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Project Title: Wheezing in early life and validating the asthma predictive index

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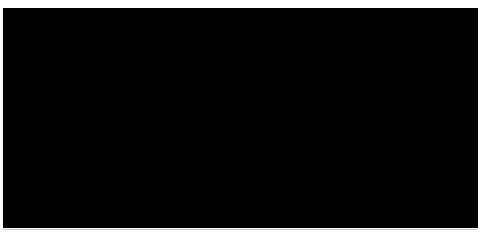
SUMMARY: (no more than 250 words single spaced)

Background: The asthma predictive index (API) and modified versions (mAPI and m2API) have been used to identify children wheezing in early life who are at risk of developing asthma by school age.
Objectives: To validate the predictive indices in a Canadian population-based sample by comparing the indices at 3 years of age to physician-diagnosed asthma at 3 years of age.
Methods: Child health questionnaires and clinical assessments were used to determine positive predictive indices among 416 subjects from the Winnipeg site of a national populated-based birth cohort. Performance measures of the indices were calculated using binomial distribution and 95% confidence interval (95% CI).
Results: The loose API had the highest sensitivity at 66.7% (95% CI, 44.9-88.4) when compared to physician-diagnosed asthma, but as the wheezing frequency criterion increased the sensitivity decreased to 23.5% (3.4-43.7) as observed in the mAPI.
Conclusions: The best asthma predictive index to predict an asthma diagnosis at 3 years of age is the m2API. However, none of the indices have a high enough sensitivity to support a recommendation for exclusive use of an index when assessing a child's risk of asthma. The indices did perform similarly in the CHILD study compared to findings in the TCRS and COAST study, and in fact the sensitivity and specificity were slightly higher in the CHILD cohort.



ACKNOWLEDGEMENTS:
I gratefully acknowledge the support by one or more of the following sponsors;
H.T. Thorlakson Foundation
Dean, Faculty of Medicine
Manitoba Health Research Council
Manitoba Institute of Child Health
Kidney Foundation of Manitoba
Leukemia and Lymphoma Society of Canada
Other:
CancerCare Manitoba
Manitoba Medical Service Foundation
Associate Dean (Research), Faculty of Medicine
Heart and Stroke Foundation
Health Sciences Centre Research Foundation

Introduction & Background

Asthma is one of the most common chronic diseases of childhood and its prevalence is increasing worldwide [1,2,3]. Asthma is an inflammatory disease of the airways defined in the 1999 Canadian asthma consensus report as variable airflow limitation and hyperresponsiveness to endogenous or exogenous stimuli resulting in paroxysmal or persistent symptoms of dyspnea, chest tightness, wheezing, sputum production, and cough [4]. It is estimated to affect 300 million people worldwide with the highest prevalence in developed countries. The burden of illness associated with asthma is substantial. Asthma has an annual worldwide mortality rate of 250,000 deaths and the number of disability-adjusted life years (DALYs) lost is 15.3 million worldwide. Most asthma-related deaths are preventable and are more common in developing countries where early medical attention is difficult to obtain during an attack and long-term management is poor [5].

Based on data from the 1994/95 National Longitudinal Survey of Children and Youth (NLSCY) and 1994/95 National Population Health Survey (NPHS), the prevalence of asthma among Canadian children in early life (0-4 year olds) is 7% and subsequently increases to 13% by school age (5-14 year olds) [6]. According to the Manitoba provincial healthcare registry, the prevalence of asthma among 7 year olds in 2002 was 12.4% [7]. The 2003 Canadian Community Health Survey (CCHS) estimates that the overall rate of asthma is 8.4% among Canadians 12 years of age and older, 7.1% among males and 9.6% among females [8]. Asthma is more common in boys than girls during childhood, however after puberty the prevalence of asthma is greater in females than males [9]. The male-to-female prevalence of asthma changes with age from 65:35 in children to 50:50 in adolescence, and then to 35:65 in adults [10]. The TRacking Adolescents' Individual Lives Survey (TRAILS) study supports this ratio in which a similar asthma prevalence of 7.4-7.7% among girls and boys at 11.1 years of age transitioned to 6.2% in females and 4.3% in males by 16.3 years of age [11]. This higher prevalence of asthma in post-pubertal females compared to males was attributed to the higher incidence and lower remission rate of asthma among females.

In the later half of the 20th century there has been a rise in the prevalence of asthma, although this appears to have recently plateaued or slightly declined in some countries [3]. The prevalence of an asthma diagnosis among Canadian children under 15 years of age increased from 2.5% in 1978/79 to 11.2% in 1994/95, representing a total of 672,000 children by 1994/95 [6]. A further increase was observed among Canadian children under 12 years of age from 11% in 1994/95 to 13% in 2000/01, representing an increase in almost 70,000 children over 5 years [12]. In a similar trend, the age and sex standardized prevalence of asthma increased from 8.5% in 1996 to 13.3% in 2005 among all ages of the population living in Ontario, Canada. This increase was mostly attributable to the early years of the study since the prevalence began to plateau near the end [13].

The estimated direct cost of asthma in Canada in 1990 was $306 million, which is mostly attributable to medication use, hospital admissions, and physician visits [14]. In 2004, the estimated cost for just the urgent care of uncontrolled asthma in Canada was $162 million [15]. Asthma among Canadian children was associated with increased school absenteeism, limitations in activity, and lower scores on standardized math and reading tests [16]. The increasing prevalence of asthma and associated costs highlight the personal and economic burden of the disease.

Asthma defined by the 1999 Canadian asthma consensus report is descriptive in nature and therefore relies on the physician's judgment to integrate patient clinical history and pulmonary

function tests (PFTs) to diagnose asthma [4]. A clinical history of paroxysmal or persistent symptoms of dyspnea, chest tightness, wheezing, sputum production, and cough is supportive of an asthma diagnosis. PFT criteria for diagnosis of asthma in children 6 years of age and over requires demonstration of reversible airway obstruction on spirometry from a reduced FEV_1/FVC to an increase in FEV_1 by ≥12% post-bronchodilator or following a course of controller treatment. Alternatively the child may have variability in peak expiratory flow (PEF) of ≥20% post-bronchodilator or following a course of controller treatment, or have a decrease in FEV_1 by ≥20% with provocative methacholine concentration (PC20) of <4mg/mL, or have a decrease in FEV_1 of ≥10-15% following exercise. Children under 6 years of age usually cannot properly perform PFTs, thus diagnosing asthma in early life relies on the clinical history with emphasis on risk factors such as atopic characteristics and family history, and occasionally physical exam findings [17].

Most asthma-related symptoms begin early in life when children with asthma wheeze, but not all children who wheeze develop asthma [18]. Wheezing is common in early life but non-specific to asthma. Other common causes of wheezing in early childhood are viral respiratory tract infections and congenital abnormalities [19]. The Tucson Children's Respiratory Study (TCRS) is a longitudinal prospective birth cohort study that followed 1246 healthy newborns to examine the impact of various risk factors on the development of lower respiratory tract illnesses (LRTIs) and chronic airway diseases [20]. In the TCRS, 1 in 3 children experienced an episode of wheezing associated with a LRTI in the first 3 years of life [21]. Approximately 60% of these children had transient early wheezing with no wheezing by 6 years of age while the remaining 40% had persistent wheezing that continued to 6 years of age. Transient early wheezing was associated with maternal smoking and reduced length-adjusted maximal expiratory flow at functional residual capacity (V_{max}FRC) both by 1 year and at 6 years of age. To calculate V_{max}FRC, external pressure was rapidly applied to the chest at the end of tidal inspiration, resulting in chest compression and forceful expiration of air, and the V_{max}FRC represents the flow of expired air at the end of tidal expiration. Persistent wheezing was associated with maternal asthma, elevated IgE levels, and reduction in pulmonary function from no significant difference at 1 year in V_{max}FRC compared to children who never wheezed, to an increased likelihood of reduced V_{max}FRC at 6 years. These persistent wheezers are at risk of developing asthma as 46% were diagnosed with asthma at 6 years of age [21]. Wheezing is therefore an important sign to consider when assessing a child's risk of developing asthma.

Asthma predictive index

A clinical index to predict asthma in wheezy children, the asthma predictive index (API), was created by the Tucson group using data from the TCRS, which identified children with wheezing in the first 3 years of life who are at risk of developing asthma by school age [22]. A positive "loose" API is defined as an early wheezer (any wheezing in the first 3 years of life) and either one major or two minor criteria (Table 1). A positive "stringent" API is defined as an early frequent wheezer (≥ 3 on a 1-5 scale from "very rarely" to "on most days") and either one major or two minor criteria [22,23]. The specific criteria will be covered in the material and methods. Since not all wheezy children develop asthma, the API could be a valuable clinical tool to predict the risk of developing asthma in early life wheezers. It is important to determine which children are at high risk of developing asthma because the difficulty with diagnosing asthma in children under 6 years of age and the under diagnosis of asthma in early life may be contributing to the increased asthma-related morbidity and poorer control observed in early life compared to school age [23]. This emphasizes the importance of identifying children at high risk of developing asthma because they may benefit from earlier initiation and adherence to controller therapy if an asthma diagnosis is made sooner. Results from the PEAK study showed an increase in the

number of asthma-episode free days when children with a positive modified API were treated for 2 years with inhaled corticosteroids [24].

The TCRS collected data from questionnaires at enrollment about parental history of asthma while questionnaires about child health and child history of respiratory conditions were collected at age 2, 3, 6, 8, 11, and 13 years. The questionnaires completed at age 2 and 3 years confirmed the history of the child's chest ever sounding wheezy, wheezing frequency, wheezing associated with colds, and atopic findings such as self-reported history of MD-diagnosed (physician-diagnosed) allergic rhinitis and MD-diagnosed eczema in the previous year. The questionnaires completed at age 6, 8, 11, and 13 years confirmed a child's history of wheezing and it's frequency in the past year. Child blood specimens were collected at 10.6 months for identification of eosinophilia ≥4% of the total white blood cell count. The primary outcome was the development of "active asthma" at 6, 8, 11, and/or 13 years of age. "Active asthma" was defined as a child having a physician diagnosis of asthma with at least one asthma episode in the past year or more than 3 episodes of wheezing in the past year [22]. There is no single diagnostic marker for asthma but the API applies parameters that are shown to be risk factors for the development of asthma, particularly the atopic characteristics and parental history of asthma [18,25,26].

According to Castro-Rodríguez, univariate analysis of the API variables showed significance in their ability to predict the development of asthma. The suggested combination of major and minor criteria for the API was selected because it produced the highest specificity and positive predictive value. The "loose" API has a sensitivity (95% CI) ranging from 39.3% (35.5-43.1%) to 56.6% (53.3-59.9%) showing a decrease in sensitivity with increasing age of asthma diagnosis from 6 to 13 years. This is in contrast to the "stringent" API with a higher wheezing frequency criterion, which had a lower sensitivity ranging from 14.8% (12.1-17.5%) to 27.5% (24.6-30.4%). The "stringent" API had a specificity of 96.1% (94.8-97.4%) to 97% (95.7-98.3%), positive predictive value (PPV) of 42.0% (38.7-45.3%) to 51.5% (47.7-55.3%), and negative predictive value (NPV) of 84.2% (81.4-87.0%) to 91.6% (89.8-93.4%) compared to an asthma diagnosis amongst 6-13 years of age. The "loose" API had a similarly high NPV of 86.5% (83.9-89.1%) to 93.9% (92.4-95.4%) but lower specificity of 79.6% (76.9-82.3%) to 82.1% (79.1-85.1%) and lower PPV of 26.2% (23.4-29.0%) to 31.7% (28.1-35.3%) [22]. The positive likelihood ratio (LR+) of the loose API ranged from 1.9 to 2.9 and the negative likelihood ratio (LR-) ranged from 0.54 to 0.75. Overall, with an increasing age of asthma diagnosis the sensitivity and NPV decreased while the specificity and PPV increased.

Modified asthma predictive index

The modified API (mAPI) is an adaptation of the API created for use in the Prevention of Early Asthma in Kids (PEAK) trial, which studied a cohort of children between 2 to 3 years of age who are at high risk of developing asthma [27]. Children at high risk of developing asthma are often sensitized to allergens in early life and more specifically aeroallergens, therefore the mAPI was modified to include sensitization to allergen(s) in its major and minor criteria [28,29]. The wheezing frequency criterion was also changed in the mAPI to ≥ 4 episodes of wheezing in the past 12 months with at least one confirmed by a physician (Table 1). Results from this study demonstrated an increase in the number of asthma-episode free days when children with a positive mAPI at age 2-3 were treated for 2 years with inhaled corticosteroids, although this did not modify the natural course of the disease once therapy was discontinued for a year [24]. The mAPI was not statistically assessed in the PEAK study but it was assessed in the Childhood Origins of ASThma (COAST) study along with the m2API, which is similar to the mAPI but with

a wheezing criteria of ≥ 2 episodes of wheezing in the past 12 months with at least one confirmed by a physician [30].

The COAST study is a high-risk birth cohort of 289 infants with parental sensitization to aeroallergen(s) and/or physician-diagnosed asthma. In this study investigators applied the mAPI and m2API at 1, 2, and 3 years of age and compared results to a diagnosis of asthma at 6, 8, and 11 years of age. Results from assessment of the indices at 3 years compared to asthma at 6, 8 and 11 years revealed a sensitivity (95% CI) ranging from 28% (19-38%) to 32% (21-43%) in the m2API and 17% (8.4-25%) to 19% (9.3-28%) in the mAPI, and specificity of ≥ 97% in both indices [30]. In comparison to the performance of the loose API in the TCRS, the mAPI and m2API exhibited lower sensitivity but greater specificity in the COAST study, and the decrease in sensitivity was most pronounced in the mAPI where the wheezing frequency criterion was the most strict. The increase in specificity may be attributed to the inclusion of sensitization to aeroallergens and food and the reduced timeframe of consideration for wheezing episodes to the past 12 months since this would possibly reduce additional false positives and give a more accurate measure of true negatives. The LR+ is higher in the m2API at 10 (4.1-29) to 16 (5.4-48) and the mAPI at 19 (3.6-100) to 55 (3.3-913) compared to the API at 1.9 to 2.9. The LR- is lower in the API at 0.54 to 0.74 compared to the m2API at 0.70 (0.59-0.83) to 0.73 (0.63-0.84) and the mAPI at 0.82 (0.73-0.92) to 0.84 (0.75-0.93) [30]. When interpreting the LR+ and LR- it is important to note that the TCRS for the loose API represents a general population of children whereas the COAST study for the modified indices was applied to a high-risk birth cohort.

Application of the indices to the CHILD study Winnipeg cohort

It is important to identify children at risk of developing asthma in order to implement early intervention to control the disease, minimize the burden of illness, prevent long-term complications, and if possible, prevent development of the disease. The API, mAPI, and m2API are fairly simple and have potential for use by physicians as predictive tools to determine whether a child wheezing in early life is at an increased risk of developing asthma by school age [22,27,28]. These indices need to be validated in different populations in order to determine the strength of their predictive value before they are applied in a clinical setting. The objective of my project was to validate the loose API, mAPI, and m2API in a Canadian population-based sample from the CHILD study by applying the indices at 3 years of age and comparing the results to physician-diagnosed asthma at age 3. We hypothesize that the performance measures of the predictive indices in the CHILD study will be similar to those observed in the TCRS and COAST study, as previously discussed, but our results may be less specific because the comparison is made to an earlier age of asthma diagnosis (age 3).

Materials & Methods

Study population

The Canadian Healthy Infant Longitudinal Development (CHILD) study is a national population-based birth cohort of more than 3600 subjects followed from the prenatal period to 5 years of age across Vancouver, Edmonton, Winnipeg, and Toronto sites. The focus of the study is to identify the role of genes and environment on the development of allergy and asthma. The Winnipeg, Manitoba site recruited 1050 mothers to the study, 50 from the pilot cohort and 1000 from the general cohort. Recruitment of the pilot cohort occurred between summer 2008 to December 2008 and the general cohort between summer 2009 to December 2011. Pregnant women were recruited mostly during the 2nd or 3rd trimester at prenatal clinics, physicians' offices, prenatal classes, local shopping centres, farmers' markets, and the Winnipeg Baby and

Kids Show. After post-partum screening, infants 35 weeks of age or older were enrolled based on further inclusion and exclusion criteria (www.canadianchildstudy.com). The data collection period is currently ongoing and at this time, 1034 subjects are active participants in the Winnipeg site. The analysis undertaken in this report consists of 416 children from the Winnipeg site who have completed the 3 year clinical assessment for asthma, including 48 from the pilot cohort and 368 from the general cohort. Informed parental consent was given and ethics approval was obtained from the University of Manitoba Health Research Ethics Board.

Predictive indices

The API, mAPI, and m2API were applied to 416 subjects at 3 years of age. A positive loose API is defined as an early wheezer (any wheezing in the first 3 years of life) and either one major (parental MD-diagnosed asthma or MD-diagnosed atopic dermatitis in the child) or two minor criteria (MD-diagnosed allergic rhinitis, wheezing without a cold, or blood eosinophilia ≥ 4%) [22]. The m2API and mAPI are an adaptation of the API with the addition of sensitization to ≥ 1 aeroallergen(s) to the major criteria and sensitization to peanut, milk, or egg to the minor criteria and removal of MD-diagnosed allergic rhinitis from the minor criteria [28]. The wheezing frequency criterion was also changed to ≥ 2 episodes of wheezing in the past 12 months in the m2API and ≥ 4 episodes of wheezing in the past 12 months in the mAPI. A positive modified index is defined as meeting the respective wheezing criterion and either one major or two minor criteria [30]. Table 1 provides a comparison of the 3 indices with the only difference between the m2API and mAPI being the wheezing criteria.

Criteria for predictive indices in the CHILD study

In the CHILD study, parents completed child health questionnaires addressing the child's history of wheezing at 3 months, 6 months, 1 year, 1.5 years, 2 years, 2.5 years, and 3 years. Parents were asked if in the past the child had a wheezing noise (whistling sound) coming from his/her chest, the number of wheezing episodes (defined as wheeze > 15 minutes with each episode separated from another by at least 7 days), and if any wheezing episodes occurred without a cold ("wheezing without a cold"). Report of wheezing was categorized as "any wheezing in the first 3 years of life", "≥ 4 episodes of wheezing in the past 12 months", and/or "≥ 2 episodes of wheezing in the past 12 months". Father and mother health questionnaires at 18 weeks prenatal and 1 year collected parental report of physician-diagnosed asthma ("parental MD-asthma"). Child blood specimen collected at 1 year was analyzed for eosinophil count ≥ 4% of the total white blood cell count ("blood eosinophilia ≥ 4%").

Children were seen by a physician at the 3 year clinical assessments where a physician-diagnosis of asthma ("MD-diagnosed asthma"), allergic rhinitis ("MD-allergic rhinitis"), and/or atopic dermatitis ("MD-atopic dermatitis") could be made. Allergic sensitization to aeroallergens ("sensitization to ≥ 1 aeroallergen(s)") and foods ("sensitization to ≥ 1 food allergen(s)") at 3 years was determined by allergy skin prick testing (SPT) performed at the 3 year clinical assessment. Allergy SPT was performed for 17 allergens (*Alternaria alternata*, *Cladosporium*, *Penicillium* mixed, *Aspergillus fumigatus*, cat hair (standardized), dog epithelium, *D. pteronyssinus*, *D. farinae*, cockroach (German), trees midwest, grass mix, weeds, ragweed mixed, peanut, milk (whole cow's), egg white, and soybean; ALK-Abello Pharmaceuticals, Inc.) in accordance with the standard operating procedures developed by CHILD using Duotips II (Lincoln Diagnostics, Inc.) [31]. Soybean sensitization, although not in the original mAPI and m2API, was tested on all children and if positive, it was considered positive for sensitization to ≥ 1 food allergen(s). Additional food allergens (sesame and hazelnut) were tested if parents had concern about specific allergens and if positive, it was considered positive for sensitization to ≥

1 food allergen(s). The AllerGeek Expert System solved for the area of the wheal and diameter of a circle with the corresponding area. An allergen producing a wheal diameter of ≥ 2 mm was considered a positive allergen response. Results were included in the analysis if the histamine response was > 0.0 mm or a negative histamine was seen in a child with a positive allergen response, but results were excluded if there was a negative histamine and negative allergen response.

Statistical analysis of index performance

Descriptive variables for the cohort were analyzed by describing the mean ± standard deviation or percentage. Analysis of the predictive indices was completed using SASv9.3®. The performance measures were calculated using binomial distribution and a 95% confidence interval (95% CI) in order to obtain the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR-). The sensitivity represents the proportion of 3 year olds with MD-diagnosed asthma who had a positive predictive index at 3 years and the specificity represents the proportion of 3 year olds without MD-diagnosed asthma who had a negative predictive index. The PPV is the proportion of 3 year olds with a positive predictive index who developed MD-diagnosed asthma by 3 years and the NPV is the proportion of 3 year olds with a negative predictive index who did not developed MD-diagnosed asthma by 3 years. The LR+ is the likelihood that a 3 year old with MD-diagnosed asthma had a positive predictive index compared to a 3 year old without MD-diagnosed asthma having a positive predictive index. The LR- is the likelihood that a 3 year old with MD-diagnosed asthma had a negative predictive index compared to a 3 year old without MD-diagnosed asthma having a positive predictive index. For interpreting the likelihood ratios, we are assuming that the prevalence of asthma in this CHILD sample is representative of asthma prevalence in the general population of children in Manitoba.

Results

At the time of this analysis, 416 children had completed their 3 year clinical assessment and had data entered into the database. Our sample consists of 50.6% females and 49.4% males and report of maternal and paternal MD-diagnosed asthma was 27.7% and 17.5%, respectively. Table 2 summarizes additional characteristics of the children. Table 3 presents the prevalence of individual parameters from the predictive indices. In the first 3 years of life, 31.4% had at least 1 episode of wheezing but in the past 12 months, only 6.6% experienced 2 or more episodes of wheezing and even less had 4 or more. The most common major criterion among the subjects was parental MD-asthma at 41.0% and the most common minor criterion was blood eosinophilia ≥ 4% at 16.6%. The prevalence of “physician-diagnosed asthma” at 3 years was 4.6% (19 children) and the prevalence of “no asthma” was 89.2% (371 children). Since asthma can be difficult to diagnose in early life, 6.3% (26 children) with a borderline clinical picture were identified as having “possible asthma”. Of the 3 predictive indices, the loose API was positive in 17.8% whereas the m2API and mAPI were positive in only 4.5% and 1.6%, respectively (Table 4). As the frequency of wheezing episodes required for the index to be positive increased, the number of subjects with a positive index decreased.

Analysis of the loose API compared to physician-diagnosed asthma at 3 years revealed a sensitivity of 66.7% and specificity of 84.4% (Table 5). The modification of the API to a more strict wheezing criterion and inclusion of sensitization to allergens created the mAPI which had a lower sensitivity at 23.5% and higher specificity at 99.5%. The wheezing criterion in the m2API is less strict and thus the sensitivity was improved to 58.8% and the specificity remained high at 98.1%. The strongest PPV was exhibited by the mAPI at 66.7% while the loose API had the

weakest PPV at 16.4%. The NPV was more than 96% for all of the predictive indices. Among all of the indices, there was a reduction in sensitivity and NPV and increase in specificity and PPV when both MD-diagnosed asthma and possible asthma were included as the primary outcome. The LR+ of the loose API showed a slight increase in the likelihood of asthma while the LR+ in the m2API and mAPI was very high at 30.3 and 42.5 respectively, but the confidence intervals of the modified indices are quite large with the mAPI CI crossing 1. The LR- of the indices all showed that a negative predictive index decreased the likelihood of asthma with the LR- ranging from 0.05 in the loose API to as low as 0.004 in the mAPI.

To address the issue of missing data, if a child was missing data for one or more of the parameters in the major criteria then the major criteria for that child was declared as missing data. This was similarly done with the minor criteria. On that note, the sensitivity for the loose API for example improved from 63.2% to 66.7% when we took this conservative approach to incomplete data, instead of assuming that incomplete data was negative rather than missing. At the time of submission we were unable to apply this conservative approach to the wheezing criteria, therefore if at least one child health questionnaire about wheezing was completed but others were missing then the data was included in the analysis.

Discussion

Based on evaluation of the sensitivity and specificity, we found that the m2API had the best predictive value for MD-diagnosed asthma at 3 years of age. The m2API had a sensitivity of 58.8% and specificity of 98.1% but with this lower than preferred sensitivity for a clinical tool, a number of children with positive indices will not have asthma by 3 years of age. It may be possible that these children will develop asthma by school age but based on the COAST study, the sensitivity for the m2API at age 3 compared to asthma at age 6 is even lower at 30%. The indices did perform similarly in the CHILD study compared to findings in the TCRS and COAST study. In fact our results showed a slightly higher sensitivity and specificity across all 3 indices, and we had expected to see a lower specificity as a result of using an earlier age of asthma diagnosis.

The probability of a 3 year old with MD-diagnosed asthma having a positive predictive index at 3 years increased as the criterion for wheezing frequency decreased. This is reflected in the higher sensitivity of the loose API and m2API of 66.7% and 58.8% respectively, compared to the lower sensitivity of 23.5% in the mAPI. Castro-Rodríguez argued that an observed increase in sensitivity with a looser index reflects cases of childhood asthma where symptoms progress from mild in early life to increasing severity with age [22]. However, a looser index still exhibited higher sensitivity when children were diagnosed with asthma at age 3. It was highly probable for a 3 year old without MD-diagnosed asthma to have a negative predictive index, as reflected in the m2API and mAPI specificity of 98.1% and 99.5% respectively, but this was reduced to 84.4% in the loose API.

The index with the strictest wheezing frequency criterion was also the most reliable index to show a relationship between a positive index and subsequent MD-diagnosed asthma by age 3. The probability that a child with a positive mAPI had MD-diagnosed asthma at 3 years was 66.7%, in comparison to 58.8% in the m2API and 16.4% in the loose API. The PPV was increased to 100% in the mAPI when a positive index was compared to an outcome of MD-diagnosed or possible asthma. The NPV was similarly high across all 3 indices, suggesting it is highly probable that a child does not have asthma when any of the predictive indices are negative.

A positive mAPI increased the likelihood of having MD-diagnosed asthma by 42.5 (95% CI, -26.8-111.7) while a positive m2API increased the likelihood by 30.3 (4.9-55.7). These two values represent large increases in the likelihood of asthma, however the confidence intervals are large and cross 1 in the mAPI, therefore diminishing the significance of these findings. The large confidence intervals may be due to the smaller sample size. The LR+ of the loose API is 4.27 (2.56-5.99) suggesting a positive loose API slightly increased the likelihood of MD-diagnosed asthma at 3 years. A notable strength of all 3 indices is that a negative predictive index decreased the likelihood of asthma, and this is probably the best application for these indices. It is also important to note that 6 children diagnosed with asthma had a negative loose API (Table 4) and this may represent children who have a cough variant of asthma in which coughing rather than wheezing is the primary symptoms and therefore have a negative predictive index.

One of the strengths of this study is the comparison of a positive predictive index to the gold standard of physician-diagnosed asthma. The outcome of “asthma” in the TCRS and COAST study does not come directly from physician reports and is rather defined according to a set of criteria (Table 1), whereas subjects in the CHILD study had a clinical assessment. Similarly, allergic rhinitis and atopic dermatitis were also diagnosed by a physician at the clinical assessments and were not biased by parents’ recall. Another strength of the study is that it is a population-based prospective birth cohort representative of the urban and rural areas of Manitoba, Canada and can therefore be generalized to the general population.

We recognize that one of the weaknesses of the study is parental report of child wheezing and how this can be subject to parents’ interpretation of what wheezing is. This is an unavoidable limitation of the predictive indices, which is minimized by creating a standardized definition of wheezing in the questionnaires. The CHILD study has collected a large amount of information from its subjects, but with this strength comes the associated risk of incomplete data due to participants skipping any given number of questionnaires. Since the indices pull from data collected at multiple time points, there are children with incomplete data included in the indices. However, strategies employed by CHILD staff for participant follow-up and retention in the study help to reduce the number of incomplete questionnaires. Sensitivity analysis will be conducted once the dataset is complete at which point we can analyze missing wheezing data as “non-wheezy children” or as all missing information. It was not possible to complete all of these sensitivity analyses at the time of this submission.

Traditionally the indices were applied during the first 3 years of life and compared to an asthma diagnosis by age 6 to predict the likelihood of developing asthma by school age. At this point in time, most of the CHILD cohort has not yet reached 5 years of age and thus the results presented here are limited to comparison of the indices to physician-diagnosed asthma at 3 years. Future application of these indices to the complete national CHILD cohort at 3 years of age and comparison with physician-diagnosed asthma at 5 years of age would be of great value in order to validate its predictive accuracy of asthma by school age in the Canadian population. The sensitivity of the indices may also improve as the age of asthma diagnosis increases. This further analysis will be completed once the dataset is complete. This step would provide further guidance as to the potential use of the API in a clinical setting for the Canadian population.

Since wheezing is common in early life, this can prolong the period before an asthma diagnosis is made. It is important to determine which children are at high risk of developing asthma because these children would likely benefit from earlier initiation of controller therapy associated with an earlier diagnosis. Alternatively, in those children who are unlikely to develop asthma a more conservative approach may be taken but further studies are needed to determine the best

practice. Continued application of the indices in prospective studies and randomized control trials is needed to further validate the indices in other countries and show any benefits of intervention in the high risk group.

In conclusion, the m2API is the best asthma predictive index to use at 3 years of age to predict an asthma diagnosis at age 3. However, none of the indices have a high enough sensitivity to recommend exclusive use of the index to identify which children have current asthma. The predictive indices may instead be better used to identify which children are not at high risk of developing asthma because a child with a negative predictive index is unlikely to have asthma. The indices did perform similarly in the CHILD study compared to findings in the TCRS and COAST study, and in fact the sensitivity and specificity were slightly higher in the CHILD cohort.

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Figures, Figure Legends, and Tables

Table 1. Comparison of the loose API, m2API, and mAPI criteria

Loose API[†]	m2API[‡]	mAPI[‡]
Wheezing frequency		
Any wheezing in the first 3 years of life	≥ 2 episodes of wheezing in the past 12 months	≥ 4 episodes of wheezing in the past 12 months
Major criteria		
Parental MD-asthma MD-atopic dermatitis	Parental MD-asthma MD-atopic dermatitis Sensitization to ≥ 1 aeroallergen(s)	
Minor criteria		
MD-allergic rhinitis Wheezing without a cold Blood eosinophilia ≥ 4%	Sensitization to either peanut, milk, or egg Wheezing without a cold Blood eosinophilia ≥ 4%	
Outcome: "Asthma"		
Parental report of MD-diagnosed asthma with ≥ 1 asthma episode in the past year, or ≥ 4 episodes of wheezing in the past year	At least one in the past 12 months: 1) MD-diagnosed asthma 2) Salbutamol use for cough or wheeze 3) Daily use of controller medication 4) Step up plan (such as salbutamol or ICS use during illness) 5) Prednisone use for asthma exacerbation	

* A positive predictive index is defined as meeting the wheezing frequency and either 1 major or 2 minor criteria for the corresponding index

[†] Created in the TCRS by Castro-Rodríguez JA, et al. Am J Respir Crit Care Med. 2000 Oct;162(4Pt1):1403-6.

[‡] Validated in the COAST study by Chang TS, et al. J Allergy Clin Immunol Pract. 2013 Mar;1(2):152-6.

Table 2. Demographics and characteristics of the Winnipeg CHILD cohort (n=416)	
Gender (n=395)	n (%)
Male	195 (49.4)
Female	200 (50.6)
Ethnicity*	
Maternal (n=398)	
Caucasian	329 (82.7)
First nations	24 (6.0)
Other	98 (24.6)
Paternal (n=384)	
Caucasian	306 (79.7)
First nations	23 (6.0)
Other	95 (24.7)
Gestational age (n=347)	
≥ 37 weeks	333 (96.0)
< 37 weeks	14 (4.0)
Mode of delivery (n=372)	
Vaginal	306 (82.3)
Caesarian section	66 (17.7)
Exclusivity of breastfeeding (n=331)	
≥ 6 months	233 (70.4)
< 6 months	98 (29.6)
Parental asthma	
Maternal (n=368)	102 (27.7)
Paternal (n=371)	65 (17.5)
Prenatal maternal smoking (n=396)	
	27 (6.8)

* Parents could identify with multiple ethnicities; therefore the sum of the variable responses is greater than the sample size.

Table 3. Prevalence of individual parameters from the indices at 3 years		
Wheezing criteria	Yes % (n)	No % (n)
Loose API: Any wheezing in first 3 years of life	31.4 (130)	68.6 (284)
mAPI: ≥ 4 episodes in past 12 months	2.1 (8)	97.9 (370)
m2API: ≥ 2 episodes in past 12 months	6.6 (25)	93.4 (353)
Major criteria		
Parental MD-asthma*	41.0 (150)	59.0 (216)
MD atopic dermatitis (includes possible)	11.5 (48)	88.5 (368)
Sensitization to ≥ 1 aeroallergen	4.0 (16)	96.0 (388)
Minor criteria		
Sensitization to ≥ 1 food allergen	4.2 (17)	95.8 (387)
MD-allergic rhinitis (includes possible)	5.1 (21)	95.0 (395)
Wheezing without a cold*	10.9 (45)	89.1 (367)
Blood eosinophilia ≥ 4%	16.6 (64)	83.4 (322)

*Represent values applied to criteria in m2API and mAPI [less missing data in loose API; parent asthma 40.4% (150), no parent asthma 59.6% (221), wheeze without cold 10.9% (42), no wheeze without cold 89.1% (344) in loose API]

Table 4. Prevalence of positive and negative indices at 3 years compared to MD-diagnosed asthma at 3 years

MD-diagnosed asthma 3YR	Loose API (n=414)		m2API (n=378)		mAPI (n=378)	
	Positive % (n)	Negative % (n)	Positive % (n)	Negative % (n)	Positive % (n)	Negative % (n)
Yes	2.9 (12)	1.5 (6)	2.7 (10)	1.9 (7)	1.1 (4)	3.4 (13)
No or possible	14.9 (61)	80.7 (330)	1.9 (7)	93.7 (354)	0.5 (2)	95.0 (359)
Yes or possible	5.1 (21)	5.6 (23)	3.2 (12)	7.7 (29)	1.6 (6)	9.3 (35)
No	12.7 (52)	76.5 (313)	1.3 (5)	87.8 (332)	0.0 (0)	89.2 (337)
Total	**17.8 (73)**	**82.4 (341)**	**4.5 (17)**	**95.5 (361)**	**1.6 (6)**	**98.4 (372)**

Table 5. Performance of the loose API, m2API, and mAPI at 3 years compared to asthma diagnosis at 3 years

MD-diagnosed asthma 3YR	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	LR+ (95% CI)	LR- (95% CI)
Loose API						
Yes	66.7 (44.9-88.4)	84.4 (80.1-88.0)	16.4 (7.9-24.9)	98.2 (96.8-99.6)	4.27 (2.56-5.99)	0.05 (0.02-0.09)
Yes or possible	47.7 (33.0-62.5)	85.8 (82.2-89.3)	28.8 (18.4-39.2)	93.2 (90.5-95.9)	3.35 (2.01-4.69)	0.07 (0.05-0.10)
m2API						
Yes	58.8 (35.4-82.2)	98.1 (96.6-99.5)	58.8 (35.4-82.2)	98.1 (96.6-99.5)	30.3 (4.9-55.7)	0.01 (0.00-0.02)
Yes or possible	29.3 (15.3-43.2)	98.5 (97.2-99.8)	70.6 (48.9-92.3)	92.0 (89.2-94.8)	19.7 (0.1-39.3)	0.01 (0.00-0.02)
mAPI						
Yes	23.5 (3.4-43.7)	99.5 (98.7-100)	66.7 (29.0-100)	96.5 (94.6-98.4)	42.5 (-26.8-111.7)	0.004 (-0.002-0.010)
Yes or possible	14.6 (3.8-25.5)	100 (100-100)	100 (100-100)	90.6 (87.6-93.6)	Undefined	0.853