**A Personalized Asthma Risk Score (PARS) to Better Predict Asthma Development in Young Children**

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**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 due to a lack of better alternatives.

**Objective:** To develop a personalized tool to predict asthma development in young children.

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

**Results:** PARS reliably predicted asthma development in CCAAPS children (sensitivity: 0.64, specificity: 0.80). While both the PARS and API predicted asthma in high-risk children, PARS had improved ability to predict asthma in children with fewer risk factors when compared to the API. Variables that were informative for the PARS included parental asthma (OR=1.92; 95% CI [1.17 – 3.17]), eczema (OR=1.84 [1.09 – 3.06]), early wheezing (OR=2.87 [1.52 – 5.37]), wheezing apart from colds (OR=2.66 [1.39 – 5.17]), African-American race (OR=2.02 [(1.18 – 3.45]), and ≥2 positive skin prick tests (SPT; OR=2.70 [1.52 – 4.79]). PARS performed similarly in a second independent cohort, the IOW (sensitivity: 0.69, specificity: 0.79) demonstrating its validity and generalizability.

**Conclusions:** The PARS performed better than the API in the children with fewer risk factors. This is significant as these children are the most common, the most difficult to predict, and are likely to be the most amenable to prevention strategies.

**Key Messages:**

* We have developed a Personalized Asthma Risk Score (PARS) that relies on factors that are routinely collected in the assessment of a child being evaluated for possible allergy and/or asthma.
* Calculating PARS does not require blood tests and can be easily implemented in an office setting.
* PARS had an improved ability to predict asthma development in children with fewer risk factors who are most likely to respond to prevention interventions and, therefore, may be a more useful clinical and research tool.
* In order to facilitate easy implementation of PARS in clinical and research settings, we have included a PARS scoring sheet that includes the decision tool, as well as the clinical interpretations. Further, A PARS web application, which provides fast and easy calculation of the PARS, is accessible at: [https://pars.research.cchmc.org](https://pars.research.cchmc.org/).

**Capsule Summary:** PARS relies on clinical and demographic data collected in the office setting. PARS better predicted children at moderate risk for asthma compared to the API, arguably the most common and the most difficult to predict.

**Keywords:** asthma prediction score, persistent wheezing, sensitization, childhood asthma

**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

mAPI Modified Asthma Predictive index

OR Odds Ratio

PARS Personalized Asthma Risk Score

ROC Receiver Operator Characteristics

SPT Skin Prick Test

PPV Positive Predictive Value

NPV Negative Predictive Value

**INTRODUCTION**

Asthma affects 25.7 million people in the US including 7.0 million children1, and its global pharmacotherapeutic costs exceed $5 billion per year2. Primary prevention of asthma has been identified as a key public health goal in order to decrease morbidity, mortality, and economic burden of disease. Recently, an Asthma Birth Cohort Workshop, jointly sponsored by the National Institute of Allergy and Infectious Disease (NIAID), the National Heart, Lung, and Blood Institute (NHLBI), and the European Commission Framework Program for Research and Technological Development 7 (Mechanisms of the Development of Allergy, MeDALL), 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 in 20004. The stringent definition of the API has a high specificity (96%), but relatively low sensitivity (28%)4. As such, while it is useful for predicting which children will *not* develop asthma, it leaves much room for improvement in terms of identifying children who *will*.

 Our group and others have attempted to improve the API by making the criteria more stringent, adding additional criteria, or through the development of new predictive indices. These have resulted in a marginal improvement in the ability to forecast which children will develop asthma 5-15. These additional criteria have ranged from sensitization to aero- and food allergens 7, 9 to the addition of non-invasive measures such as FeNO 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 develop disease. Herein, we utilize 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 an independent birth cohort, the 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 parent(s) between 2001 and 2003 in Cincinnati, Ohio and Northern Kentucky16. Infants were identified by birth records. Eligible parents had at least one allergy symptom and were skin prick test (SPT) positive to at least one aeroallergen16. Children were examined annually at ages 1, 2, 3, 4 and 7 years of age for the development of allergic disease and clinically evaluated for asthma development at age 7 years. At each annual exam, parents reported symptoms and frequency of wheeze, wheezing apart from colds, and skin and allergy symptoms were recorded.

**Asthma Determination in CCAAPS**

Asthma was defined at age 7 years in CCAAPS by reported symptoms and objective measures of lung function17. Spirometry testing was performedaccording to ATS-ERS guidelines18. Each child participant completed at least four acceptable maneuversafter 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 FEV1) or a positive methacholine challenge test result17.

**Eczema, Allergic Rhinitis, and Wheeze Definitions in CCAAPS**

During the clinical exam, the children were defined as having eczema if the parent(s) reported frequent skin scratching for ≥6 months AND ≥6 months of redness/red spots, raised bumps, or rough dry skin in the first three 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 exam 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 episodes of wheezing in the past 12 months (top 15th percentile) at the ages 1, 2 or 3 years clinical exams. Wheezing without a cold was defined as present if the parental reported total number of episodes of wheezing minus the number of wheezing episodes that occurred after a cold was >0 at ages 1, 2 and 3 years.

**Skin Prick Testing in CCAAPS**

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

**Replication Cohort (IOW)**

The replication population consisted of children (n=1,456) born and enrolled between January 1, 1989 and February 28, 1990 in the Isle of Wight (IOW), a UK whole population birth cohort study20, 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 (n=112) based on a minimum criteria of physician-diagnosed asthma plus wheeze in the previous 12 months, using a validated questionnaire22. At every follow-up, detailed questionnaires were completed with the parents for each child regarding asthma and allergy prevalence. Skin-prick testing (SPT) was performed in most children seen at 4 years (n=981) to a panel of common inhaled and food allergens (Biodiagnostics, Reinbek, Germany). This included house dust mite (*Dermatophagoides 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 physiological saline to act as positive and negative controls, respectively. Mean wheal diameter of 3 mm greater than the negative control was regarded as a positive reaction. Eczema was defined as chronic or chronically relapsing, itchy dermatitis lasting >6 weeks with characteristic morphology and distribution.

**Statistical Analyses**

The prevalence of each potential predictor in asthmatics and non-asthmatics was evaluated and logistic regression was performed to assess the significance of each predictor on asthma. All the potential predictors were defined 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 PARS model, with a p value cutoff point at 0.05 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. To predict the asthma risk using PARS, a logistic regression model of asthma on PARS was conducted to calculate the predicted asthma risk.

The original API published by Castro-Rodriguez et al. had both a loose and a stringent definition.4 The loose definition was defined by being an “early wheezer” plus one major criteria or two minor criteria. The stringent definition was defined by being an “early frequent wheezer” and one major or two minor criteria4. These predictive criteria were then applied to “active asthma” defined at ages 6, 8, 11 and 13 years in children participating in the Tucson Children’s Respiratory Study.4 Since the asthma diagnosis in CCAAPS was performed at age 7 years, we compared our results to the API at age 6 years. We applied the loose and stringent API index to the CCAAPS cohort, with the exception of eosinophilia as a minor criterion since that measure was not available. Model discrimination was evaluated by the area under the receiver operator characteristics (ROC) curve. Model precision was evaluated by the Hosmer-Lemeshow goodness-of-fit statistic. Area under the curve (AUC) was calculated and compared to assess discriminatory power of API and PARS. All the analyses were performed in R23.

For replication in IOW, weights multiplied by the predictors for each subject were used to calculate PARS. Logistic regression was used to evaluate AUC for the continuous PARS measures and the sensitivity, specificity and predictive values were estimated using a threshold = 6.

**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 1). 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 since 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(s) with asthma (p=0.0005), have eczema < age 3 years (p=0.0004), wheeze apart from colds, have early wheeze and early frequent wheezing (all p<0.0001), have a probable or definitive clinician diagnosis of AR in the first 3 years of life (p=0.0016), be African-American (p=0.0004) and be polysensitized (have two or more positive SPTs to aeroallergens or foods, p=0.0004) compared to children who did not have asthma at age 7 years (Table I).

**Application of the original API to the CCAAPS Cohort**

As a reference, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and AUC published by Castro-Rodriguez et al. for the API in the Tucson Children's Respiratory Study at age 6 years is shown in Table IIa4. We applied the loose and stringent API criteria to the CCAAPS cohort, with the exception of eosinophilia as a minor criterion since that measure was not available. Nonetheless, our results for the loose index API are identical to the published results (Table IIb), with the sensitivity and specificity at 0.57 and 0.81, respectively. The PPV was markedly higher in the CCAAPS cohort (0.37 compared to 0.26) while the NPV was slightly higher in the original Tucson cohort (0.94 compared to 0.91). The AUC were identical at 0.69 for both the CCAAPS and Tucson cohorts (Table IIa and b). Using the stringent criteria, the CCAAPS cohort had slightly higher sensitivity, PPV and AUC, but slightly lower specificity and NPV (Table IIa and b).

**Development of the PARS**

There were three variables in the original univariate screen that evaluated SPT results (Table I). As all three were significant, we opted to include the 3-level variable for number of SPT as prior studies have demonstrated that individuals with sensitivity to two or more allergens are at a higher risk of asthma24 and because the number of SPT was highly significant in our cohort. Since “early wheezing before age 3 years” and “early frequent wheezing” were collinear, we only included ”early wheezing before age 3 years” as it was present at a much higher frequency in the asthmatics (68.4%) compared to early frequent wheezing (37.9%). These two variables, along with all factors listed in Table I that were independently associated with asthma, were then included in a multivariate logistic model of asthma risk. We performed backward elimination, and AR was eliminated with a p-value of 0.58, likely because of collinearity with other variables (data not shown). All remaining factors had a p-value <0.05 (Table III). The ORs for each factor were 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. The scores range from 0-15. Since SPT positive can result in either a weight of 1 or 3, a score of 14 is unattainable given the weighting of the ORs. A PARS scoring sheet that includes the decision tool, as well as the interpretive data is included in Supplementary Figure I.

**Observed and Predicted PARS with Asthma Risk at age 7 years in the CCAAPS Cohort**

The gray bars in Figure 1A display the observed distribution of the PARS in the CCAAPS cohort and the 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 = 0 to 80% for children with a PARS = 15 (Figure 1A). The predicted and observed scores show a high level of precision (Supplementary Table I), reflected by a p-value = 0.80 for the Hosmer-Lemeshow goodness of fit statistic (data not shown). The green shaded portion of each bar reflects the proportion of children that were predicted to have asthma according to the original loose definition of the API for each level of PARS. For PARS of 8-15, there was strong concordance with the API (≥ 75%, Figure 1, Supplemental Table I). In contrast, for PARS of 5-7, there was poor concordance with the API (13-30%, Figure 1A, Supplemental Table I). The PARS was superior to API in predicting asthma in children with lower risk scores.

**Comparison of Published API to PARS**

In order to compare the discriminatory power of the published API versus PARS, AUC was calculated. Figure 2 depicts the ROC curves. Since the loose API had a higher AUC compared to the stringent API, we used the loose API to compare to PARS. The solid gray ROC curve was reported in the original API paper 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 index to the CCAAPS birth cohort. The solid blue ROC curve was obtained by applying the PARS model to the CCAAPS birth cohort. The shaded gray area between the green and blue lines shows the proportion of children that were missed by the API but detected by PARS. The AUC from the original API was 0.69 ± 0.0264 (Figure 2, solid gray line), which was identical to the AUC calculated when we applied the published loose API to the CCAAPS data (AUC=0.69 ± 0.027, blue dotted line, Figure 2). The PARS model was significantly higher (AUC=0.80 ± 0.025) than both the original loose API model (p=0.002) and the model applying the loose API index to the CCAAPS data (p=0.003), suggesting that the PARS better discriminates between asthma and non-asthma compared to the original loose API.

 We then compared the sensitivity, specificity, PPV and NPV of the PARS model to the original loose API. We evaluated the sensitivity and specificity of the PARS model at a cut point of 7, (Figure 2, blue triangle). Sensitivity and PPV of PARS were superior to the loose API at 0.64 and 0.38 (Table IIc) compared to 0.57 and 0.26 (Table IIa), respectively. The specificity and NPV were almost identical to the loose API (Table IIa and c).

**Replication of PARS in the IOW Cohort**

In order to determine whether the PARS model is robust across different populations and demonstrate its validity, we applied both the loose API index and the PARS in a second independent cohort, the IOW birth cohort study. IOW is a general population birth cohort on a different continent and the children were recruited 10 years prior to CCAAPS. The gray bars in Figure 1B display the observed distribution of the PARS in the IOW 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 4% for children with a PARS of 0 to 74% for children with a PARS of 13 (Figure 1B, Supplemental Table I). The predicted and observed scores show a high level of precision (Supplementary Table I), reflected by a p-value of 0.97 for the Hosmer-Lemeshow goodness of fit statistic (data not shown) for each PARS. Similar to what was observed for CCAAPS, PARS of 8-13 displayed strong concordance with the API in IOW children (≥74%, Figure 1B, Supplemental Table I). In contrast, for PARS of 5-7 there was poor concordance with the API (39-45%, Figure 1B, Supplemental Table I).

The observed distribution of the PARS in the IOW cohort and the asthma prevalence at age 10 years performed very similarly as 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, Figure 2), which was similar to AUCs of the original loose API and the loose API applied to the CCAAPS cohort (both 0.69, Table IIa and b). The solid red ROC curve was obtained by applying the PARS model to the IOW cohort (AUC (0.80 ± 0.020), Figure 2). The PARS model was again superior to the loose API in the IOW cohort (AUC 0.80 versus 0.67, p < 0.0001, Figure 2). The PARS model applied to the IOW cohort had a greater sensitivity (0.69) than the original loose API (0.57) and the PARS model applied to CCAAPS (0.64, Table IIc), highlighting the validity and robustness of the PARS model. The PPVs were similar in the CCAAPS and IOW PARS models, but are both greater than the PPV of the loose API index model. The models were similar with respect to specificity and NPV.

**DISCUSSION**

For clinicians and researchers, the ability to accurately predict which children will develop asthma continues to be a challenge. The various asthma prediction matrices to-date have traditionally used a combination of major and minor criteria to give a binary yes/no as to whether or not a child will develop asthma. However, modifications of the original API are needed that specifically take into consideration the unique asthma risk of an individual child within the context of their specific combination of risk factors in order to better identify children from low to high risk of developing asthma. Therefore, in the development of the PARS, we systematically determined independent risk factors for asthma development and then evaluated them together in a multivariate model. We incorporated parental asthma, wheezing unrelated to colds, and eczema as factors (as in the original4 and modified API [mAPI]9), but have improved detection by including mono- and poly-sensitization as separate factors, early wheezing (before age 3 years), and also being of the African American race as risk factors. Notably, the improved prediction was evident in children with intermediate API risk, whom previously were the most difficult to identify.

The PARS had a higher AUC (0.80 [PARS] compared to 0.69 [API]), sensitivity (0.64 compared to 0.57), and PPV (0.38 compared to 0.26) without sacrificing specificity (0.80 compared to 0.81), or NPV (0.92 compared to 0.94) compared to the loose index of the API. We replicated the results of the PARS model in the IOW cohort with even higher sensitivity 0.67 and similar specificity, PPV and NPV, highlighting the robustness of the model in a distinct population. The IOW is a population birth cohort in contrast to CCAAPS, which is a high-risk birth cohort such that each participant has at least one atopic parent. Further, IOW is on a different continent, separated in time (children were recruited 10 years prior to CCAAPS), and does not include African-Americans (one of the scoring criteria). Further, the asthma diagnosis in the IOW was determined at a different age (10 years), the diagnostic criteria were different, and no data were collected at age 3 years. Despite these differences, PARS was superior to the API and able to reliably predict asthma risk in both CCAAPS and IOW, highlighting the validity and broad applicability of the PARS tool.

In 2015, a systematic review of 30 predictive models for asthma development in children was performed25 and our PARS model either out performs or is more non-invasive each of the models reported. Of the 23 models developed for the general child population, PARS outperformed in AUC, sensitivity or PPV when compared to 16 of the models. The remaining models with higher sensitivity or AUC required invasive biologic sampling, PFT or aren’t generalizable. Of the models developed for the primary care setting, PARS outperformed in AUC, sensitivity or PPV in 5 of 6 models; the sixth requires a blood draw for specific IgE. Therefore, the PARS model is the most accurate, non-invasive asthma predictive tool to date.

Our findings have a tremendous potential impact. PARS is superior to API specifically in children with moderate risk for asthma. These children are arguably the children who would be most amenable to respond favorably to prevention strategies. These children would have been missed by the API. This is a critical finding because the API has been and continues to be used to populate clinical trials aimed at asthma prevention. One of these was the Prevention of Early Asthma in Kids (PEAK) trial, which sought to determine if the natural course of childhood asthma could be altered in children aged 2-3 years by treating with fluticasone propionate for two years. However, during the observation period, there were no differences in episode-free days, number of exacerbations, or lung function between the groups. While the API is an excellent tool for determining which children will not develop asthma, the PPV of 0.26 indicates that only 1.04 of every 4 children that screen positive will develop disease. Thus, only 74 of the 285 children participating in PEAK would ever have gone on to develop asthma, greatly reducing power to detect the treatment effect. The PARS achieved a 46% increase over the API in PPV, where 1.52 of every 4 children with a score of 7 will develop asthma. The continuous nature of the PARS score would enable clinical trials to be populated with a much higher degree of certainty that the subjects would go on to develop asthma. It is important to note that PARS is superior to API in predicting asthma in children with moderate risk without sacrificing the ability to detect children with high risk.

There are significant additional advantages of the PARS when compared to other predictive models. Most importantly, PARS is a continuous, quantitative scoring system that allows for identification of children who have moderate risk of developing asthma but are API negative. These at-risk children are the most challenging to identify but are particularly of importance because they are the most common. It is critical to correctly identify these children in order to develop and implement prevention and early intervention strategies. PARS also does not require a blood sample and can be completed with skin testing alone to determine sensitization. In contrast, to both the API and other predictive indices, the PARS does not rely on a blood eosinophil level as a criteria. Since a blood count and a differential are not routinely part of the routine allergy or asthma workup, the PARS may be more clinically useful and readily applicable in an office setting. In addition, even without all criteria an estimate of risk can be determined. For instance prior to skin testing, a pre-test risk score can be estimated and a post-test risk range given the results of the skin test can be calculated.

The PARS model also included clinical and demographic factors to enhance the ability to predict asthma compared to the API. Polysensitization (≥2 aero or food allergens) was significantly predictive of asthma development in the CCAAPS population. This finding is in contrast to the modified API (mAPI) which defined sensitization to ≥1 aeroallergen as a major criteria and sensitization to food (egg, milk, peanut) as a minor criteria26. While we did evaluate multiple models defining sensitization to aeroallergens, foods and a combination of the two, polysensitization to any two or more allergens was the most predictive of asthma in our cohort. Polysensitization reflects a greater degree of atopy so this finding is not unexpected. Indeed, both children and adults are significantly more likely to have asthma if ≥1 sensitization is detected by SPT, with ORs increasing as the number of positive tests increase24. Further, in asthmatics, symptom scores and total IgE are higher in subjects that are polysensitized than those that are monosensitized27. We did not see a significant association between monosensitization and asthma, but included it with a weight of 1 (rounding the OR of 1.33) since the original variable associated in the univariate screen was the 3-level variable of 0, 1 or ≥2 SPT+. We did evaluate a model where monosensitization was assigned a weight of 0, but the AUC was unchanged at 0.80 (data not shown).

The PARS is the first asthma predictive index to utilize race, specifically African American self-identification, as a predictive factor for the development of asthma. There is an increased burden of disease in African American individuals28. Past studies have found an association with asthma,29-31, increased total serum IgE31, higher rate of hospitalization and death due to asthma28, and decreased pulmonary function32 in African Americans. Both African ancestry and psychosocial and socioeconomic factors are likely involved. Flores et al, utilizing genetic analysis of ancestral informative markers in a case-control study of self-reported African Americans, found African ancestry to be associated with asthma30. In addition, psychosocial factors and social economic status plays a role in the severity of asthma, and level of asthma control33.

 PARS has some important limitations. Because CCAAPS and IOW sampled primarily white and African American children, PARS may not be applicable to all populations, specifically those with a higher proportion of Hispanic or Latino individuals whose asthma risk may be higher than whites or African-Americans34. Since the CCAAPS population is ~20% African-American, we were unable to stratify PARS by race. Therefore, future studies need to be performed to replicate these results and validate the use of the PARS in additional populations. There is no agreement in the literature regarding when prevention strategies should be instituted and it is possible that age three is too late. In any case, PARS will be useful to identify children for early clinical intervention and potential disease modification strategies. Although PARS does not require a blood test, the need for skin prick testing may require a referral to a specialist.

 In conclusion, we have developed a new asthma risk assessment scoring system that can quickly and easily be utilized in the clinical setting to assess asthma risk in children. The PARS performed better than the original API in AUC and sensitivity without sacrificing specificity, and is particularly better able to distinguish among the intermediate scoring patients, which are arguably the most difficult group to predict. In order to facilitate easy implementation of PARS in clinical and research settings, we have included a PARS scoring sheet that includes the decision tool, as well as the clinical interpretations. Further, A PARS web application, which provide fast and easy calculation of the PARS, is accessible at: [https://pars.research.cchmc.org](https://pars.research.cchmc.org/). Through 6 simple yes/no questions, the application calculates the risk score and provides the interpretation of the results. The responsive design permits viewing on all devices formats/screen sizes. In addition, the groundwork has been laid that allows for easy communication with 3rd party applications such as EMRs through [RESTful web services](https://en.wikipedia.org/wiki/Representational_state_transfer).

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| **Table I. Demographic and Clinical Characteristics During the First 3 Years of Life in Asthmatics and Non-Asthmatics in CCAAPS.** |
|  | Non-asthma(N=494) | Asthma(N=95) | p value\* |
| Parental asthma | 37.7% (186) | 56.8% (54) | 0.0005 |
| Eczema before age 3 years | 24.0% (118) | 42.6% (40) | 0.0004 |
| Wheezing apart from colds | 12.0%   (59) | 45.3% (43) | <0.0001 |
| Early wheezing (before age 3 years) | 29.4% (145) | 68.4% (65) | <0.0001 |
| Early frequent wheezing | 10.3%   (51) | 37.9% (36) | <0.0001 |
| AR (clinician diagnosis probable or definite) | 35.1% (172) | 52.7% (49) | 0.0016 |
| African-American | 19.4%   (96) | 36.8% (35) | 0.0004 |
| Male Sex | 53.6% (265) | 61.1% (58) | 0.18 |
| SPT+ to ≥ 1 aeroallergen | 53.5% (264) | 71.6% (68) | 0.0009 |
| SPT+ to ≥ 1 food allergen | 16.2%   (80) | 26.3% (25) | 0.02 |
| Number of SPT+ (aero or food) |  |  |  |
|  0 SPT+ | 42.6% (210) | 25.3% (24) | 0.0004 |
|  1 SPT+ | 19.1%   (94) | 14.7% (14) |
|  ≥2 SPT+ | 38.3% (189) | 60.0% (57) |
| AR= allergic rhinitis, SPT=skin prick test, \*P value was obtained by logistic regression model  |

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| **Table II. Application of Published API Criteria and PARS to the CCAAPS and IOW Birth Cohorts.** |
| 1. Published API of Asthma at Age 6 years in the Tucson Children’s Respiratory Study
 |
|  | Sensitivity | Specificity | PPV | NPV | AUC |
| Loose API Index | 0.57 | 0.81 | 0.26 | 0.94 | 0.69 |
| Stringent API Index | 0.28 | 0.96 | 0.48 | 0.92 | 0.62 |
| 1. Application of Published API Criteria to CCAAPS and IOW Cohorts.
 |
|  | Sensitivity | Specificity | PPV | NPV | AUC |
| Loose API Index (CCAAPS) | 0.57 | 0.81 | 0.37 | 0.91 | 0.69 |
| Stringent API Index (CCAAPS) | 0.34 | 0.93 | 0.49 | 0.88 | 0.64 |
| Loose API Index (IOW) | 0.47 | 0.86 | 0.37 | 0.91 | 0.67 |
| 1. Comparison of Loose API to PARS Model in the CCAAPS and IOW Cohorts
 |
|  | Sensitivity | Specificity | PPV | NPV | AUC |
| Loose API Index | 0.57 | 0.81 | 0.26 | 0.94 | 0.69 |
| PARS in CCAAPS(at cut-point of 7) | 0.64 | 0.80 | 0.38 | 0.92 | 0.80 |
| PARS in IOW(at cut-point of 6) | 0.69 | 0.79 | 0.37 | 0.94 | 0.80 |
| API=Asthma Predictive Index, AUC=area under the curve, CCAAPS=Cincinnati Childhood Allergy and Air Pollution Study, IOW=Isle of Wight Study, PPV=positive predictive value, NPV=negative predictive value, PARS=Personalized Asthma Risk Score |

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| **Table III. Multivariate Logistic Model of Factors Predicting Asthma in the CCAAPS Cohort.**  |
| Factor | p value | Coefficient | Odds Ratio (95% CI) | Weight |
| Parental asthma | 0.0095 | 0.65 | 1.92 (1.17 – 3.17) | 2 |
| Eczema before age 3 years | 0.0204 | 0.61 | 1.84 (1.09 – 3.06) | 2 |
| Wheezing apart from colds | 0.0034 | 0.98 | 2.66 (1.39 – 5.17) | 3 |
| Early wheezing (before age 3 years) | 0.0010 | 1.05 | 2.87 (1.52 – 5.37) | 3 |
| SPT+ to aero and/or food allergens1 SPT+ ≥2 SPT+ | 0.46130.0007 | 0.280.99 | 1.33 (0.62 – 2.82)2.70 (1.52 – 4.79) | 13 |
| African-American Race | 0.0099 | 0.70 | 2.02 (1.18 – 3.45) | 2 |

**Figure Legends**

**Figure 1:** Predicted (closed circle) versus observed (gray bars) asthma prevalence by asthma prediction score in CCAAPS (A) and IOW (B). The green shading depicts the proportion of children that were predicted to have asthma according to the original loose definition of the API of those that were observed to have asthma.

**Figure 2:** Comparison of ROC curves between API and PARS.The dotted lines indicate API applied to the two cohorts; solid lines indicate PARS applied to the two cohorts. Blue lines indicate CCAAPS and red lines indicate IOW. Model discrimination was evaluated by the area under ROC curve. Model discrimination for the CCAAPS PARS model was excellent (AUC=0.80; p<0.001), and was significantly higher than the API loose index (p=0.002), and also was higher than the model applying the loose API to CCAAPS (p=0.003). Model discrimination for the IOW PARS model was excellent (AUC=0.80; p<0.001), and was significantly higher than the API loose index (p=0.0004), and also was higher than the model applying the loose API to IOW (p<0.0001). Blue and red triangles are the points at which sensitivity and specificity were assessed for PARS in CCAAPS (≥7) and IOW (≥6), respectively. The shaded gray area between the green and blue lines shows the proportion of children that were missed by the API but detected by PARS.