiagnosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wheezy chest apart from colds in the past 12 months</td>
<td>78</td>
<td>97</td>
<td>0.75</td>
<td>(-) used different questionnaire</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(-) part of objective diagnosis was acute asthmatic symptoms or peak flow variability</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>however did not state where these results were from (ie. parental report, documented in chart)</td>
<td></td>
</tr>
<tr>
<td>Present study</td>
<td>Physician history and objective tests</td>
<td>MD dx asthma ever</td>
<td>75</td>
<td>92</td>
<td>0.67</td>
<td>(+) objective testing used and algorithm for reference standard clearly defined</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MD dx asthma ever AND wheezing or medication use in the last 12m</td>
<td>72</td>
<td>95</td>
<td>0.67</td>
<td>(+) standardized method for methacholine challenge used</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ever wheeze</td>
<td>100</td>
<td>81</td>
<td>0.81</td>
<td>(-) no longitudinal followup</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wheeze in the last 12m</td>
<td>69</td>
<td>94</td>
<td>0.63</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Results different from published because they have been corrected for verification bias\(^{145, 184}\)
Appendix 3: Table of pediatric studies assessing the accuracy of administrative databases for asthma

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference standard</th>
<th>Database definition</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Youden's index</th>
<th>(+) Advantages</th>
<th>(-) Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juhn</td>
<td>Chart review</td>
<td>One diagnosis of asthma in the database (inpatient or outpatient)</td>
<td>24</td>
<td>98</td>
<td>0.22</td>
<td>(+) Clear criteria used to ascertain asthma diagnosis from chart</td>
<td>(-) May not be generalized to older children</td>
</tr>
<tr>
<td>Wakefield</td>
<td>Physician diagnosed asthma based on medical record, responses to Easy Breathing™ Questionnaire</td>
<td>1 ER or outpatient or inpatient claim with asthma as the primary or secondary diagnosis in the last year</td>
<td>61</td>
<td>98</td>
<td>0.59</td>
<td>(+) Included prescription data</td>
<td>(-) Unclear if physician not involved in the care of the child established the reference standard</td>
</tr>
<tr>
<td>Wakefield</td>
<td>Physician diagnosed asthma based on medical record, responses to Easy Breathing™ Questionnaire</td>
<td>1 ER or outpatient or inpatient claim with asthma as the primary or secondary diagnosis in the last year or 2 prescription claims for asthma medication</td>
<td>80</td>
<td>93</td>
<td>0.73</td>
<td>(+) Included prescription data</td>
<td>(-) Unclear if physician not involved in the care of the child established the reference standard</td>
</tr>
<tr>
<td>Moth</td>
<td>Asthma diagnosis in the National Patient Registry or from questionnaire sent to patient’s general practitioner</td>
<td>One prescription in last 12 months except for liquid beta-agonist</td>
<td>96</td>
<td>43</td>
<td>0.39</td>
<td>(+) Clinically relevant medication algorithms tested</td>
<td>(-) Risk of incorporation bias, physician that entered diagnosis for the National Patient Registry likely the same person that submitted data to the pharmacy database</td>
</tr>
<tr>
<td></td>
<td></td>
<td>One prescription except for liquid beta-agonist and inhaled beta-agonist only once</td>
<td>83</td>
<td>73</td>
<td>0.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any drug except liquid beta-agonist and inhaled beta agonist only once or inhaled steroid only once</td>
<td>63</td>
<td>86</td>
<td>0.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Reference standard</td>
<td>Database definition</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Youden's index</td>
<td>(+) Advantages</td>
<td>(-) Disadvantages</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>----------------</td>
<td>------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Kozyrskyj</td>
<td>One prescription for an asthma drug in the provincial database</td>
<td>One physician encounter for asthma or asthma-like condition (bronchitis or bronchiolitis) in one year</td>
<td>74</td>
<td>91</td>
<td>0.65</td>
<td>(-) Inclusion of bronchiolitis and bronchitis as part of the definition</td>
<td>(-) Risk of incorporation bias, physician that entered diagnosis for database likely prescribed the medication</td>
</tr>
<tr>
<td>5-15 years</td>
<td>N=174208</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manitoba Health Services Insurance Plan (Canada)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>To</td>
<td>Chart review</td>
<td>2 outpatient visits within 2 years and/or 1 or more hospitalizations</td>
<td>89</td>
<td>72</td>
<td>0.61</td>
<td>(+) Chart review conducted by two physician not involved in patient’s care</td>
<td>(+) Able to assess agreement between physicians (-) No pharmacy data</td>
</tr>
<tr>
<td>0-18 years</td>
<td>N=630</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ontario Asthma Surveillance Information System (Canada)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kozyrskyj</td>
<td>Pediatric allergist’s clinical diagnosis of asthma in the same year</td>
<td>One hospitalization or 2 physician visits or 4 prescriptions</td>
<td>47</td>
<td>92</td>
<td>0.39</td>
<td>(+) Independent reference standard</td>
<td>(-) Unclear how clinical diagnosis was made (-) Small age range</td>
</tr>
<tr>
<td>7-8 years</td>
<td>N=723</td>
<td>One hospitalization or 1 physician visit or 2 prescriptions</td>
<td>77</td>
<td>92</td>
<td>0.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manitoba Health Services Insurance Plan (Canada)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current study</td>
<td>Pediatric allergist or respirologist’s diagnosis of asthma (lifetime and within the last year)</td>
<td>2 outpatient visits within 2 years and/or 1 or more hospitalizations</td>
<td>91</td>
<td>71</td>
<td>0.62</td>
<td>(+) Independent reference standard</td>
<td>(-) Small sample size (-) Small age range (-) No pharmacy data</td>
</tr>
<tr>
<td>9-12 years</td>
<td>N=178</td>
<td>1 outpatient visit or hospitalization in the last year</td>
<td>36</td>
<td>90</td>
<td>0.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ontario Asthma Surveillance Information System (Canada)</td>
<td>1 outpatient visit or hospitalization in the last 2 years</td>
<td></td>
<td>52</td>
<td>81</td>
<td>0.34</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 4: Comparison of predictive values at different asthma prevalence rates

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>5%</th>
<th>10%</th>
<th>15%</th>
<th>20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Q</td>
<td>Q + BHR</td>
<td>Q</td>
<td>Q + BHR</td>
</tr>
<tr>
<td>PPV</td>
<td>19%</td>
<td>29%</td>
<td>33%</td>
<td>47%</td>
</tr>
<tr>
<td>NPV</td>
<td>99%</td>
<td>97%</td>
<td>98%</td>
<td>94%</td>
</tr>
</tbody>
</table>

PPV: positive predictive value, NPV: negative predictive value

1 Definition of asthma used to determine sensitivity and specificity

Data from Jenkins et al.\(^1\)

Q = questionnaire based definition (wheeze in past 12m) had sensitivity of 85%, specificity of 81%

Q + BHR = questionnaire + bronchial hyperreactivity had sensitivity of 47% and specificity of 94%