

Validation of the Asthma Predictive Index and comparison with simpler clinical prediction rules

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Background: The loose and stringent Asthma Predictive Indices (API), developed in Tucson, are popular rules to predict asthma in preschool children. To be clinically useful, they require validation in different settings.

Objective: To assess the predictive performance of the API in an independent population and compare it with simpler rules based only on preschool wheeze.

Methods: We studied 1954 children of the population-based Leicester Respiratory Cohort, followed up from age 1 to 10 years. The API and frequency of wheeze were assessed at age 3 years, and we determined their association with asthma at ages 7 and 10 years by using logistic regression. We computed test characteristics and measures of predictive performance to validate the API and compare it with simpler rules.

Results: The ability of the API to predict asthma in Leicester was comparable to Tucson: for the loose API, odds ratios for asthma at age 7 years were 5.2 in Leicester (5.5 in Tucson), and positive predictive values were 26% (26%). For the stringent API, these values were 8.2 (9.8) and 40% (48%). For the simpler rule early wheeze, corresponding values were 5.4 and 21%; for early frequent wheeze, 6.7 and 36%. The discriminative ability of all prediction rules was moderate (*c* statistic ≤ 0.7) and overall predictive performance low (scaled Brier score $< 20\%$). **Conclusion:** Predictive performance of the API in Leicester, although comparable to the original study, was modest and similar to prediction based only on preschool wheeze. This highlights the need for better prediction rules. (J Allergy Clin Immunol 2011;■■■:■■■-■■■.)

Key words: Asthma, wheeze, children, prognosis, prediction, longitudinal, cohort study, validation

The Asthma Predictive Index (API), developed in the Tucson Children's Respiratory Study (TCRS), is a clinical tool to predict

Abbreviations used

API: Asthma Predictive Index
EFW: Early frequent wheeze
EW: Early wheeze
LRC: Leicester 1998b Respiratory Cohort
NPV: Negative predictive value
OR: Odds ratio
PPV: Positive predictive value
TCRS: Tucson Children's Respiratory Study

the risk of asthma at school age in preschool children.¹ The authors defined 2 prediction rules: the loose API for a medium and the stringent API for a high risk of later asthma. The API is a popular clinical prediction rule and is commonly considered the standard to which new rules are compared.²⁻⁵ It has been used for various purposes, such as recruiting high-risk children for clinical trials^{6,7} or testing whether physiological measurements distinguish between medium and high-risk groups.^{8,9} It has also been widely advertised for use in clinical management of preschool wheeze.¹⁰⁻¹⁴

But how well does the API predict development of asthma in different settings? Testing the accuracy of prediction rules in different populations (external validation) is crucial for application in clinical practice.¹⁵⁻¹⁹ Two previous studies have compared the performance of the API with that of novel risk scores, but without comparing its performance with the original study and discussing its applicability in the new setting.^{4,5} Besides its performance, another important criterion for acceptance of prediction rules in clinical practice is ease of implementation.^{15,18,20} The API is a rather complex prediction rule based on frequency of early wheeze (none, infrequent, frequent) combined with information on family and personal history (parental asthma, eczema, allergic rhinitis, wheeze without colds) and eosinophil counts. Clinical patterns of early wheeze are known to be strong predictors of later respiratory disease on their own.^{2-5,21,22} This raises the question of how much prognostic information is gained by the additional complexity of the API.

The aims of this study were, first, to validate the API in an independent, longitudinal, population-based cohort and, second, to compare its performance with simpler prediction rules based only on the frequency of preschool wheezing.

METHODS

Study populations

Development cohort. The TCRS, a birth cohort study in Arizona, contacted 1596 healthy infants between 1980 and 1984.²³ Baseline clinical information for the API was assessed from questionnaires at enrollment and at

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TABLE I. Characteristics of the development and validation cohorts

Characteristics	Development cohort: TCRS*		Validation cohort: LRC†	
Location	Tucson, Ariz		Leicester, UK	
Climate	Desert		Temperate maritime	
Recruitment year	1980-1984		1998	
Study design	Prospective cohort		Prospective cohort	
Recruitment	Healthy infants seeing pediatricians of a large HMO in Tucson		Random sample from the general population	
Age at recruitment (y)	0		1	
Mother's ethnicity (%)	White (80) Mexican American (20)		White (81) South Asian (19)‡	
Sex (% males)	49		52	
Children contacted (N)	1596		4300	
Questionnaire survey§	0 y			
	2 y (1.6 ± 0.4)	1246 (100%)	2 y (1.5 ± 0.3)	3392 (100%)
	3 y (2.9 ± 0.5)	1055 (85%)	3 y (2.5 ± 0.3)	2405 (71%)
	6 y (6.3 ± 0.9)	940 (75%)	7 y (6.5 ± 0.3)	2405 (71%)
	11 y (10.9 ± 0.6)	1025 (82%)	10 y (9.8 ± 0.3)	2092 (62%)
Blood sample	1 y (0.9 ± 0.1)	955 (77%)		1521 (45%)
		912 (73%)		

HMO, Health maintenance organization; UK, United Kingdom.

*Data as reported by Castro-Rodriguez et al,¹ Taussig et al.^{23,24}†Data as reported by Kuehni et al.²⁵

‡Indian, Pakistani, or Bangladeshi origin.

§Includes only surveys used for validation of the API in LRC. Data are mean age at survey (mean years ± SD), number responded (response rate calculated on the basis of children who replied to first survey).

ages 2 and 3 years and from a blood sample at age 1 year; the outcome asthma was assessed at ages 6, 8, 11, and 13 years (Table I).^{1,24}

Validation cohort. The Leicester 1998b Respiratory Cohort (LRC, www.leicestercohorts.org) is a population-based stratified random sample of children recruited in 1998 at the age of 1 year in Leicestershire, United Kingdom, that includes 3500 white and 800 South Asian children.²⁵ Parents received standardized questionnaires at the child's age of 2, 3, 5, 7, and 10 years (Table I), with questions on respiratory symptoms, diagnoses and treatments, environmental exposures, parental history of atopic diseases, ethnicity, and socioeconomic situation.^{26,27} The Leicestershire Health Authority Research Ethics Committee approved the study.

Outcome and prediction rules

In both cohorts, clinical information assessed at the ages of 2 and 3 years was used to define prediction rules for active asthma at school age (6 and 11 years in TCRS; 7 and 10 years in LRC). Table II shows definitions of predictor and outcome variables and prediction rules in both cohorts. In TCRS, asthma was predicted by using the API only.¹ In LRC, we predicted asthma by using (1) the API, (2) simpler prediction rules based only on frequency of wheeze, and (3) a random rule to illustrate the predictive performance of chance alone. While the performance of random rules is predictable, they are useful to put the performance of the other rules into perspective.

Loose and stringent API. As originally proposed, the API was based on 7 clinical features (predictor variables) assessed in the first 3 years of life: early wheeze (EW), early frequent wheeze (EFW), wheeze without colds, parental asthma, personal history of eczema, allergic rhinitis, and blood eosinophils.¹ We approximated the API by using similar or comparable information from LRC. The 3 wheeze variables could be matched closely, whereas some adaptations were made for parental asthma, eczema, and allergic rhinitis; eosinophilia was replaced by a surrogate (Table II).

As in the original study, a child with EW and 1 of 2 major risk factors (parental asthma, personal eczema) or 2 of 3 minor risk factors (allergic rhinitis, wheeze without colds, eosinophilia) was assigned a medium risk of later asthma (positive loose API). A child with EFW and the same combination of risk factors was considered at high risk of later asthma (positive stringent API).

Frequency of wheeze. A child with EW was assigned a medium risk, a child with persistent EW or EFW a high risk, and a child with persistent EFW a very high risk.

Random rules. Preschool children were randomly assigned positive random 1 and random 2 rules with probabilities equal to the prevalence of the loose and stringent indices, respectively.

Statistical analyses

As in the original study, only children with complete information on all predictor variables or with sufficient information to confirm a positive loose or stringent API were included in the analysis.¹

First, we compared the prevalence of asthma, the predictor variables, and prediction rules between the 2 cohorts. Second, we compared the performance of the API in the development (TCRS) and validation (LRC) cohorts. Third, we compared the performance of the API with that of simpler and random prediction rules. This comparison was restricted to data from LRC only.

We used a variety of measures to compare predictive performance across cohorts and prediction rules, including the standard test characteristics odds ratio (OR), sensitivity, specificity, and positive (PPV) and negative predictive values (NPV). Sensitivity measures the fraction of children with later asthma who were identified as at risk at preschool age; specificity measures the fraction of children without later asthma who were not identified as at risk. Clinically more relevant are PPV, the probability of later asthma in a child identified as at risk, and NPV, the probability of no later asthma in a child not identified as at risk.

We also assessed measures of discrimination, calibration, and overall predictive performance of the API. *Discrimination* is the ability of a rule to correctly distinguish between children with and without asthma. We assessed discrimination by using the concordance (*c*) statistic. Discrimination is not better than chance if *c* = 0.5, moderate if *c* > 0.6, good if *c* > 0.8, and perfect if *c* = 1.¹⁶ *Calibration* is the extent of agreement between predicted risk and the frequency of observed outcomes; for example, if a 20% probability of asthma is predicted, the observed frequency of asthma will be close to 20% for a well calibrated rule. As a measure of calibration, we compared PPV (the predicted probability of asthma for those with a positive API) and 1 – NPV (the predicted probability for those with a negative API) between the 2 cohorts. As a summary measure of *overall predictive performance*, combining discrimination and calibration, we used the scaled Brier score, which measures the average difference between predicted and actual outcomes.^{17,28} The scaled Brier score ($\text{Brier}_{\text{scaled}} = 1 - \text{Brier}/\text{Brier}_{\text{max}}$) ranges from 0% for a noninformative model to 100% for a perfect prediction of outcomes. Overall performance could be assessed in LRC only.

TABLE II. Definitions and prevalences of outcome and predictor variables, prediction, and random rules in the development and validation cohorts

Variable	Development cohort: TCRS*		Validation cohort: LRC	
	Definition	n/N (%)	Definition	n/N (%)
Outcome variables				
Asthma	“Doctor-diagnosed asthma and ≥ 1 attack in the last 12 mo” or “ ≥ 3 attacks in the last 12 mo”: 6 y	112/1014 (11.0)	“Doctor-diagnosed asthma and ≥ 1 attack in the last 12 mo” or “ ≥ 4 attacks in the last 12 mo”: 7 y	220/1916 (11.5)
Asthma	Identical to above: 11 y	150/947 (15.8)	Identical to above: 10 y	147/1397 (10.5)
Predictor variables used in API				
Wheeze				
EW	Chest ever sounded wheezy: 2 or 3 y†	579/1077 (53.8)	Wheezing or whistling in the chest ever: 2 or 3 y	1475/3388 (43.5)
EFW	Value ≥ 3 on a frequency scale (1, rarely; 5, on most days): 2 or 3 y	115/1077 (10.7)	≥ 4 attacks in the last 12 mo: 2 or 3 y	487/3371 (14.4)
Major risk factors				
Parental asthma	Either father or mother with doctor-diagnosed asthma: 0 y‡	248/1071 (22.7)	Either father or mother with self-reported asthma/wheeze and hay fever/eczema: 2 y§	803/3314 (24.2)
Eczema	Doctor-diagnosis in the last 12 mo: 2 or 3 y	129/1071 (12.0)	Parental report in the last 12 mo: 2 and 3 y	593/3001 (19.8)
Minor risk factors				
Wheeze without cold	Wheezing apart from colds: 2 or 3 yr	161/1079 (14.9)	Wheezing even without colds: 2 or 3 y	491/3363 (14.6)
Allergic rhinitis	Stuffy, runny, or itchy nose apart from colds in the last 12 mo and a doctor said it was a result of allergies: 2 or 3 y	180/1066 (16.9)	Runny or blocked nose apart from colds in the last 12 mo that interfered at least a little with the child’s daily activities: 2 or 3 y	696/3382 (20.6)
Eosinophilia	Circulating eosinophils $\geq 4\%$ of total white blood cells: 1 y¶	94/912 (10.3)	Surrogate: Wheeze or cough triggered by food: 2 y	351/3155 (11.1)
Prediction rules				
Loose API	EW and 1 major or 2 minor risk factors	233/986 (23.6)	EW and 1 major or 2 minor risk factors	757/2948 (25.7)
Stringent API	EFW and 1 major or 2 minor risk factors	63/1002 (6.3)	EFW and 1 major or 2 minor risk factors	308/2838 (10.9)
EW			EW	1475/3388 (43.5)
Persistent EW			Wheezing or whistling in the chest in the last 12 mo: 2 and 3 y	362/2971 (12.2)
EFW			EFW	487/3371 (14.4)
Persistent EFW			≥ 4 attacks in the last 12 mo: 2 and 3 y	76/3227 (2.4)
Random 1			Randomly assigned with a probability equal to the prevalence of the loose API	848/3393 (25.0)
Random 2			As above, probability equal to the prevalence of the stringent API	368/3393 (10.8)

*Data as reported by Castro-Rodriguez et al.¹

†Positive answer in questionnaire survey at either age 2 or 3 years.

‡Positive answer at enrollment.

§Positive answer to both “asthma or wheeze” and “hay fever or eczema”; positive answer at 2 years.

||Positive answer at both age 2 and 3 years.

¶Determined from a blood sample taken at age 1 year.

To test the robustness of the findings, we performed 3 sensitivity analyses. First, we altered the definitions of the predictor variables parental asthma, eczema, allergic rhinitis and eosinophilia. Second, we restricted the analysis to children who wheezed during the first 3 years of life because this subgroup represents a clinically relevant group in whom a prediction of risk for later asthma is important. Third, we altered the definition of the outcome by (1) including the current use of asthma medication and (2) replacing it with current wheeze.

All analyses were performed by using Stata (release 11.0; Stata Corp, College Station, Tex). We used 2-sided *t* tests and a significance level of .05.

RESULTS

Study populations

The TCRS and LRC are large, unselected, mixed-ethnicity prospective cohorts with comparable sex balances and ages at

follow-ups (Table I). Children in LRC were recruited ~15 years later, live in a different climate zone, and provided no blood sample.

In LRC, 3392 of 4300 invited children replied to the first postal questionnaire, and 2948 provided enough information at baseline to determine the API, of whom 1954 also provided information on asthma at 7 or 10 years. These children did not differ from those with incomplete data in terms of sex (53% vs 52% males among those with complete/incomplete data, respectively; *P* = .52) or parental history of asthma (26% vs 26%; *P* = .95) but were more likely to have white parents (90% vs 84%; *P* < .001) and live in a less deprived area (28% vs 17% in the least deprived quartile of the Townsend score; *P* < .001) and less likely to have reported symptoms of early wheeze (41% vs 49%; *P* < .001) and to have been assigned a positive loose (25% vs 28%; *P* = .03)

TABLE III. Comparison of the performance of the API in predicting asthma at school age in the development (TCRS) and validation (LRC) cohorts

Risk of asthma	Cohort	API*	N	Pos rules (%)	OR	Sens (%)	Spec (%)	PPV (%)	NPV (%)	c†	Brier scaled (%)‡
Age 6-7 y											
Medium	TCRS§	Loose	921	23.6	5.5	57	81	26	94	0.69¶	NA
	LRC	Loose	1731	24.2	5.2	57	80	26	94	0.68	12
High	TCRS	Stringent	937	6.3	9.8	28	96	48	92	0.62	NA
	LRC	Stringent	1683	9.7	8.2	37	93	40	93	0.65	16
Age 10-11 y											
Medium	TCRS	Loose	861	23.6	2.6	40	80	27	88	0.60	NA
	LRC	Loose	1291	23.0	5.7	57	81	25	94	0.69	10
High	TCRS	Stringent	875	6.3	4.3	15	96	42	88	0.56	NA
	LRC	Stringent	1257	9.0	6.7	32	94	35	92	0.63	11

c, c Statistic; NA, not available; Pos, positive; Sens, sensitivity; Spec, specificity.

*Details described in the Methods section and Table II.

†Discriminative ability is not better than chance if $c = 0.5$, moderate if $c > 0.6$, good if $c > 0.8$, and perfect if $c = 1$.

‡Brier scaled measures overall performance; it ranges from 0% for a noninformative model to 100% for a perfect prediction.

§Data as reported by Castro-Rodriguez et al.¹

||Prevalence at baseline (3 years).

¶Calculated on the basis of published values of sensitivity and specificity.

or stringent API (10% vs 12%; $P = .06$). Also in TCRS, fewer positive indices among those followed up were observed.¹

Prevalence of outcome and prediction rules

The outcome of interest, active asthma at school age, was equally prevalent in both cohorts at 6 to 7 years (11.5% in LRC vs 11.0% in TCRS) but less prevalent in LRC at 10 to 11 years (10.5% vs 15.8%; Table II). Prevalence of EW was lower in LRC (43.5% vs 53.8%), whereas prevalence of EFW (14.4% vs 10.7%) and loose (25.7% vs 23.6%) and stringent indices (10.9% vs 6.3%) were somewhat higher. Among children with a positive API, only a minority was classified on the basis of the surrogate for eosinophilia (<4% for both rules).

Comparison of the API between TCRS and LRC

Association between the API and asthma at 7 and 10 years in LRC was comparable to published data from the TCRS (Table III; see this article's Table E1 in the Online Repository at www.jacionline.org for CIs).¹ In both cohorts, the odds of developing asthma increased similarly with a positive loose API (OR, 5.2 in LRC at age 7 years vs 5.5 in TCRS at age 6 years) and a positive stringent API (OR, 8.2 vs 9.8). Predictive values of both indices were also similar (loose API, PPV 26% vs 26%, NPV 94% vs 94%; stringent API, PPV 40% vs 48%, NPV 93% vs 92%). In both cohorts, specificity and NPV were high ($\geq 80\%$ and $\geq 88\%$, respectively), whereas sensitivity and PPV were moderate at both outcome ages (15% to 57% and 25% to 48%, respectively).

However, sensitivity of the stringent API was higher in LRC than in TCRS (37% vs 28% at 6-7 years; 32% vs 15% at 10-11 years). Also, the discriminative ability of the API was similar or higher in LRC but remained poor to moderate in both cohorts ($0.56 \leq c \leq 0.69$). Regarding calibration, the API slightly overestimated the risk of asthma in LRC for high-risk groups (positive stringent API) and older age (10-11 years; Fig 1). Within LRC, overall predictive performance was low (Brier_{scaled}, 10% to 16%).

Similar results were obtained after modifying the definitions of parental asthma, eczema, allergic rhinitis, and eosinophilia (see this article's Table E2 in the Online Repository at www.jacionline.org).

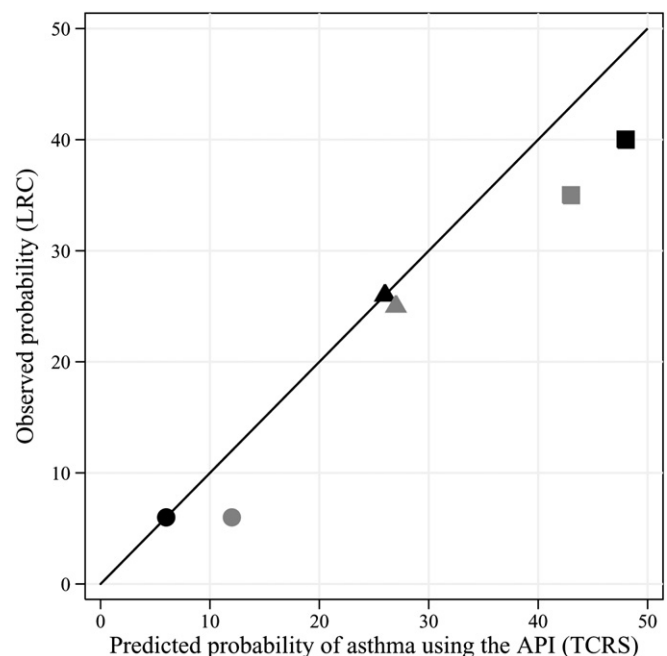


FIG 1. Calibration of the API. Risk of asthma at ages 6 to 7 years (black) and 10 to 11 years (gray) in TCRS (predicted risk) and LRC (observed risk) for children classified as negative loose API (circle), positive loose API (triangle), and positive stringent API (square). The diagonal line indicates perfect calibration.

Comparison of the API with simpler prediction rules within LRC

Having found a similar predictive accuracy of the API in LRC, we then compared the performance of the API within LRC to (1) the simpler rules based on frequency of wheeze only and (2) the noninformative random rules.

Predictive performance of the simpler rules was largely comparable to API at both ages 7 and 10 years (Fig 2; Table IV; see this article's Table E3 in the Online Repository at www.jacionline.org for CIs). EW had higher sensitivity and lower specificity but OR, PPV, NPV, and c statistic comparable to those of the loose API.

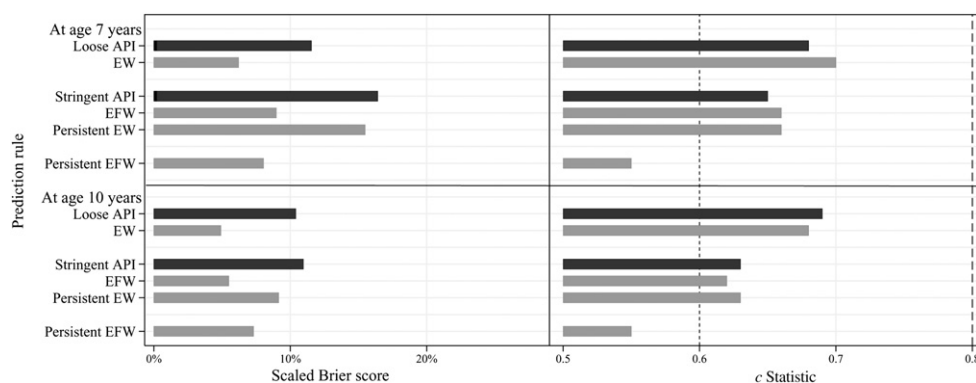


FIG 2. Overall predictive performance ($Brier_{scaled}$) and discriminative ability (c) of the API (black) and simpler prediction rules (gray) in predicting asthma at ages 7 and 10 years in the LRC. $Brier_{scaled}$, 0% for a noninformative model, 100% for a perfect prediction; c statistic, 0.5 for no, >0.6 for moderate (short dash), >0.8 for good discrimination (dash).

TABLE IV. Comparison of the performance of different prediction rules in predicting asthma at school age within the validation cohort (LRC)

Risk of asthma	Prediction rule*	N	Pos rules (%)	OR	Sens (%)	Spec (%)	PPV (%)	NPV (%)	$c^{\dagger}$	Brier scaled (%) ‡
Age 7 y										
Medium	Loose API	1731	24.2	5.2	57	80	26	94	0.68	12
	EW	1910	40.4	5.4	75	64	21	95	0.70	6
	Random 1	1914	25.0	1.1	27	75	13	89	0.49	0
High	Stringent API	1683	9.7	8.2	37	93	40	93	0.65	16
	EFW	1901	13.0	6.7	41	91	36	92	0.66	9
	Persistent EW	1799	12.8	6.7	41	91	34	93	0.66	15
Very high	Random 2	1914	11.6	1.1	12	89	12	89	0.48	0
	Persistent EFW	1870	2.5	9.5	12	99	51	90	0.55	8
Age 10 y										
Medium	Loose API	1291	23.0	5.7	57	81	25	94	0.69	10
	EW	1396	38.5	4.4	70	65	19	95	0.68	5
	Random 1	1396	24.2	1.1	27	76	12	90	0.51	0
High	Stringent API	1257	9.0	6.7	32	94	35	92	0.63	11
	EFW	1391	11.9	4.9	34	91	30	92	0.62	6
	Persistent EW	1326	12.3	5.2	36	90	29	93	0.63	9
Very high	Random 2	1396	11.4	1.3	14	89	13	90	0.50	0
	Persistent EFW	1378	2.3	12.0	12	99	55	91	0.55	7

c , c Statistic; Pos , positive; $Sens$, sensitivity; $Spec$, specificity.

*Details described in the Methods section and Table II.

† Discriminative ability is not better than chance if $c = 0.5$, moderate if $c > 0.6$, good if $c > 0.8$, and perfect if $c = 1$.

‡ Brier scaled measures overall performance; it ranges from 0% for a noninformative model to 100% for a perfect prediction.

All these values were comparable between EFW and the stringent API. At age 7 years, for instance, ORs for asthma were 6.7 for EFW versus 8.2 for the stringent API; sensitivity, 41% versus 37%; specificity, 91% versus 93%; PPV, 36% versus 40%; NPV, 92% versus 93%; and discriminative abilities (c), 0.66 versus 0.65. However, overall predictive performance ($Brier_{scaled}$) was lower for the simpler rules (EW 6% vs loose API 12%; EFW 9% vs stringent API 16%). Persistent EW was similar to the stringent API in all measures, including overall predictive performance ($Brier_{scaled}$ 15% for persistent EW vs 16% for stringent API; 9% vs 11% for ages 7 and 11 years, respectively). Persistent EFW, the strictest prediction rule, had the highest OR (9.5 at age 7 years; 12.0 at age 10 years), specificity (99% both ages), and PPV (51%, 55%), but the lowest sensitivity (12% both ages) and poor discriminative ability ($c < 0.6$).

The random rules showed no discriminative ability ($c \sim 0.5$) and poor overall predictive performance ($Brier_{scaled}$

~ 0) but high specificity (75% to 89%) and NPV ($\sim 90\%$; Table IV).

Sensitivity analyses including only early wheezers led to some differences in predictive performance of all rules (see this article's Table E4 in the Online Repository at www.jacionline.org). For the stringent API at age 7 years, for instance, sensitivity increased from 37% (main analysis) to 49%, and PPV remained the same (40%), whereas specificity decreased from 93% to 81%, NPV from 93% to 86%, discriminative ability from 0.68 to 0.59, and overall predictive performance from 12% to 4%. However, EFW and persistent EW performed comparably as the API in this population too (EW not applicable because of 100% prevalence).

Sensitivity analyses using an alternative asthma definition also led to some differences in the performance measures, but simpler rules were again largely comparable to the API (see this article's Tables E5 and E6 in the Online Repository at www.jacionline.org).

DISCUSSION

We found that the API developed in Tucson predicted asthma at school age in Leicestershire similarly, despite disparities in location, recruitment period, and predictor variables. This supports the generalizability of the API to other settings. Its predictive accuracy, however, was modest, and simpler rules based only on frequency of preschool wheeze showed comparable performance, suggesting that the additional criteria included in the API—1 of them requiring a blood sample—do not improve prediction substantially.

In our study, frequency of early wheeze was the single most important predictor of asthma at school age. The importance of this predictor has long been recognized, and it has been included in several prediction rules.^{2-5,21,22,29,30} Our results further extend the conclusions of 2 other studies: in a nested case control study, Devulapalli et al⁴ developed a severity score based on recurrent bronchial obstruction, which showed similar predictive accuracy as the API. Also, Ly et al,² among children of atopic parents, observed predictive accuracy of “recurrent early wheeze” and “frequent early wheeze,” similar to our variables persistent EW and persistent EFW.

The use of complex rather than simple prediction rules is only worthwhile if added benefits outweigh added costs. In the case of the API, added costs are considerable, including a blood test. Our results suggest that, certainly in situations where the added information is not easily available or affordable, such as in large-scale epidemiologic studies or in general pediatric practice, simpler rules based only on early wheezing patterns can effectively replace the API. It should be kept in mind, however, that although these prediction rules are an improvement over chance prediction, their predictive accuracy for individual children is limited, and the prediction should be interpreted with care.

Furthermore, the broad recommendation of the API in guidelines and position papers for any kind of research question¹⁰⁻¹⁴ should be reconsidered, and rules tailored to specific situations may be required. The importance of different performance measures depends on the aim of prediction, and no single prediction rule is likely to suit all purposes. Discriminatory ability is crucial when the aim is to target costly preventive interventions to a high-risk group, good calibration is important for unbiased prediction of prognosis in the clinical setting,¹⁷ and a high NPV is essential when the aim is to rule out the possibility of later asthma. The API has been particularly praised for its ability to rule out asthma at school age.^{13,31,32} Our study shows, however, that prediction based on wheeze alone results in an equally high NPV as prediction based on the API (NPV 92% to 95% for wheeze vs 92% to 94% for the API), and that a NPV of ~90% is also attained by chance prediction. The reason for this high value is that only ~10% of unselected children will have asthma at school age. By using early prognostic information, the API and simpler rules do, however, reduce the risk of later asthma for children with a negative prediction rule from 10% to 11%, to 4% to 8% (1 – NPV).

In addition, the definition of the study population used to develop a rule should fit the research question. To be relevant in a primary care setting of preschool children presenting with wheeze, for instance, the predictive performance should be evaluated among children with preschool wheeze only. These children have an elevated risk for later asthma, and in our sensitivity analysis, the API showed a lower NPV (86% to 92%) in this group than in the main analysis including all children (92%

to 94%; by definition, this sensitivity analysis does not affect PPV; Table E4). In contrast, if the aim is to predict later asthma in the population at large, regardless of early wheeze—for example, to target primary prevention measures—then predictive performance needs to be assessed in a sample including all preschool children.

The modest performance of all tested prediction rules demonstrates that reliable, early identification of children at risk of developing asthma remains unsatisfactory. For instance, 60% of children with preschool wheeze and a positive stringent API would not develop asthma by age 7 years (1 – PPV), whereas 14% of those with preschool wheeze and a negative stringent API would (1 – NPV; Table E4). This situation cannot be easily remedied by using rules that require more severe symptoms. For instance, our strictest rule, persistent EFW, although resulting in the highest PPV (51% to 55%), showed poor sensitivity (12%). The rule thus improved prediction for the few children who remained included but missed a significant proportion of preschoolers at risk of later asthma. Others have reported similar results.^{3,29,33} Recent proposals of prediction rules for asthma suggest ways to improve predictive accuracy. Notably, scoring rules based on regression models may enhance predictive performance.^{5,29} However, development of such models must take care to avoid overfitting, which reduces the generalizability of results to children not contained in the development data set. Methods such as penalized regression and resampling techniques help to avoid overfitting.¹⁷ Another way to improve predictive accuracy is the inclusion of better early predictors, such as a more detailed assessment of atopy (degree of sensitization to specific allergens instead of the binary result “sensitized/non-sensitized”),^{34,35} other physiological measurements such as exhaled nitric oxide or lung function,³⁶ asthma-related genes, and potential interactions between these various predictors.^{34,35}

A strength of this study is the comparable information collected at similar ages in both cohorts. Definitions of predictors and outcomes were comparable except for eosinophilia, which was replaced by a surrogate measure. However, among children with a positive API in LRC, few (<4%) were classified on the basis of the surrogate, making a distortion of results unlikely. Although validation of prediction models in other settings is commonly limited by differences in available variables, recruitment criteria, ages at prediction, and follow-up or study size, external validation remains crucial. Our results show that the predictive performance of the API is robust against some modification of predictors. Changes in definition of the strongest predictor, frequency of early wheeze, are, however, relevant. In our analysis, a different scale for frequency of wheeze might have led to the higher prevalence, sensitivity, and discriminative ability of the stringent API in LRC compared with TCRS (Tables II and III).

The size of our population was adequate: we had well over 100 cases of asthma,¹⁶ allowing relevant differences in performance to be detected. A limitation of the original study that we had to retain for comparability is the inclusion criteria: selecting only children with sufficient data to determine a positive API artificially increased the prevalence of positive test results. Differences between the children included for analysis and the general population may have thus influenced results in both cohorts.

In conclusion, this analysis found a similar performance of the API in the validation and development cohorts, but no substantial benefit of using the API to predict later asthma compared with

simpler prediction rules based only on frequency of wheeze. For clinical purposes, simpler rules might currently be preferred because they do not require a blood sample and are easier to use. Development of more accurate prediction rules is needed.

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Clinical implications: A simple question about frequency of preschool wheeze predicts asthma at school age with accuracy comparable to the API and might thus be preferable.

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TABLE E1. Comparison of the performance of the API in predicting asthma at school age in the development (TCRS) and validation (LRC) cohorts including CIs

Risk of asthma	Cohort	API*	N	Pos rules (%)	OR (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	c†	Brier scaled (%)‡
Age 6-7 y											
Medium	TCRS§	Loose	921	23.6	5.5 (3.5-8.4)	57 (53-60)	81 (78-83)	26 (23-29)	94 (92-95)	0.69¶	NA
	LRC	Loose	1731	24.2	5.2 (3.8-7.2)	57 (50-64)	80 (78-82)	26 (21-30)	94 (92-95)	0.68	12
High	TCRS	Stringent	937	6.3	9.8 (5.6-17.2)	28 (25-30)	96 (95-98)	48 (44-51)	92 (90-93)	0.62	NA
	LRC	Stringent	1683	9.7	8.2 (5.7-11.9)	37 (30-44)	93 (92-95)	40 (32-48)	93 (91-94)	0.65	16
Age 10-11 y											
Medium	TCRS	Loose	861	23.6‡	2.6 (1.8-3.8)	40 (37-43)	80 (77-82)	27 (24-30)	88 (85-90)	0.60	NA
	LRC	Loose	1291	23.0	5.7 (3.9-8.2)	57 (48-66)	81 (78-83)	25 (20-31)	94 (93-96)	0.69	10
High	TCRS	Stringent	875	6.3‡	4.3 (2.4-7.8)	15 (13-17)	96 (95-97)	42 (39-45)	88 (83-88)	0.56	NA
	LRC	Stringent	1257	9.0	6.7 (4.3-10.5)	32 (24-41)	94 (92-95)	35 (27-45)	92 (91-94)	0.63	11

c, c Statistic; NA, not available; Pos, positive.

*Details described in the Methods section and Table II.

†Discriminative ability is not better than chance if $c = 0.5$, moderate if $c > 0.6$, good if $c > 0.8$, and perfect if $c = 1$.

‡Brier scaled measures overall performance; it ranges from 0% for a noninformative model to 100% for a perfect prediction.

§Data as reported by Castro-Rodriguez et al.¹

||Prevalence at baseline (3 years).

¶Calculated on the basis of published values of sensitivity and specificity.

TABLE E2. Comparison of the performance of the API in predicting asthma at school age in the validation (LRC) cohort

API	Alternatively defined variable	N	Pos rules (%)	OR	Sens (%)	Spec (%)	PPV (%)	NPV (%)	c*	Brier scaled (%)†
Age 7 y										
Loose‡	No changes§	1731	24.2	5.2	57	80	26	94	0.68	12
	Parental asthma	1744	27.4	5.5	62	77	25	94	0.70	11
	Eczema¶	1845	27.8	4.4	58	76	23	94	0.67	8
	Allergic rhinitis#	1738	25.5	5.3	59	79	25	94	0.69	11
	Allergic rhinitis**	1720	22.8	5.0	54	81	25	94	0.68	13
Stringent‡‡	Eosinophilia††	1754	24.5	4.9	56	79	25	94	0.68	11
	No changes	1683	9.7	8.2	37	93	40	93	0.65	16
	Parental asthma	1690	10.4	8.3	39	93	39	93	0.66	17
	Eczema	1798	10.2	7.5	36	93	39	92	0.65	13
	Allergic rhinitis	1686	10.4	8.0	38	93	39	93	0.66	16
	Allergic rhinitis	1676	9.0	7.9	34	94	39	93	0.64	17
	Eosinophilia	1721	9.7	7.7	35	93	39	92	0.64	15
Age 10 y										
Loose	No changes	1291	23.0	5.7	57	81	25	94	0.69	10
	Parental asthma	1301	25.8	6.0	62	78	25	95	0.67	10
	Eczema	1362	26.7	4.5	58	77	23	94	0.67	7
	Allergic rhinitis	1295	24.6	5.2	58	79	24	94	0.68	9
	Allergic rhinitis	1284	22.0	5.7	56	82	26	94	0.69	10
Stringent	Eosinophilia	1304	23.4	5.7	58	81	26	94	0.69	9
	No changes	1257	9.0	6.7	32	94	35	92	0.63	11
	Parental asthma	1261	9.6	6.7	33	93	35	93	0.63	11
	Eczema	1325	9.5	6.2	32	93	34	92	0.62	9
	Allergic rhinitis	1259	9.8	6.1	32	93	33	92	0.63	10
	Allergic rhinitis	1250	8.2	7.2	30	94	37	92	0.62	11
	Eosinophilia	1286	8.9	6.6	31	94	36	92	0.62	9

Sensitivity analysis uses altered definitions of the predictor variables parental asthma, eczema, allergic rhinitis, or eosinophilia.

c, c Statistic; Pos, positive; Sens, sensitivity; Spec, specificity.

*Discriminative ability is not better than chance if $c = 0.5$, moderate if $c > 0.6$, good if $c > 0.8$, and perfect if $c = 1$.

†Brier scaled measures overall performance; it ranges from 0% for a noninformative model to 100% for a perfect prediction.

‡Medium risk of asthma: early wheeze and 1 major (parental asthma, eczema) or 2 minor (allergic rhinitis, wheeze without colds, eosinophilia) risk factors.

§Details described in the Methods section and Table II.

||Defined as a parental report of asthma or wheeze in the questionnaire survey at 2 years.

¶Defined as a positive answer to a doctor-diagnosis of eczema in the last 12 months in the questionnaire survey at either age 2 or 3 years.

#Defined as a positive answer to runny or blocked nose apart from colds in the last 12 months in the questionnaire survey at 2 or 3 years.

**Defined as a runny nose that limited the child's activity moderately instead of only little.

††Defined as a positive answer to wheeze or cough triggered by food in questionnaire survey at either age 2 or 3 years.

‡‡High risk of asthma: early frequent wheeze and 1 major (parental asthma, eczema) or 2 minor (allergic rhinitis, wheeze without colds, eosinophilia) risk factors.

TABLE E3. Comparison of the performance of different prediction rules in predicting asthma at school age within the validation cohort (LRC) including CIs

Risk of asthma	Prediction rule*	N	Pos rules (%)	OR (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	c†	Brier scaled (%)‡
Age 7 y										
Medium	Loose API	1731	24.2	5.2 (3.8-7.2)	57 (50-64)	80 (78-82)	26 (21-30)	94 (92-95)	0.68	12
	EW	1910	40.4	5.4 (3.9-7.4)	75 (69-81)	64 (62-66)	21 (19-24)	95 (94-96)	0.70	6
	Random 1	1914	25.0	1.1 (0.8-1.6)	27 (22-34)	75 (73-77)	13 (10-16)	89 (87-90)	0.49	0
High	Stringent API	1683	9.7	8.2 (5.7-11.9)	37 (30-44)	93 (92-95)	40 (32-48)	93 (91-94)	0.65	16
	EFW	1901	13.0	6.7 (4.9-9.1)	41 (34-48)	91 (89-92)	36 (30-42)	92 (91-93)	0.66	9
	Persistent EW	1799	12.8	6.7 (4.8-9.4)	41 (34-49)	91 (89-92)	34 (28-40)	93 (92-94)	0.66	15
Very high	Random 2	1914	11.6	1.1 (0.7-1.7)	12 (8-17)	89 (87-90)	12 (8-17)	89 (87-90)	0.48	0
	Persistent EFW	1870	2.5	9.5 (5.3-17)	12 (8-17)	99 (98-99)	51 (36-66)	90 (89-91)	0.55	8
Age 10 y										
Medium	Loose API	1291	23.0	5.7 (3.9-8.2)	57 (48-66)	81 (78-83)	25 (20-31)	94 (93-96)	0.69	10
	EW	1396	38.5	4.4 (3-6.4)	70 (62-77)	65 (63-68)	19 (16-23)	95 (93-96)	0.68	5
	Random 1	1396	24.2	1.1 (0.8-1.7)	27 (20-34)	76 (74-78)	12 (8-15)	90 (88-92)	0.51	0
High	Stringent API	1257	9.0	6.7 (4.3-10.5)	32 (24-41)	94 (92-95)	35 (27-45)	92 (91-94)	0.63	11
	EFW	1391	11.9	4.9 (3.3-7.3)	34 (26-42)	91 (89-92)	30 (23-37)	92 (90-94)	0.62	6
	Persistent EW	1326	12.3	5.2 (3.5-7.8)	36 (28-45)	90 (89-92)	29 (23-37)	93 (91-94)	0.63	9
Very high	Random 2	1396	11.4	1.3 (0.8-2.2)	14 (9-21)	89 (87-91)	13 (8-19)	90 (88-91)	0.50	0
	Persistent EFW	1378	2.3	12.0 (5.8-24.6)	12 (7-19)	99 (98-99)	55 (36-73)	91 (89-92)	0.55	7

c, c Statistic; NA, not available; Pos, positive.

*Details described in the Methods section and Table II.

†Discriminative ability is not better than chance if c = 0.5, moderate if c >0.6, good if c >0.8, and perfect if c = 1.

‡Brier scaled measures overall performance; it ranges from 0% for a noninformative model to 100% for a perfect prediction.

TABLE E4. Comparison of the performance of different prediction rules in predicting asthma at school age for early wheezers in the validation cohort (LRC)

Risk of asthma	Prediction rule*	N	Pos rules (%)	OR	Sens (%)	Spec (%)	PPV (%)	NPV (%)	c†	Brier scaled (%)‡
Age 7 y										
Medium	Loose API	695	60.1	2.2	74	43	26	86	0.59	4
	Random 1	772	61.9	1.0	62	38	22	79	0.50	0
High	Stringent API	647	25.3	3.9	49	81	40	86	0.65	10
	EFW	763	32.4	3.4	55	74	36	86	0.64	6
Very high	Persistent EW	657	35.0	3.4	58	71	34	87	0.65	9
	Random 2	772	24.5	1.1	25	76	22	79	0.52	0
	Persistent EFW	732	6.4	4.6	16	96	51	82	0.56	7
Age 10 y										
Medium	Loose API	491	60.5	3.8	82	45	25	92	0.63	7
	Random 1	537	63.3	0.9	62	36	19	80	0.61	0
High	Stringent API	457	24.7	3.5	47	80	35	87	0.47	7
	EFW	532	31.0	2.5	48	73	30	86	0.63	3
Very high	Persistent EW	467	34.9	2.6	53	69	29	86	0.61	3
	Random 2	537	25.3	1.1	26	75	20	81	0.57	0
Very high	Persistent EFW	519	6.0	6.2	18	97	55	84	0.49	7

Sensitivity analysis restricts the population to children with wheeze in the first 3 years of life.

c, c Statistic; Pos, positive; Sens, sensitivity; Spec, specificity.

*Details described in the Methods section and Table II. EW omitted because of prevalence of 100%.

†Discriminative ability is not better than chance if c = 0.5, moderate if c > 0.6, good if c > 0.8, and perfect if c = 1.

‡Brier scaled measures overall performance; it ranges from 0% for a noninformative model to 100% for a perfect prediction.

TABLE E5. Comparison of the performance of different prediction rules in predicting alternatively defined asthma at school age in the validation cohort (LRC)

Risk of asthma*	Prediction rule†	N	Pos rules (%)	OR	Sens (%)	Spec (%)	PPV (%)	NPV (%)	c‡	Brier scaled (%)§
Age 7 y										
Medium	Loose API	1734	24.1	4.4	50	81	35	89	0.66	11
	EW	1913	40.4	4.5	70	66	30	91	0.68	7
	Random 1	1917	24.9	0.9	24	75	17	82	0.49	0
High	Stringent API	1686	9.7	7.3	31	94	51	88	0.63	15
	EFW	1904	13.0	5.6	34	91	46	87	0.63	8
	Persistent EW	1802	12.8	5.5	34	91	44	88	0.63	11
Very high	Random 2	1917	11.3	1.0	11	89	17	83	0.50	0
	Persistent EFW	1873	2.5	9.5	9	99	64	84	0.54	6
Age 10 y										
Medium	Loose API	1298	23.2	4.9	51	82	37	89	0.67	11
	EW	1404	38.6	3.6	64	67	28	90	0.65	6
	Random 1	1404	24.6	0.9	23	75	16	82	0.49	0
High	Stringent API	1264	9.0	6.2	27	94	48	87	0.61	11
	EFW	1399	11.9	4.9	30	92	43	86	0.61	7
	Persistent EW	1334	12.2	4.4	29	91	40	87	0.60	7
Very high	Random 2	1404	11.6	0.7	9	88	13	82	0.49	0
	Persistent EFW	1386	2.2	9.8	9	99	65	84	0.54	5

c, c Statistic; Pos, positive; Sens, sensitivity; Spec, specificity.

*Asthma defined as “a doctor-diagnosis and at least 1 attack in the last 12 months,” or “at least 4 attacks in the last 12 months,” or “the use of antiasthma treatment.” Prevalence 17.3% at 7 years, 17.1% at 10 years.

†Details described in the Methods section and Table II.

‡Discriminative ability is not better than chance if $c = 0.5$, moderate if $c > 0.6$, good if $c > 0.8$, and perfect if $c = 1$.

§Brier scaled measures overall performance; it ranges from 0% for a noninformative model to 100% for a perfect prediction.

TABLE E6. Comparison of the performance of different prediction rules in predicting current wheeze at school age in the validation cohort (LRC)

Risk of wheeze*	Prediction rule†	N	Pos rules (%)	OR	Sens (%)	Spec (%)	PPV (%)	NPV (%)	$c‡$	Brier scaled (%)§
Age 7 y										
Medium	Loose API	1724	24.2	4.0	50	80	30	90	0.65	10
	EW	1903	40.4	4.3	70	65	27	92	0.67	6
High	Random 1	1907	25.1	0.9	24	75	15	84	0.51	0
	Stringent API	1676	9.8	5.8	29	93	42	89	0.61	13
	EFW	1893	13.1	4.9	34	91	39	88	0.62	7
	Persistent EW	1793	12.8	5.8	36	91	40	90	0.64	14
Very high	Random 2	1907	10.6	1.2	12	90	18	85	0.51	0
	Persistent EFW	1863	2.5	6.4	9	99	51	86	0.54	6
Age 10 y										
Medium	Loose API	1289	23.1	4.5	51	81	31	91	0.66	10
	EW	1394	38.6	3.4	64	66	24	91	0.65	5
High	Random 1	1394	25.4	1.0	25	75	14	85	0.50	0
	Stringent API	1256	9.1	5.1	26	94	39	89	0.60	10
	EFW	1389	11.9	3.7	27	91	34	88	0.59	4
	Persistent EW	1324	12.3	4.4	31	91	36	89	0.61	7
Very high	Random 2	1394	10.9	1.0	11	89	15	85	0.50	0
	Persistent EFW	1376	2.2	8.4	9	99	57	86	0.54	5

c , c Statistic; *Pos*, positive; *Sens*, sensitivity; *Spec*, specificity.

*Wheeze defined as at least 1 attack of wheezing in the last 12 months. Prevalence 24.1% at 7 years, 23.2% at 10 years.

†Details described in the Methods section and Table II.

‡Discriminative ability is not better than chance if $c = 0.5$, moderate if $c > 0.6$, good if $c > 0.8$, and perfect if $c = 1$.

§Brier scaled measures overall performance; it ranges from 0% for a noninformative model to 100% for a perfect prediction.