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Evaluation of the Modified Asthma Predictive Index in High-Risk Preschool Children

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Abstract

BACKGROUND—Prediction of subsequent school-age asthma during the preschool years has proven challenging.

OBJECTIVE—To confirm in a *post hoc* analysis the predictive ability of the modified Asthma Predictive Index (mAPI) in a high-risk cohort and a theoretical unselected population. We also tested a potential mAPI modification with a 2-wheezing episode requirement (m^2API) in the same populations.

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METHODS—Subjects (n = 289) with a family history of allergy and/or asthma were used to predict asthma at age 6, 8, and 11 years with the use of characteristics collected during the first 3 years of life. The mAPI and the m^2API were tested for predictive value.

RESULTS—For the mAPI and m^2API, school-age asthma prediction improved from 1 to 3 years of age. The mAPI had high predictive value after a positive test (positive likelihood ratio ranging from 4.9 to 55) for asthma development at years 6, 8, and 11. Lowering the number of wheezing episodes to 2 (m^2API) lowered the predictive value after a positive test (positive likelihood ratio ranging from 1.91 to 13.1) without meaningfully improving the predictive value of a negative test. Posttest probabilities for a positive mAPI reached 72% and 90% in unselected and high-risk populations, respectively.

CONCLUSIONS—In a high-risk cohort, a positive mAPI greatly increased future asthma probability (eg, 30% pretest probability to 90% posttest probability) and is a preferred predictive test to the m^2API. With its more favorable positive posttest probability, the mAPI can aid clinical decision making in assessing future asthma risk for preschool-age children.

Keywords

Asthma; Wheezing; Children; Asthma predictive index; Modified asthma predictive index

Asthma is one of the most common chronic diseases of childhood. Up to 50% of children wheeze at least once during the preschool years.[1] Although many of these children go on to develop asthma, our ability to predict school-age asthma based on early life characteristics is currently limited. Early identification of persons at risk of disease can be used to identify children that require closer monitoring and may be ideal candidates for prevention strategies or interventions. Therefore, accurate prediction of asthma development is highly desirable for clinicians, families, and researchers.

One of the first rule-based predictive models for early identification of children at high risk of subsequent asthma was the Asthma Predictive Index (API),[2] developed in the Tucson Children's Respiratory Study, which evaluated an unselected general cohort of 1246 infants. Both a "stringent" (Table I) and "loose" index were used to predict asthma at ages 6, 8, 11, and 13 years, based on questionnaire data from ages 2 and 3 years. The positive likelihood ratio (LR^+) and negative likelihood ratio (LR^-) for asthma diagnosis at age 6 with the use of the stringent index were 7.4 and 0.75, respectively.

Because children with a positive API are at increased risk of developing asthma, a modified Asthma Predictive Index (mAPI) (Table I), which used more objective criteria than the API, was used as entry criteria for the Preventing Early Asthma in Kids clinical trial.[3] The study showed decreased exacerbations, decreased controller medication usage, and increased episode-free days in 2- to 3-year-old children with a positive mAPI treated with inhaled corticosteroids compared with placebo.[4]

Guidelines from national and international organizations have discussed school-age asthma prediction. The European Respiratory Society stated asthma predictive models have only been used in retrospective epidemiologic studies and have limited clinical value.[5] The Global Initiative for Asthma suggested atopy or allergic sensitization could provide predictive support that a wheezing child may have asthma in the future.[6] The Global Initiative for Asthma stated that application of the API in other countries and clinical situations was needed before recommending widespread use, although application in a lower- to middle-income country was recently performed.[7] Based in large part on the results of the Preventing Early Asthma in Kids trial, the National Asthma Education and Prevention Program's Guidelines for Diagnosis and Management of Asthma from 2007 recommended

initiating long-term control therapy in children from birth to 4 years old who are positive for the mAPI to reduce impairment and exacerbation risk.[8]

Because the mAPI has never been critically assessed, we prospectively evaluated the mAPI and a potential modification of it in the high-risk Childhood Origins of ASThma (COAST) cohort, a patient population most likely to seek preschool allergy-and asthma-related care.

METHODS

Study cohort

A total of 289 newborns were enrolled from November 1998 through May 2000 in the COAST study as previously described.[9] To qualify, at least 1 parent was required to have respiratory allergies (defined as 1 or more positive aeroallergen skin tests) and/or a history of physician-diagnosed asthma. The University of Wisconsin Human Subjects Committee approved this study, and informed consent was obtained from the parents. Assent was obtained from the children at age 8 years.

Current asthma was clinically diagnosed at 6, 8, and 11 years of age, based on at least 1 of the following in the previous year as previously described[10,11]: (1) physician diagnosis of asthma; (2) use of albuterol for coughing or wheezing episodes (prescribed by physician); (3) use of a daily controller medication; (4) step-up plan, including use of albuterol or short-term use of inhaled corticosteroids during illness; and (5) use of prednisone for asthma exacerbation. Sufficient data were available to make a diagnosis of current asthma for 259 (73 asthma, 186 no asthma), 238 (78 asthma, 160 no asthma), and 217 (66 asthma, 151 no asthma) children at age 6, 8, and 11 years, respectively. We used data during year 1 (birth to 11 months), year 2 (12–23 months), or year 3 (24–35 months) to predict asthma at age 6, 8, and 11 years.

Atopic dermatitis was defined as physician diagnosed, either documented by a health care provider in the medical record or by parental report of physician-diagnosed atopic dermatitis on historical questionnaires, as previously described.[10]

Allergic sensitization was determined as previously described.[12] Briefly, blood was collected at ages 1, 2, and 3 years, and total IgE and specific IgE to dog, cat, *Alternaria alternata, Dermatophagoides farinae, Dermatophagoides pteronyssinus*, peanut, milk, and egg were measured by using automated fluoroenzyme immunoassays (Unicap 100; Pharmacia and Upjohn Diagnostics, Kalamazoo, Mich). Allergen-specific IgE ≥0.35 kU/L was considered positive, and sensitivity for detection of total IgE was 2 kU/L.

Predictive models

The prediction models, mAPI and a potential modification of the mAPI, were evaluated in the high-risk COAST birth cohort. This evaluation was performed as a *post hoc* analysis and not prespecified in the original COAST protocol. To review, the mAPI is positive when a patient has ≥4 wheezing episodes in a year, which we term the *primary threshold*. The patient also must fulfill what we term as the *secondary threshold*, which is met by meeting at least 1 major criterion or at least 2 minor criteria. The major criteria include parental history of asthma, physician-diagnosed atopic dermatitis, and allergic sensitization to at least 1 aeroallergen. The minor criteria include wheezing unrelated to colds, peripheral blood eosinophils ≥4%, and allergic sensitization to milk, egg, or peanuts. Table I summarizes the mAPI and how it compares with the stringent API.[3] We did not compare the mAPI with the loose API, given the latter has a lower specificity. The modified mAPI (m^2API) used ≥2 wheezing episodes as the primary threshold.

Performance measures

The LR of a test result is the probability of that test result in a patient with disease divided by the probability of that test result in a patient without disease.[13] Positive LRs range from 1 to ∞ (higher is better) and negative LRs range from 0 to 1 (lower is better). Negative LRs below 0.5 are more clinically meaningful, whereas those above 0.5 are poorly predictive. LR confidence intervals were calculated with the delta method.[14]

The posttest probability of disease can be easier than LRs to interpret. The probability of developing asthma after a diagnostic test is performed (posttest probability) depends on the LR and the patient's probability of developing asthma before the test is performed (pretest probability). To compare the mAPI and API, which were evaluated in cohorts with different asthma prevalences, we calculated posttest probability of asthma development considering a low pretest probability (11%), which would be reasonable in an unselected population, and a high pretest probability (30%), which would be reasonable in patients with asthma risk factors (eg, family history of asthma and/or allergies). The value of 11% was selected because this was the prevalence in the unselected Tucson Children's Respiratory Study cohort.[2] The value of 30% was selected for all asthma diagnosis years because the prevalence in our high-risk COAST cohort was 28%, 33%, and 30% for asthma diagnosis at age 6, 8, and 11 years. When the pretest probability is the same as the disease prevalence, positive predictive value is the same as the positive posttest probability and negative predictive value is 1 minus the negative posttest probability.

RESULTS

Table II shows the percentage of subjects with mAPI and m^2API criteria. Few subjects met the primary threshold of ≥4 wheezing episodes, whereas slightly more had ≥2 wheezing episodes. A majority of subjects (64%) had parental asthma and approximately two-thirds of those who met the primary threshold fulfilled the secondary threshold with this criterion.

Table III shows the sensitivity, specificity, LR^+, LR^-, and posttest probabilities of the mAPI in unselected and high-risk populations for asthma diagnosis at year 6, 8, and 11 from years 1, 2, and 3. The maximum LR^+ for asthma diagnosis at any year from years 1, 2, and 3 was 6.1, 14, and 55, respectively, whereas the minimum LR^- was 0.90, 0.89, and 0.82, respectively. With the use of the prediction of year 6 asthma diagnosis in a population with a pretest probability of 11% as an example, the posttest probabilities for a positive mAPI and negative mAPI at age 3 years were 72% and 9%, respectively (Table III). In a high-risk population (pretest probability of 30%), the posttest probabilities for a positive mAPI and negative mAPI at age 3 years were 90% and 26%, respectively (Table III). The positive posttest probabilities in year 8 and 11 asthma diagnosis were 96% and 89%, respectively.

As the threshold for the number of wheezing illnesses decreased to 2 (m^2API), negative test results were still poorly predictive, whereas positive test results were less predictive. The maximum LR^+ for asthma diagnosis at any year from years 1, 2, and 3 was 3.5, 6.5, and 16, respectively, whereas the minimum LR^- was 0.85, 0.71, and 0.70, respectively. With the use of the prediction of year 6 asthma diagnosis in a population with a pretest probability of 11% as an example, the posttest probabilities for a positive m^2API and negative m^2API at age 3 years were 67% and 8%, respectively (Table IV). In a high-risk population (pretest probability of 30%), the posttest probabilities for a positive m^2API and negative m^2API at age 3 years were 87% and 23%, respectively (Table IV).

For year 6 asthma diagnosis, the mAPI had marginally improved LR^+ compared with the m^2API (eg, LR^+ from year 3 was 21 versus 16, respectively). For year 8 and year 11 asthma diagnosis, which are important time points for prediction of more persistent asthma, the

mAPI had substantially improved LR^+ than the m^2API from all preschool years. The LR^+ from year 3 at year 8 and year 11 asthma diagnosis were 55 and 19, respectively, for the mAPI versus 13 and 10, respectively, for the m^2API.

DISCUSSION

We prospectively confirmed the diagnostic utility of the mAPI at 1, 2, and 3 years of age for asthma diagnosis at years 6, 8, and 11 in a well-characterized high-risk birth cohort of children and a theoretical unselected population. With the use of the mAPI, a positive test greatly increased the probability of future asthma risk (eg, 30% pretest future asthma probability to 90% posttest future asthma probability), whereas a negative test provided a small reduction in future asthma probability (eg, 30% pretest future asthma probability to 26% posttest future asthma probability). The m^2API in which 2 instead of 4 wheezing episodes were required for a positive test provided poorer positive posttest probability without meaningfully improving the negative posttest probability.

As one's clinical impression would suspect, predictive ability increased if the prediction year and diagnosis year were closer. Histologic airway changes have been reported to begin sometime between 2 and 3 years of age,[15] and the positive mAPI posttest probability in an unselected population increased dramatically from 43% to 64% to 72% from years 1, 2, and 3 for age 6 asthma diagnosis.

Reported benefits of the API include ease of application in a clinical setting and the ability to rule out asthma.[16] Compared with the API, the mAPI was superior for future asthma prediction after a positive test. The LR^+ of the API was 7.4, 4.9, and 3.8 for year 6, 8, and 11 asthma diagnosis, respectively.[2] This is compared with the LR^+ of the mAPI of 21, 55, and 19 for year 6, 8, and 11 asthma diagnosis, respectively. The positive posttest probability in a high-risk patient increases to >89% for all asthma diagnosis years. The mAPI had superior predictive ability after a positive test than the m^2API, particularly for year 8 and year 11 asthma diagnosis. The m^2API had a LR^+ of 16, 13, and 10 for years 6, 8, and 11 asthma diagnosis. Although the mAPI is preferred, one potential benefit of the m^2API is that a clinician must only wait for a patient to have 2 as opposed to 4 wheezing episodes in a given year before taking action. This action may involve doing nothing, closer monitoring, or altering therapy. Given their high LR^-, the API, mAPI, and m^2API do not have a clinically meaningful predictive ability after a negative test.

The mAPI overcomes some diagnostic drawbacks of the original API as well. The primary threshold in the API is "early frequent wheezing." Wheezing frequency was determined by questionnaire (scaled 1 to 5, from "very rarely" to "on most days"), and a score of ≥3 was considered early frequent wheezing. In contrast, the mAPI asks the parent to recall the specific number of wheezing episodes. In addition, the API uses physician-diagnosed allergic rhinitis, which is often difficult to diagnosis and distinguish from infectious rhinitis in preschool-age children. Instead, the mAPI uses a quantifiable *in vitro* IgE determination or skin prick test to establish allergic sensitization to aeroallergens and foods. One or both of these tests are readily available to many clinicians. The wheezing frequency questionnaire used in the Tucson Children's Respiratory Study and allergic rhinitis in preschool children were not assessed in COAST, precluding direct evaluation of the API.

Additional asthma predictive models were developed from the Environment and Childhood Asthma study,[17] the Isle of Wight study,[18] and the Prevention and Incidence of Asthma and Mite Allergy study.[19] Devulapalli et al[17] analyzed a nested case–control study within the Environment and Childhood Asthma study that used 2-year-old children with ≥2 episodes of bronchial obstruction and those without bronchial obstruction to define a score that

predicted asthma at age 10. An Oslo severity score (0–12) was calculated with the number or persistence of bronchial obstructive episodes and the number of hospital admissions for bronchial obstruction from 0 to 2 years of age. A severity score cutoff of 7 had a LR^+ of 3.9 and LR^- of 0.78. Compared with the Oslo severity score, the mAPI had a better LR^+, but worse LR^-, whereas the m^2API had a better LR^+ and LR^-. Both the Isle of Wight and Prevention and Incidence of Asthma and Mite Allergy studies predicted asthma from age 4, whereas we focused on predicting asthma in younger children, making direct comparisons more difficult.

The strengths of this study include the use of a well-characterized birth cohort and a predefined asthma definition. A limitation is the smaller sample size compared with larger epidemiologic cohort studies. The larger confidence intervals for LRs result from the combined variance of sensitivity and specificity. However, a tradeoff between sample size and a comprehensively characterized birth cohort was necessary. Assessment of the mAPI in a high-risk birth cohort is an additional limitation. These study results are most applicable to children with a family history of asthma or allergy, but they may generalize less well to children without a family history of asthma or allergy. However, we believe the high-risk population could be considered the most relevant to clinicians because parents with a history of allergic disease and/or asthma will more likely be interested in the probability that their child will develop asthma. In addition, we have presented results that use a theoretical unselected population with an asthma prevalence that is based on previously published data to better compare with the API. This conversion assumes asthma and nonasthma populations are similar in COAST and the unselected population.

In conclusion, we have demonstrated that a positive mAPI substantially increases probability of future asthma, whereas a negative mAPI does not provide a clinically meaningful decrease in future asthma probability. Although asthma prediction during early life remains challenging, the mAPI's high predictive ability of school-age asthma after a positive test can have clinical value for identifying children at risk of asthma persisting into school age and beyond. Ultimately, the findings in this study may help clinicians and scientists better identify at-risk children, allowing for earlier diagnosis and targeted prevention strategies.

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Abbreviations used

API	Asthma predictive index
COAST	Childhood Origins of ASThma
LR	Likelihood ratio
mAPI	Modified Asthma Predictive Index
m^2API	Modified Asthma Predictive Index with ≥2 wheezing episodes as the primary threshold

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What is already known about this topic?

Prediction of subsequent school-age asthma during the preschool years has proven challenging. Predictive indices have been used as selection criteria for clinical studies without evaluation.

What does this article add to our knowledge?

We prospectively evaluated the modified Asthma Predictive Index and a potential modification in a high-risk population.

How does this study impact current management guidelines?

The high predictive ability of future school-age asthma after a positive modified Asthma Predictive Index in the preschool years demonstrates its usefulness as a clinical tool.

TABLE I

Criteria for stringent API and mAPI

Stringent API			
Primary	Early frequent wheezer (≥3 on 1–5 rating scale)		
AND			
Secondary	At least 1 major:	OR	At least 2 minor:
	Parental physician-diagnosed asthma		Wheezing unrelated to colds
	Physician-diagnosed atopic dermatitis		Eosinophils ≥4% in circulation
			Physician-diagnosed allergic rhinitis
mAPI			
Primary	≥4 wheezing episodes in a year		
AND			
Secondary	At least 1 major:	OR	At least 2 minor:
	Parental physician-diagnosed asthma		Wheezing unrelated to colds
	Physician-diagnosed atopic dermatitis		Eosinophils ≥4% in circulation
	Allergic sensitization to at least one aeroallergen		Allergic sensitization to milk, egg, or peanuts

TABLE II

Percentage of subjects in year 1, 2, and 3 with mAPI and m^2API criteria

Criteria	Year 1	Year 2	Year 3
No. of wheezing episodes ≥4	5.0	4.6	5.0
No. of wheezing episodes ≥2	13	15	10
Major criteria			
Parental asthma	64	64	64
Atopic dermatitis	25	30	24
Positive aeroallergen IgE	13	19	25
Minor criteria			
Wheeze unrelated to colds	14	8.1	4.2
Peripheral eosinophils ≥4%	19	20	18
Positive food allergen IgE	25	27	29

TABLE III

mAPI sensitivity, specificity, positive LR, negative LR, and posttest probabilities of asthma in unselected and high-risk populations at year 6, 8, and 11 from years 1, 2, and 3

					Unselected (11% pretest)		High risk (30% pretest)	
Year	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**LR^+ (95% CI)**	**LR^- (95% CI)**	**Positive posttest (%)**	**Negative posttest (%)**	**Positive posttest (%)**	**Negative posttest (%)**
Age 6 asthma diagnosis								
1	11% (4.2–19)	98% (96–100)	6.1 (1.8–21)	0.90 (0.83–0.98)	43	10	73	28
2	12% (4.2–19)	99% (98–100)	14 (2.6–80)	0.89 (0.82–0.97)	64	10	86	28
3	17% (8.4–25)	99% (98–100)	21 (4.0–112)	0.84 (0.75–0.93)	72	9	90	2%
Age 8 asthma diagnosis								
1	8.2% (2.2–14)	98% (97–100)	5.3 (1.3–22)	0.93 (0.87–1.0)	40	10	69	29
2	11% (3.9–18)	99% (98–100)	12 (2.1–64)	0.90 (0.83–0.97)	59	10	83	28
3	19% (8.8–25)	100% (99–100)	55 (3.3–913)	0.83 (0.75–0.92)	87	9	96	26
Age 11 asthma diagnosis								
1	11% (3.6–18)	98% (95–100)	4.9 (1.4–17)	0.91 (0.83–1.0)	38	10	68	28
2	11% (3.6–19)	98% (96–100)	6.8 (1.7–28)	0.90 (0.83–0.98)	46	10	75	28
3	19% (9.3–28)	99% (97–100)	19 (3.6–100)	0.82 (0.73–0.92)	70	9	89	26

High Risk (30% pretest), 30% high-risk COAST population pretest probability of asthma; *Unselected (11% pretest)*, 11% theoretical unselected population pretest probability of asthma.

TABLE IV

m^2API sensitivity, specificity, positive LR, negative LR, and posttest probabilities for asthma in unselected and high-risk populations at year 6, 8, and 11 from years 1, 2, and 3

					Unselected (11% pretest)		High risk (30% pretest)	
Year	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**LR^+ (95% CI)**	**LR^- (95% CI)**	**Positive posttest (%)**	**Negative posttest (%)**	**Positive posttest (%)**	**Negative Posttest (%)**
Age 6 asthma diagnosis								
1	21% (11–30)	93% (90–97)	3.1 (1.6–6.3)	0.85 (0.75–0.96)	28	10	57	27
2	33% (22–44)	95% (92–98)	6.5 (3.2–13)	0.71 (0.60–0.83)	45	8	74	23
3	30% (20–41)	98% (96–100)	16 (5.4–48)	0.71 (0.61–0.83)	67	8	87	23
Age 8 asthma diagnosis								
1	18% (9.8–27)	95% (91–98)	3.5 (1.6–7.8)	0.86 (0.77–0.96)	30	10	60	27
2	31% (21–41)	95% (91–98)	5.9 (2.8–12)	0.73 (0.62–0.85)	42	8	72	24
3	28% (19–38)	98% (95–100)	13 (4.4–39)	0.73 (0.63–0.84)	62	8	85	24
Age 11 asthma diagnosis								
1	16% (7.0–24)	92% (87–96)	1.9 (0.88–4.1)	0.92 (0.82–1.0)	19	10	45	28
2	29% (18–40)	92% (87–96)	3.5 (1.8–6.8)	0.77 (0.66–0.91)	30	9	60	25
3	32% (21–43)	97% (94–100)	10 (4.1–29)	0.70 (0.59–0.83)	57	8	82	23

Unselected (11% pretest), 11% theoretical unselected population pretest probability of asthma; *High Risk (30% pretest)*, 30% high-risk COAST population pretest probability of asthma.