A Pediatric Asthma Risk Score to better predict asthma development in young children

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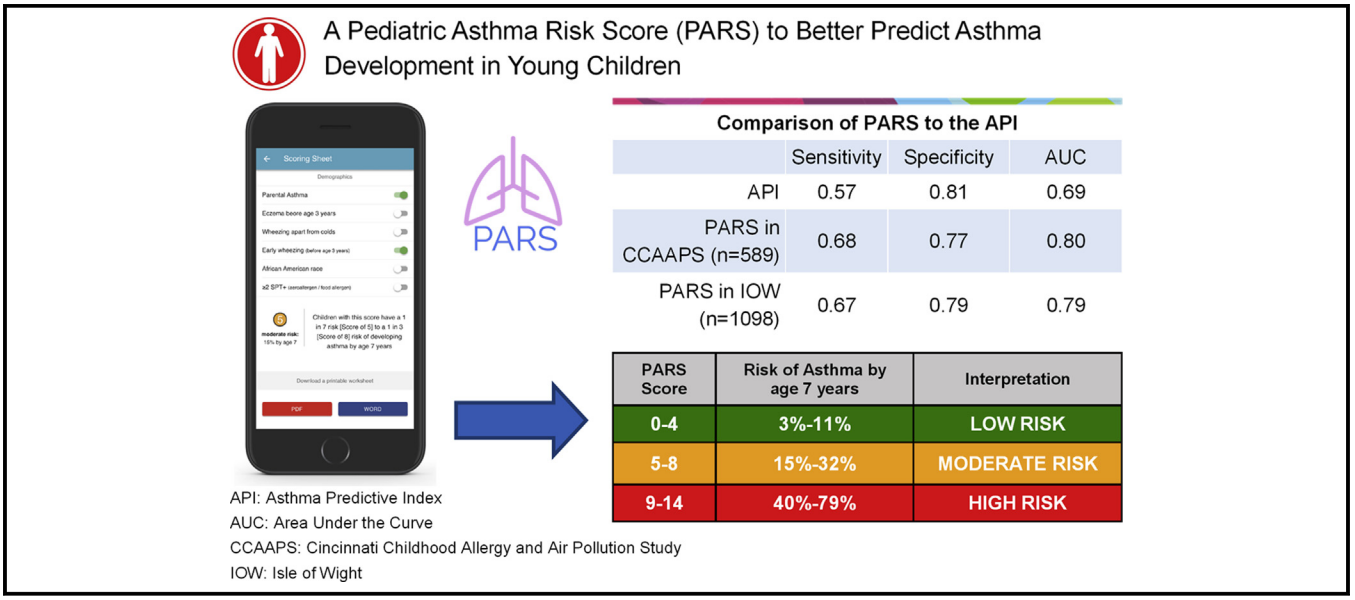
GRAPHICAL ABSTRACT



Background: Asthma phenotypes are currently not amenable to primary prevention or early intervention because their natural history cannot be reliably predicted. Clinicians remain reliant on poorly predictive asthma outcome tools because of a lack of better alternatives.

Objective: We sought to develop a quantitative personalized tool to predict asthma development in young children.

Methods: Data from the Cincinnati Childhood Allergy and Air Pollution Study (n = 762) birth cohort were used to identify factors that predicted asthma development. The Pediatric Asthma Risk Score (PARS) was constructed by integrating demographic and clinical data. The sensitivity and specificity of PARS were compared with those of the Asthma Predictive Index (API) and replicated in the Isle of Wight birth cohort.

Results: PARS reliably predicted asthma development in the Cincinnati Childhood Allergy and Air Pollution Study (sensitivity = 0.68, specificity = 0.77). Although both the PARS and API predicted asthma in high-risk children, the PARS had improved ability to predict asthma in children with mild-to-moderate asthma risk. In addition to parental asthma, eczema, and wheezing apart from colds, variables that predicted asthma in the PARS included early wheezing (odds ratio [OR], 2.88; 95% CI, 1.52-5.37), sensitization to 2 or more food allergens and/or aeroallergens (OR, 2.44; 95% CI, 1.49-4.05), and African American race (OR, 2.04; 95% CI, 1.19-3.47). The PARS was replicated in the Isle of Wight birth cohort (sensitivity = 0.67, specificity = 0.79), demonstrating that it is a robust, valid, and generalizable asthma predictive tool.

Conclusions: The PARS performed better than the API in children with mild-to-moderate asthma. This is significant because these children are the most common and most difficult to predict and might be the most amenable to prevention strategies. (J Allergy Clin Immunol 2018;■■■:■■■-■■■.)

Key words: *Asthma prediction score, persistent wheezing, sensitization, childhood asthma*

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Abbreviations used
API: Asthma Predictive Index
AR: Allergic rhinitis
AUC: Area under the curve
CCAAPS: Cincinnati Childhood Allergy and Air Pollution Study
IOW: Isle of Wight
LR: Likelihood ratio
mAPI: Modified Asthma Predictive Index
NPV: Negative predictive value
OR: Odds ratio
PARS: Pediatric Asthma Risk Score
PPV: Positive predictive value
ROC: Receiver operating characteristics
SPT: Skin prick test

Asthma affects 25.7 million persons in the United States, including 7.0 million children,[1] and its global pharmacotherapeutic costs exceed $5 billion per year.[2] Primary prevention of asthma has been identified as a key public health goal to decrease morbidity, mortality, and the economic burden of disease.

Recently, an Asthma Birth Cohort Workshop, which was jointly sponsored by the National Institute of Allergy and Infectious Disease; the National Heart, Lung, and Blood Institute; and the European Commission Framework Program for Research and Technological Development 7 (Mechanisms of the Development of Allergy), was convened to review the findings from asthma/allergy birth cohorts and identify key knowledge gaps and research priorities. In their summary they conclude that current asthma phenotypes are not amenable to primary prevention or early intervention because "their natural history cannot be reliably predicted."[3] They identified that a key research priority need is to develop better tools that reliably predict the development of asthma in young children and better align natural history with mechanisms.

Several tools have tried to address this need. The most widely used and most validated is the Asthma Predictive Index (API), which was developed by Castro-Rodriguez et al[4] in 2004. The stringent definition of the API has a high specificity (96%) but relatively low sensitivity (28%).[4] As such, although it is useful for predicting which children will not have asthma, it leaves much room for improvement in terms of identifying children who will have asthma.

Our group and others have attempted to improve the API by making the criteria more stringent, adding additional criteria, or developing new predictive indices. These efforts have resulted in a marginal improvement in the ability to forecast which children will have asthma.[5-15] These additional criteria have ranged from sensitization to aeroallergens and food allergens[7,9] to addition of noninvasive measures, such as fraction of exhaled nitric oxide[11-13] and inclusion of environmental exposures.[15] Further improvements will help enable identification of those who would benefit most from preventative interventions before they have the disease. Here we use the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS) birth cohort to develop a new personalized predictive algorithm that integrates clinical and demographic factors and compare this new tool directly to the API. We then replicated our findings in the independent Isle of Wight (IOW) birth cohort.

METHODS

Primary population (CCAAPS)

Subjects were obtained from participants in CCAAPS, a birth cohort of 762 infants born to atopic parents between 2001 and 2003 in Cincinnati, Ohio, and Northern Kentucky.[16] Infants were identified by birth records. Eligible parents had at least 1 allergy symptom and had positive skin prick test (SPT) responses to at least 1 aeroallergen.[16] Children were examined annually at ages 1, 2, 3, 4, and 7 years of age for the development of allergic disease and objectively evaluated for asthma development at age 7 years. At each annual examination, parents reported symptoms, and frequency of wheeze, wheezing apart from colds, and skin and allergy symptoms were recorded. Children objectively assessed for asthma at age 7 years were included in this analysis (n = 589).

Asthma determination in CCAAPS

Asthma was defined at age 7 years in CCAAPS based on reported symptoms and objective measures of lung function.[17] Spirometric tests were performed according to American Thoracic Society–European Respiratory Society guidelines.[18] Each child participant completed at least 4 acceptable maneuvers after the spirometers were verified for volume accuracy. Children were defined as having asthma if the parent reported asthma symptoms (tight or clogged chest or throat in the past 12 months, difficulty breathing or wheezy after exercise, wheezing or whistling in the chest in the previous 12 months, or a previous doctor's diagnosis of asthma) and the child demonstrated either significant airway reversibility (>12% increase in FEV_1) or a positive methacholine challenge test result.[17]

Eczema, allergic rhinitis, and wheeze: Definitions in CCAAPS

During the clinical examination, children were defined as having eczema if the parent or parents reported frequent skin scratching for 6 or more months and 6 or more months of redness/red spots, raised bumps, or rough dry skin in the first 3 years of life.[19] The children were defined as having allergic rhinitis (AR) if the clinician indicated a "probable" or "definitive" diagnosis of AR at the age 1, 2, or 3 years clinical examination based on SPT results and symptoms. Early wheezing was defined as any parental report of wheeze in the first 3 years of life. Early frequent wheezing was defined as 10 or more episodes of wheezing in the past 12 months (top 15th percentile) at the age 1, 2, or 3 years clinical examinations. Wheezing without a cold was defined as present if the parent-reported total number of episodes of wheezing minus the number of wheezing episodes that occurred after a cold was more than 0 at ages 1, 2 and 3 years.

SPTs in CCAAPS

At each examination, CCAAPS children underwent SPTs to 15 aeroallergens (meadow fescue, timothy, white oak, maple mix, American elm, red cedar, short ragweed, *Alternaria* species, *Aspergillus fumigatus*, *Penicillium* species mix, and *Cladosporium* species), cat, dog, German cockroach *(Blattella germanica)*, dust mite mix (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), and 2 foods (cow's milk and hen's egg).[16] A positive SPT response was defined as a wheal of 3 mm or more larger than that that elicited by the saline control after 15 minutes.

Replication cohort (IOW birth cohort)

The replication population consisted of children (n = 1456) born and enrolled between January 1, 1989, and February 28, 1990, in the IOW birth cohort, a United Kingdom whole population birth cohort study.[20,21] Approval for the study was obtained from the local research ethics committee. Children were phenotyped for asthma at ages 1, 2, 4, and 10 years, with asthma diagnosis at age 10 years (n = 1368) based on a minimum criterion of physician-diagnosed asthma plus wheeze in the previous 12 months by using a validated questionnaire.[22] At every follow-up, detailed questionnaires were completed with the parents for each child regarding asthma and allergy

prevalence. SPTs were performed in children at 1, 2, and 4 years of age (n = 1098) to a panel of common inhaled and food allergens (Biodiagnostics, Reinbek, Germany). This included house dust mite *(D pteronyssinus)*, grass pollen mix, cat and dog epithelia, *Alternaria alternata*, *Cladosporium herbarum*, cow's milk, hen's egg, soya, cod, wheat, and peanut plus histamine and physiologic saline solution to act as positive and negative controls, respectively. A mean wheal diameter of 3 mm greater than that elicited by the negative control was regarded as a positive reaction. Eczema was defined as chronic or chronically relapsing itchy dermatitis lasting more than 6 weeks with characteristic morphology and distribution.

Statistical analyses

The prevalence of each potential predictor in asthmatic and nonasthmatic subjects was evaluated, and logistic regression was performed to assess the significance of each predictor on asthma. All the potential predictors were defined by using data collected during the first 3 years of life, and asthma was defined at age 7 years. All potential predictors were included in the logistic regression model at the first step. Backward selection was used to develop the final Pediatric Asthma Risk Score (PARS) model, with a *P* value cutoff at .05 and the odds ratio (OR) for each predictor calculated. A weight was assigned to each predictor by rounding the OR to the nearest whole number. These weights were then used to calculate the PARS for each subject in the CCAAPS cohort. A logistic regression model of asthma on the PARS was conducted to calculate the predicted asthma risk to predict the asthma risk by using the PARS.

The original API published by Castro-Rodriguez[4] has arguably been the gold standard to which predictive indices are compared and has been highly replicated, and many studies use it for patient selection.[23,24] The API had both a loose and a stringent definition, with the loose definition having greater sensitivity.[4] The loose definition was defined by being an "early wheezer" plus 1 major criterion or 2 minor criteria. The stringent definition was defined by being an "early frequent wheezer" and having 1 major criterion or 2 minor criteria.[4] These predictive criteria were then applied to "active asthma" defined at the ages of 6, 8, 11, and 13 years in children participating in the Tucson Children's Respiratory Study.[4]

Because the asthma diagnosis in CCAAPS was performed at age 7 years, we compared our results with those of the API at age 6 years. We applied the loose and stringent API to the CCAAPS cohort, with the exception of eosinophilia as a minor criterion because that measure was not available. In addition, we applied the modified Asthma Predictive Index (mAPI), an index that uses more objective criteria than the API, to the CCAAPS populations, again with the exception of the eosinophilia criterion. We compared our results with the diagnostic utility of the mAPI at age 3 years for asthma diagnosis at age 6 years because this had the greatest sensitivity.[14]

Logistic regression was used to evaluate the area under the curve (AUC) for continuous PARS measures, and the sensitivity, specificity and predictive values were estimated by using a threshold of 6 (the point that maximized sensitivity and specificity). Model discrimination was evaluated by using the area under the receiver operating characteristics (ROC) curve. Model precision was evaluated by using the Hosmer-Lemeshow goodness-of-fit statistic. The AUC was calculated and compared to assess the discriminatory power of the API and PARS. For replication in the IOW birth cohort, weights summed by the predictors for each subject were used to calculate PARS. All analyses were performed in R software.[25]

RESULTS

Demographics and clinical attributes of the CCAAPS cohort

Of the 762 active participants in the CCAAPS cohort, 589 were objectively assessed for asthma development at age 7 years, and the prevalence of asthma at age 7 years was 16% (n = 95, Table I). We evaluated parental asthma, eczema, early wheezing, wheezing apart from colds, early frequent wheezing, AR, race, sex, and SPT status as potential factors in our score because these contribute to asthma risk and are easily assessed during outpatient visits. The children who had asthma at age 7 years were more likely to have a parent or parents with asthma ($P = .0005$), have eczema before age 3 years ($P = .0004$), have wheeze apart from colds, have early wheeze and early frequent wheezing (all $P < .0001$), have a probable or definitive clinician diagnosis of AR in the first 3 years of life ($P = .0016$), be African American ($P = .0004$), and be polysensitized (have ≥2 positive SPT responses to aeroallergens or foods, $P = .0001$) compared with children who did not have asthma at age 7 years (Table I).

TABLE I. Demographic and clinical characteristics during the first 3 years of life in asthmatic and nonasthmatic subjects in CCAAPS

	Nonasthmatic subjects (n = 494)	Asthmatic subjects (n = 95)	*P* value*
Clinical risk factors			
Eczema before age 3 y	24.0% (118)	42.6% (40)	.0004
Wheezing apart from colds	12.0% (59)	45.3% (43)	<.0001
Early wheezing (before age 3 y)	29.4% (145)	68.4% (65)	<.0001
Early frequent wheezing	10.3% (51)	37.9% (36)	<.0001
AR (clinician's diagnosis probable or definite)	35.1% (172)	52.7% (49)	.0016
Positive SPT response to ≥1 aeroallergen	53.5% (264)	71.6% (68)	.0009
Positive SPT response to ≥1 food allergen	16.2% (80)	26.3% (25)	.02
Positive SPT response to aeroallergens/food allergens (≥2 positive SPT response)	38.3% (189)	60.0% (57)	.0001
Personal risk factors			
Parental asthma	37.7% (186)	56.8% (54)	.0005
African American race	19.4% (96)	36.8% (35)	.0004
Male sex	53.6% (265)	61.1% (58)	.18

*The *P* value was obtained by using a logistic regression model.

Application of the original API and mAPI to the CCAAPS cohort

As a reference, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratio, and AUC published by Castro-Rodriguez et al[4] for the API in the Tucson Children's Respiratory Study at age 6 years is shown in Table II. In addition, the sensitivity, specificity, and positive and negative likelihood ratios are included for the mAPI[14] from age 3 year characteristics predicting asthma at age 6 years (Table II).

We applied the criteria for the loose API, stringent API, and mAPI to the CCAAPS cohort. The loose API criteria applied to CCAAPS yielded results identical to the published results (Table II), with a sensitivity and specificity of 0.57 and 0.81, respectively. The PPV was greater in the CCAAPS cohort (0.37 compared with 0.26), whereas the NPV was slightly greater in the original Tucson cohort (0.94 compared with 0.91). AUCs were identical at 0.69 for both the CCAAPS and Tucson cohorts (Table II). By using the stringent criteria, the CCAAPS cohort had slightly greater sensitivity, PPV, and AUC but slightly lower specificity and NPV (Table II). The mAPI applied to the CCAAPS cohort had much greater sensitivity than the original (0.47 compared with 0.17) but lower specificity (0.87 compared with 0.99). Because the

TABLE II. Application of published API and mAPI criteria to the CCAAPS and IOW birth cohorts

	Sensitivity	Specificity	PPV	NPV	LR+	LR−	AUC (95% CI)
Published API of asthma at age 6 y in the Tucson Children's Respiratory Study and mAPI evaluated in the Childhood Origins of Asthma cohort							
Loose API	0.57	0.81	0.26	0.94	2.94	0.54	0.69 (0.64-0.74)
Stringent API	0.28	0.96	0.48	0.92	7.39	0.75	0.62 (0.57–0.66)
mAPI	0.17	0.99	—	—	21.0	0.84	—
Application of published API and mAPI criteria to CCAAPS and IOW birth cohorts							
mAPI (CCAAPS)	0.47	0.87	0.41	0.90	3.54	0.61	0.67 (0.62–0.72)
Stringent API (CCAAPS)	0.34	0.93	0.49	0.88	5.03	0.71	0.64 (0.59–0.68)
Loose API (CCAAPS)	0.57	0.81	0.37	0.91	2.98	0.53	0.69 (0.64–0.74)
Stringent API (IOW birth cohort)	0.29	0.95	0.50	0.89	6.03	0.75	0.62 (0.59–0.65)
Loose API (IOW birth cohort)	0.47	0.86	0.37	0.91	3.47	0.61	0.67 (0.63–0.70)
Comparison of loose API to PARS model in the CCAAPS and IOW birth cohorts							
Loose API	0.57	0.81	0.26	0.94	2.94	0.54	0.69 (0.64–0.74)
PARS in CCAAPS (at cut point of 6*)	0.68	0.77	0.37	0.93	3.02	0.41	0.80 (0.75–0.84)
PARS in IOW birth cohort (at cut point of 6*)	0.67	0.79	0.36	0.93	3.25	0.41	0.79 (0.75–0.83)

LR+, Positive likelihood ratio; *LR*−, negative likelihood ratio.
*Cut points were chosen to maximize sensitivity and specificity (see Fig 2).

loose API yielded superior results in terms of sensitivity and AUC, all comparisons between the PARS and the API are performed with the loose API definition.

Development of the PARS

There were 3 variables in the original univariate screen that evaluated SPT results (Table I). Because all 3 were significant, we opted to include the polysensitization variable (≥2 positive SPT responses to aeroallergens or food allergens) because prior studies have demonstrated that subjects with sensitivity to 2 or more allergens are at a greater risk of asthma[26] and because the number of SPTs was highly significant in our cohort (Table III). The ORs for each factor were then calculated. A weight was assigned to each factor by rounding the OR to the nearest whole number. These weights were then summed to calculate a PARS for each subject in the CCAAPS cohort. Scores range from 0 to 14, with scores of 1 and 13 being unattainable given the weighting of the ORs. A PARS scoring sheet that includes the decision tool and the interpretive data are included in Fig E1 in this article's Online Repository at www.jacionline.org.

Observed and predicted PARSs with asthma risk at age 7 years in the CCAAPS cohort

The gray bars in Fig 1, *A*, display the observed distribution of PARSs in the CCAAPS cohort and asthma prevalence at age 7 years. The predicted values are depicted by the circles connected by the red line. The predicted risk of asthma ranged from 3% for children with a PARS of 0 to 79% for children with a PARS of 14 (Fig 1, *A*). The predicted and observed scores show a high level of precision (see Table E1 in this article's Online Repository at www.jacionline.org), as reflected by a *P* value of .89 for the Hosmer-Lemeshow goodness-of-fit statistic (data not shown). The green portion of each bar reflects the proportion of asthmatic children predicted to have asthma according to the original loose definition of the API for each level of PARS. For PARSs of 7 to 14, there was strong concordance with the API (≥80%, Fig 1 and see Table E1). In contrast, for a PARS of less than 7, there was poor concordance with the API (average of 9%; Fig 1, *A*, and see Table E1). The PARS was superior to the API in predicting asthma in children with lower risk scores.

Comparison of published API scores to the PARS

The AUC from the published loose API was compared with the PARS to compare the discriminatory power of the PARS. Fig 2 depicts ROC curves. The solid gray ROC curve was reported in the original API article by using the loose index at age 6 years in the Tucson study data.[4] The blue dotted ROC curve was obtained by applying the loose API to CCAAPS. The solid blue ROC curve was obtained by applying the PARS model to the CCAAPS birth cohort. The shaded gray area between the gray and blue curves shows the proportion of children missed by the API but detected by using the PARS. The AUC from the original API was 0.69 ± 0.026 (Fig 2, solid gray line),[4] which was identical to the AUC calculated when we applied the published loose API to the CCAAPS data (AUC = 0.69 ± 0.027; Fig 2, blue dotted line). The PARS model was significantly higher (AUC = 0.80 ± 0.025) than both the original loose API model ($P = .003$) and the model applying the loose API with the CCAAPS data ($P = .004$), suggesting that the PARS better discriminates between asthmatic and nonasthmatic subjects compared with the original loose API.

We then compared the sensitivity, specificity, PPV, and NPV of the PARS model with those of the original loose API. We evaluated the sensitivity and specificity of the PARS model at a cut point of 6 (Fig 2, blue triangle). The sensitivity and PPV of the PARS were both increased by 11% at 0.68 and 0.37 (Table II) compared with 0.57 and 0.26 for the loose API (Table II), respectively. The specificity was marginally decreased, and the NPV was almost identical to the loose API (Table II).

Replication of the PARS in the IOW birth cohort

To determine whether the PARS model is robust across different populations and to demonstrate its validity, we applied both the stringent and loose API, as well as the PARS, in a second independent cohort, the IOW birth cohort study. The IOW birth cohort is a general population birth cohort on a different continent, and the children were recruited 10 years before CCAAPS. The gray bars in Fig 1, *B*, display the observed distribution of PARSs in the IOW birth cohort and asthma prevalence at age 10 years. The predicted values are depicted by the circles connected by the red line. The predicted risk of asthma ranged from

TABLE III. Multivariate logistic model of factors predicting asthma in the CCAAPS cohort

Factor	*P* value	Coefficient	OR (95% CI)	Weight
Parental asthma	.009	0.65	1.92 (1.17–3.16)	2
Eczema before age 3 y	.02	0.61	1.97 (1.09–3.06)	2
Wheezing apart from colds	.004	0.97	2.64 (1.39–5.13)	3
Early wheezing (before age 3 y)	.001	1.06	2.88 (1.52–5.37)	3
Positive SPT response to ≥2 aeroallergens and/or food allergens	.0004	0.89	2.44 (1.49–4.05)	2
African American race	.009	0.71	2.04 (1.19–3.47)	2

*Sex and AR were removed by means of backward elimination at a *P* value of greater than .05.

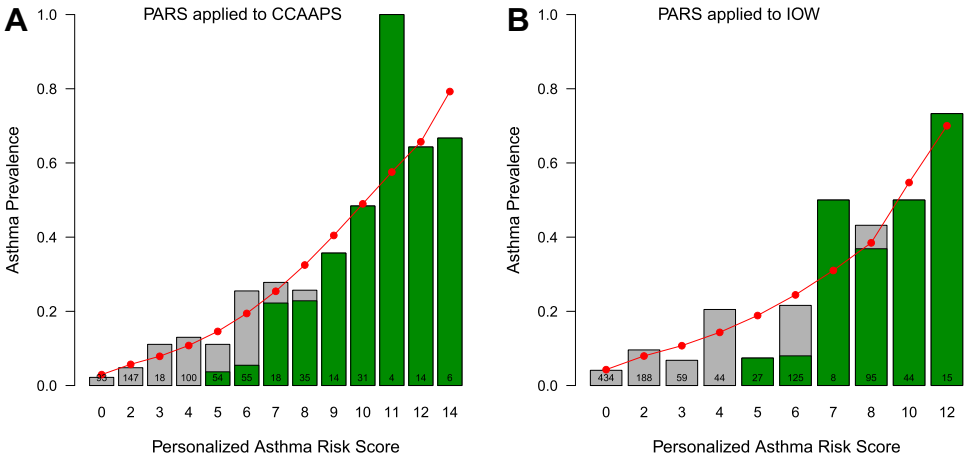

FIG 1. Predicted *(solid circles)* versus observed *(gray bars)* asthma prevalence by asthma prediction score in CCAAPS **(A)** and the IOW birth cohort **(B)**. *Green shading* depicts the proportion of children predicted to have asthma according to the original loose definition of the API of those observed to have asthma.

4% for children with a PARS of 0 to 70% for children with a PARS of 12 (Fig 1, *B*, and see Table E1). The predicted and observed scores show a high level of precision (see Table E1), as reflected by a *P* value of .99 for the Hosmer-Lemeshow goodness-of-fit statistic (data not shown). Similar to what was observed for CCAAPS, PARSs of 7 or greater displayed strong concordance with the API in IOW birth cohort children (≥85%; Fig 1, *B*, and see Table E1). In contrast, for PARSs of less than 7, there was poor concordance with the API (average of 23%; Fig 1, *B*, and see Table E1).

The observed distribution of the PARS in the IOW birth cohort and asthma prevalence at age 10 years performed very similarly to PARS applied to CCAAPS. The dotted red ROC curve was obtained by applying the loose API to the IOW birth cohort (AUC = 0.67 ± 0.019, Fig 2), which was similar to AUCs of the original loose API and the loose API applied to the CCAAPS cohort (both = 0.69, Table II). The solid red ROC curve was obtained by applying the PARS model to the IOW birth cohort (AUC = 0.79 ± 0.020, Fig 2). The PARS model was again superior to the loose API in the IOW birth cohort (AUC = 0.79 vs 0.67, $P < .0001$; Fig 2). The PARS model applied to the IOW birth cohort had a greater sensitivity (0.67) than the original loose API (0.57) and similar sensitivity to the PARS model applied to CCAAPS (0.68, Table II), highlighting the validity and robustness of the PARS model. PPVs were similar in the CCAAPS and IOW birth cohort PARS models but are both greater than the PPV of the loose API model. The models were similar with respect to specificity and NPV.

DISCUSSION

For clinicians and researchers, the ability to accurately predict which children will have asthma is a challenge. Asthma prediction matrices use a combination of major and minor criteria to give a binary yes/no response as to whether a child will have asthma. However, personalized prediction tools are needed that take into consideration the individual combination of risk factors to better estimate the spectrum of asthma risk. Therefore we developed and validated the PARS, a continuous risk score for asthma, which has increased sensitivity over the API and mAPI and captures children with mild-to-moderate risk. The PARS was developed by systematically determining risk factors for asthma in a multivariate model. Beyond API risk factors, we have improved detection by including polysensitization, early wheezing (before age 3 years), and African American race. Notably, the improved prediction was evident in children with mild-to-moderate asthma risk, who are not predicted to have asthma by the API.

The PARS is superior to the API, with an 11% increase in sensitivity. This increase is due to improved prediction in children with mild-to-moderate asthma risk. Specifically, the API identifies children at the highest risk for asthma, as shown by 100% agreement between API scores and PARSs of 9 or greater. However, 43.2% of the asthmatic patients in CCAAPS missed by the API had scores of less than 9, indicating a mild-to-moderate risk of asthma. Children with mild-to-moderate risk have fewer risk factors and might be the most likely to respond favorably to prevention strategies. This is critical because the API and mAPI are used to populate asthma prevention trials. One of

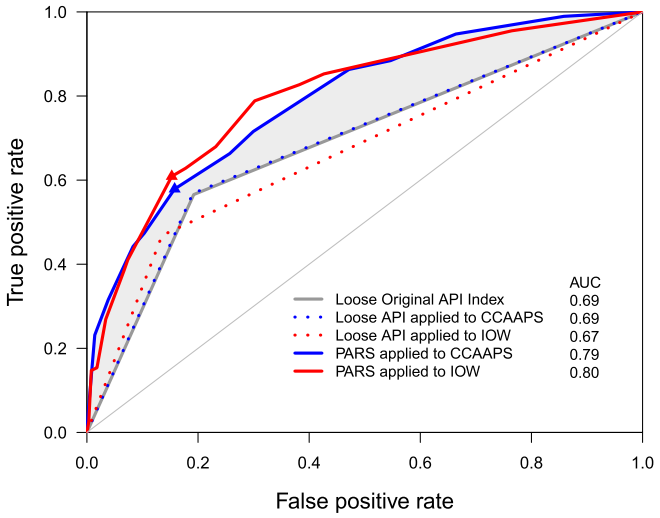

FIG 2. Comparison of ROC curves between the API and PARS. *Dotted lines* indicate the API applied to the 2 cohorts; *solid lines* indicate the PARS applied to the 2 cohorts. *Blue lines* indicate CCAAPS, and *red lines* indicate the IOW birth cohort. Model discrimination was evaluated by using the area under the ROC curve. Model discrimination for the CCAAPS PARS model was excellent (AUC = 0.80, $P < .001$) and significantly greater than that for the API loose index ($P = .002$) and also greater than the model applying the loose API to CCAAPS ($P = .003$). Model discrimination for the IOW birth cohort PARS model was excellent (AUC = 0.80, $P < .001$) and was significantly greater than for the API loose index ($P = .0004$) and also greater than that for the model applying the loose API to the IOW birth cohort ($P < .0001$). *Blue* and *red triangles* are the points at which sensitivity and specificity were assessed for the PARS in CCAAPS (≥7) and the IOW birth cohort (≥6), respectively. The *shaded gray area* between the *green* and *blue lines* shows the proportion of children missed by the API but detected by using the PARS.

these was the Prevention of Early Asthma in Kids trial, which sought to determine whether the natural course of childhood asthma could be altered in children aged 2 to 3 years by treating with inhaled fluticasone propionate for 2 years. Anti-inflammatory therapy, although effective in preventing symptoms, did not change the natural history of asthma outcomes after cessation of therapy. The continuous nature of the PARS would enable clinical trials to be populated with children with varying asthma risk. It is critical to correctly identify children across the spectrum of asthma risk because the efficacy of preventions and interventions might be greater in those with mild-to-moderate asthma risk.

Importantly, we replicated the results of the PARS model in the IOW birth cohort with almost identical sensitivity, specificity, PPV, and NPV, highlighting the robustness of the model in a distinct population. The IOW birth cohort is a population birth cohort in contrast to CCAAPS, which is a high-risk birth cohort such that each participant has at least 1 atopic parent. Furthermore, the IOW birth cohort is on a different continent and separated in time (children were recruited 10 years before CCAAPS) and does not include African Americans. Even with substantial differences between the studies, the PARS was superior to the API and able to reliably predict asthma risk in both CCAAPS and the IOW birth cohort, highlighting the validity and broad applicability of the PARS tool.

Polysensitization (≥2 aeroallergens or food allergens) was most predictive of asthma in terms of the PARS than aeroallergen or food sensitization alone. Polysensitization reflects a greater degree of atopy, and therefore this finding is not unexpected. Indeed, both children and adults are more likely to have asthma with increasing ORs as the number of positive test results increase.[26] Furthermore, in asthmatic patients total IgE levels are greater in subjects who are polysensitized than those who are monosensitized.[27] The API did not include sensitization, and the mAPI defined sensitization to 1 or more aeroallergens as a major criterion and sensitization to food (egg, milk, and peanut) as a minor criterion.[28] We recognize that SPTs might not be routinely performed in general pediatric care. However, even without skin testing information, a pretest risk score can be calculated, and a posttest range can be estimated. Furthermore, the PARS performs superiorly to the API (AUC = 0.67) without the SPT criteria in both CCAAPS and the IOW birth cohort (AUC = 0.78 and 0.72, respectively), further supporting the robustness of the model.

We also included race in the PARS. In CCAAPS race was a risk factor for asthma consistent with prior work finding higher rates of asthma and asthma severity[29-31] and poorer control[32] in African American subjects. The cause of this association is likely multifactorial and can have both a genetic and environmental basis. Flores et al,[30] using genetic analysis of ancestral informative markers in a study of self-reported African American subjects, found African ancestry to be associated with asthma, supporting a role of genetics in the increased risk. However, in Greater Cincinnati, where the CCAAPS cohort was recruited, there are still marked racial disparities. Specifically, African American subjects are more likely to live in poverty[33] and have greater exposures to traffic pollution.[34] These disparities are often seen across the United States as well.[35,36] Thus although race is an important risk factor, it is likely a result of both underlying genetic risk and sociodemographic factors. However, in populations that are much more racially homogenous, such as the IOW birth cohort, the PARS still retains excellent predictive ability.

Although our study compared the PARS and the API, there are substantial advantages of the PARS when compared with other predictive models. In 2015, a systematic review of 30 predictive models for asthma development in children was performed,[37] and our PARS model outperformed (had lower AUC, sensitivity, or PPV) and/or was less invasive (biologic sampling, spirometry, and blood draw) than all of the published models. Therefore the PARS model is the most accurate noninvasive asthma predictive tool to date.

Because a blood count and differential are not part of the routine allergy or asthma workup, the PARS might be more clinically useful and readily applicable in an office setting. To facilitate easy implementation of the PARS in clinical and research settings, we have included a PARS scoring sheet that includes the decision tool, as well as clinical interpretations. Furthermore, a PARS Web application, which provides fast and easy calculation of the PARS, is accessible at https://pars.research.cchmc.org. Through 6 simple yes/no questions, the application calculates the risk score and provides interpretation of the results. The responsive design permits viewing on all device formats/screen sizes. In addition, the groundwork has been laid that allows for easy communication with third-party applications, such as electronic medical records, through RESTful Web services.

The PARS has some opportunities for improvement. First, to ensure maximal generalizability, additional studies should be performed evaluating the PARS in other racial/ethnic groups,

specifically Hispanic or Latino populations, in which rates of asthma are greater than in white or African American subjects.[38] Furthermore, we welcome additional studies including African American subjects given that the CCAAPS population is approximately 20% African American, limiting our ability to perform race-specific analyses.

Second, there is no agreement in the literature regarding when prevention strategies should be instituted, and it is possible that the optimal window might be before age 3 years. In any case the PARS will be useful to identify children for early clinical intervention and potential disease modification strategies.

Third, clinicians are encouraged to collect information about whether the child has been wheezing at each well-child visit to minimize recall bias of parental report of wheeze.

Lastly, environmental factors were not included in the PARS at this time. Although we recognize the importance of the environment in asthma risk,[39] how to uniformly estimate exposures to ensure accuracy and generalizability while minimizing burden and cost is still an ongoing debate.

In conclusion, we have developed a new asthma risk assessment scoring system that can quickly and easily be used in the clinical setting to assess asthma risk in children. The PARS performed better than the original API and mAPI and is better able to distinguish among the mild-to-moderate scoring patients, who represent arguably the most difficult group to predict.

We thank the CCAAPS and IOW birth cohort participating children and their families.

Key messages

- **We have developed the PARS, which relies on factors that are routinely collected in the assessment of a child being evaluated for allergy, asthma, or both.**
- **The PARS had an improved ability to predict asthma development in children with fewer risk factors, who are likely amenable to respond favorably to prevention strategies, and therefore might be a more useful clinical and research tool.**
- **Calculating the PARS does not require blood tests and can be easily implemented in an office setting.**
- **To facilitate easy implementation of the PARS in clinical and research settings, we have included a PARS scoring sheet that includes the decision tool, as well as the clinical interpretations. Furthermore, a PARS Web application, which provides fast and easy calculation of the PARS, is accessible at https://pars.research.cchmc.org.**

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Pediatric Asthma Risk Score (PARS) Scoring Sheet

	Possible Scores		
	No	**Yes**	**Child's Score**
1. Parental Asthma	0	2	
2. Eczema before age 3 years	0	2	
3. Wheezing apart from colds	0	3	
4. Wheezing before age 3 years	0	3	
5. African-American Race	0	2	
6. SPT positive to ≥ 2 aero and/or food allergens	0	2	
Child's PARS (add lines 1-6 above):			

Patient Score Interpretation

Score	Risk of Asthma by age 7 years		Interpretation
0	3%	LOW RISK	Children with these scores have a 1 in 33 [score of 0] to a 1 in 9 [score of 4] risk of developing asthma by age 7 years
2	6%		
3	8%		
4	11%		
5	15%	MODERATE RISK	Children with these scores have a 1 in 7 risk [Score of 5] to a 1 in 3 [Score of 8] risk of developing asthma by age 7 years
6	19%		
7	25%		
8	32%		
9	40%	HIGH RISK	Children with these scores have a 2 in 5 [Score of 9] to a 4 in 5 [Score of 14] risk of developing asthma by age 7 years
10	49%		
11	58%		
12	66%		
14	79%		

FIG E1. PARS scoring sheet.

TABLE E1. Observed and predicted risk of asthma based on the PARS and agreement between the PARS and API

PARS	0	2	3	4	5	6	7	8	9	10	11	12	14
CCAAPS													
Observed asthma in CCAAPS	2%	5%	11%	13%	11%	25%	28%	26%	36%	48%	100%	64%	68%
PARS predicted asthma in CCAAPS	3%	6%	8%	11%	15%	19%	25%	32%	40%	49%	58%	66%	79%
API predicted asthma in CCAAPS, observed asthmatic patients	0%	0%	0%	0%	33%	21%	80%	89%	100%	100%	100%	100%	100%
IOW birth cohort													
Observed asthma in IOW birth cohort	4%	10%	7%	20%	7%	22%	50%	43%	0%	50%	NA	73%	NA
PARS predicted asthma in IOW birth cohort	4%	8%	11%	14%	19%	24%	31%	38%	47%	55%	NA	70%	NA
API predicted asthma in IOW birth cohort, observed asthmatic patients	0%	0%	0%	0%	100%	37%	100%	85%	NA	100%	NA	100%	NA

NA, Not applicable.