

The Simple 10-Item Predicting Asthma Risk in Children Tool to Predict Childhood Asthma—An External Validation



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What is already known about this topic? Several childhood asthma prediction models have been developed, but few have been externally validated.

What does this article add to our knowledge? We found that the simple 10-item Predicting Asthma Risk in Children (PARC) asthma prediction tool performed equally well in a different study population and identified symptomatic preschool children who were likely to have asthma at school age.

How does this study impact current management guidelines? PARC is a simple noninvasive tool for predicting school-age asthma in symptomatic preschool children. It can be used to recruit high-risk children for clinical trials and its use in clinical practice is ready to be tested.

BACKGROUND: External validation of prediction models is important to assess generalizability to other populations than the one used for model development. The Predicting Asthma Risk in Children (PARC) tool, developed in the Leicestershire Respiratory Cohort (LRC), uses information on preschool respiratory symptoms to predict asthma at school age. **OBJECTIVE:** We performed an external validation of PARC using the Avon Longitudinal Study of Parents and Children (ALSPAC). **METHODS:** We defined inclusion criteria, prediction score items at baseline and asthma at follow-up in ALSPAC to match those used in LRC using information from parent-reported

questionnaires. We assessed performance of PARC by calculating sensitivity, specificity, predictive values, likelihood ratios, area under the curve (AUC), Brier score and Nagelkerke's R^2 . Sensitivity analyses varied inclusion criteria, scoring items, and outcomes.

RESULTS: The validation population included 2690 children with preschool respiratory symptoms of whom 373 (14%) had asthma at school age. Discriminative performance of PARC was similar in ALSPAC (AUC = 0.77, Brier score 0.13) as in LRC (0.78, 0.22). The score cutoff of 4 showed the highest sum of sensitivity (69%) and specificity (76%) and positive and negative likelihood ratios of 2.87 and 0.41, respectively. Changes to inclusion criteria, scoring items, or outcome definitions barely altered the prediction performance.

CONCLUSIONS: Performing equally well in the validation cohort as in the development cohort, PARC is a valid tool for predicting asthma in population-based cohorts. Its use in clinical practice is ready to be tested. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:943-53)

Key words: Asthma; Wheeze; Prediction; External validation; PARC; Leicestershire respiratory cohorts; ALSPAC

Up to 40% of all preschool children have recurrent respiratory symptoms such as wheeze or cough but only about a quarter of these will have asthma at school age.¹⁻⁴ Prediction models can be useful to identify those whose problems will persist. The ability to make an accurate prognosis can guide clinical decision making and facilitate the selection of children for high-risk cohorts or clinical trials.⁵ Prediction models must be carefully developed using sound methodology for selecting prediction variables and examine discriminative performance and assess calibration.⁶

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Abbreviations used

ALSPAC- Avon Longitudinal Study of Parents And Children
 API- Asthma Predictive Index
 AUC- Area under the curve
 LR- Likelihood ratio
 LRC- Leicestershire Respiratory Cohort study
 MAS- Multicenter Allergy Study
 PARC- Predicting Asthma Risk in Children
 PIAMA- Prevalence and Incidence of Asthma and Mite Allergy
 ROC- Receiver operator curves

Prediction models may however not perform as well when applied to populations other than the ones they were developed in. External validation (in another population) is therefore necessary to assess the generalizability.^{7,8}

Several models to predict later asthma in preschool children have been developed.⁹ Most use a combination of demographic information, symptoms, and results of clinical tests (eg, lung function or allergic sensitization).¹⁰⁻¹⁷ These models are useful for specialized clinical settings, where spirometry, body plethysmography, and skin prick test can be performed. Two tools use only demographic information and symptoms; information easily obtained from parental questionnaires or when taking patient history in a medical consultation, which makes these models more widely applicable.^{18,19} One of these was developed by our group, the Predicting Asthma Risk in Children (PARC) tool. It was developed using data from the Leicestershire Respiratory Cohorts (LRCs), a population-based cohort study from the United Kingdom.¹⁹ Four childhood asthma prediction models have been externally validated. The Asthma Predictive Index (API)¹⁰ was validated in 5 external cohorts,^{11,15,20-22} the Prevalence and Incidence of Asthma and Mite Allergy (PIAMA) risk score¹⁸ was validated in 2 external cohorts,^{21,23} the Isle of Wight was validated in 1 external cohort,²⁴ and the PARC tool was validated in a German asthma cohort, where it showed good predictive properties.²⁵ However, this was a cohort in which mothers with a history of allergy were overrepresented.

We aimed to validate PARC in a larger population-based cohort in the Avon Longitudinal Study of Parents and Children (ALSPAC). We calculated measures of prediction performance and assessed the robustness of prediction performance to changes in the inclusion criteria, the prediction score items and the outcome.

METHODS

We used the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis guidelines to report this external validation study.²⁶

Predicting Asthma Risk in Children

The PARC tool was developed as a simple, low-cost, and noninvasive method to predict the risk of later asthma in symptomatic preschool children.¹⁹ It uses parental information about respiratory symptoms in 1- to 3-year-old children to predict parental reported asthma 5 years later. The 10 scoring factors are sex, age, wheeze without colds, number of wheezing episodes, shortness of breath due to wheeze, wheeze interfering with daily activities, exercise or allergy as triggers of wheeze, a history of eczema, and parental history of asthma and bronchitis. The published model was

developed using the least absolute shrinkage and selection operator penalized logistic regression to avoid overfitting and simplified into an easy-to-use tool. We validated the tool internally by using the leave-one-out cross-validation method.¹⁹ The sample size was judged to be sufficient based on the one-variable-per-ten-events rule, which suggests that at least 10 outcome events per potential predictor considered are needed, to develop a model that can generalize to other samples.⁸ We considered 38 potential binary predictors (from 24 original variables) and the sample included 345 children with asthma.

Development cohort, LCR

As described previously,¹⁹ the PARC tool was developed using data from the LRC. The LRC is a longitudinal population-based study from Leicestershire, United Kingdom.²⁷ For the development of PARC, we used data from 6808 children born in 1993-1997. Data for inclusion criteria, prediction score items, and outcomes came from questionnaires on respiratory symptoms and general health that parents completed at baseline in 1998 and 1999 when the children were aged 1-3 years and at follow-up in 2003 when the children were aged 6-8 years. The Leicestershire Health Authority Research Ethics Committee approved the Leicestershire Respiratory Cohort study.

External validation cohort, ALSPAC

In the present study, we used data from the ALSPAC cohort to validate the PARC tool. ALSPAC is a longitudinal birth cohort that recruited 14,541 pregnant women from Avon, United Kingdom, with expected delivery between April 1991 and December 1992, resulting in 14,062 live born children. The study has been described in detail previously.²⁸ Mothers and their partners filled in questionnaires about their own and their child's health approximately yearly from when the children were 6 months old. We used baseline information from the questionnaires filled in when the child was 1.5, 2.5, and 3.5 years to define inclusion criteria and calculate the prediction score and information from questionnaires completed at age 6 and 7 years to assess asthma at school age. The ALSPAC study was approved by the ALSPAC Ethics and Law Committee and from Local Research Ethics Committees.

Availability of data and material

The LRC dataset is available on reasonable request by contacting Claudia Kuehni. The ALSPAC dataset is available by proposals through the ALSPAC Executive Committee using the procedures outlined in the ALSPAC Access Policy (www.bristol.ac.uk/alspac/researchers/access/).

Inclusion criteria

We defined inclusion criteria for ALSPAC that resembled the inclusion criteria used in the LRC (Table I). We included children aged 1.5 to 3.5 years from ALSPAC who had had wheeze or cough during the past 12 months (Has your child experienced wheeze/cough during the past 12 months?) and saw a doctor for one of these problems (answer category: yes and saw a doctor) plus had valid information on current wheeze and use of asthma medication at age 7.5 years.

Calculation of prediction scores

Items used for the prediction score are presented in Table II for LRC and ALSPAC. In ALSPAC, the same questionnaires were sent to the parents at 1.5, 2.5, and 3.5 years of age. To achieve a comparable age distribution in ALSPAC as in the LRC, the baseline information was taken from the questionnaire filled at age 1.5 years

TABLE I. Inclusion criteria and outcome definitions in LRC and ALSPAC

LRC: items for inclusion criteria* (at age 1-3 y)	Answer categories	ALSPAC: items for inclusion criteria* (at age 0.5, 1.5, 2.5 y)	Answer categories	Comparability
Has your child had wheezing or whistling in the chest in the last 12 mo?	Yes, no	Has he had any of the following the last 12 mo, wheezing?	Yes and saw a doctor Yes but did not see a doctor No did not have	Good
Does your child usually have a cough without colds?	Yes, no	Has he had any of the following the last 12 mo, cough?	Yes and saw a doctor Yes but did not see a doctor No did not have	Moderate
In the last 12 mo, has your child had a dry cough at night, apart from a cough associated with a cold or a chest infection?	Yes, no	No question	—	—
How often did your child see a GP for coughing or wheezing during the last 12 mo?	Never, once, 2-3 times, 4-6 times, 7 or more times	Has he had any of the following the last 12 mo, wheezing?	Yes and saw a doctor Yes but did not see a doctor No did not have	Good
In the last 12 mo, has wheezing or asthma resulted in your child: (4 categories: referred/admitted to hospital, attending/calling ER or GP)	Yes, no	No question	—	—
LRC: items for outcome definition† (at 8 y)	Answer categories	ALSPAC: items for outcome definition† (at 7.5 y)	Answer categories	Comparability
Has your child had wheezing or whistling in the chest in the last 12 mo?	Yes, no	Has he had any of the following in the past 12 mo, wheezing?	Yes and saw a doctor Yes but did not see a doctor No did not have	Very good
Did your child take any of the following during the last 12 mo? (4 categories: inhalers by content/type)	Yes, no, don't know	Please indicate which of the following have been given to your child the last 12 mo. Asthma medication?	Never Yes for 1-2 episodes only Yes for 3 or more episodes	Very good

ALSPAC, Avon Longitudinal Study of Parents and Children; ER, emergency room; GP, general practitioner; LRC, Leicestershire Respiratory Cohort.

*Inclusion criteria LRC: wheeze or cough (cough without colds or cough at night) with 1 or more visits to the doctor for wheeze or cough during the past 12 mo). Inclusion criteria ALSPAC: wheeze or cough during the past 12 mo and saw a doctor for one of these problems (answer category: yes and saw a doctor).

†Outcome definition LRC: “Yes” to wheeze and use of asthma medication past 12 mo. Outcome definition ALSPAC: “Yes” to wheeze and use of asthma medication past 12 mo.

for 28% of the study population, at age 2.5 years for 57%, and at age 3.5 for 15%. The age at which baseline information was taken for a given child was obtained by random sampling ensuring this overall age distribution. Information on parental history of wheeze, asthma, and bronchitis came from a questionnaire sent to the mother at 12 weeks of gestation and from a questionnaire sent to the partner when the child was 33 months old. The prediction score was calculated as the sum of score points from each item (Table II). We also assigned predicted probabilities for later asthma to these scores as suggested in our report on the development of PARC.¹⁹

Definition of outcome

In the original cohort, we had defined the outcome “asthma” as “current wheeze plus use of asthma inhalers in the past 12 months.” To match this outcome definition in ALSPAC, we defined “asthma” as

“yes” to the parent-reported current wheeze (“Has he/she had wheeze in the past 12 months”) plus current use of asthma medication (“Please indicate which of the following have been given to your child in the last 12 months? Asthma medication”).

Assessing predictive performance

We assessed how well the calculated PARC prediction scores predicted later asthma in children from the ALSPAC cohort using measures of discrimination (the ability of the score to discriminate between children who had asthma at school age and those who had not) and calibration (the ability of the tool to predict the probability of later asthma).⁸ To assess discrimination, we calculated sensitivity, specificity, positive predictive value, negative predictive value, and positive and negative likelihood ratios (LRs) for each possible cutoff value of the score. We also plotted receiver operator curves (ROC)

TABLE II. Questionnaire items used for scoring and their distribution in LRC and ALSPAC

Item no.	Question item in LRC	Score value	(%)	Questionnaire item in ALSPAC	Score value	(%)	Comparability
1	What is the child's sex	Female = 0	(45)	Sex	Female = 0	(47)	Perfect
		Male = 1	(55)		Male = 1	(53)	
2	How old is the child?	1 y = 0	(27)	Age	1 y = 0	(28)	Perfect
		2 y = 1	(57)		2 y = 1	(57)	
		3 y = 1	(15)		3 y = 1	(15)	
3	In the last 12 mo, has the child had wheezing or whistling in the chest even without having a cold or flu?	No = 0	(82)	Because she was 6/18/30* mo old, has she had any periods when there was wheezing with whistling on her chest when she breathed?	No = 0	(71)	Moderate. Question does not include "without cold"
		Yes = 1	(18)		Yes = 1	(29)	
4	How many attacks of wheeze has the child had during the last 12 mo?	0-3 = 0	(77)	Has your baby ever had wheezing with whistling on her chest when she breathed?	0-3 = 0	(82)	Very good
		>3 = 2	(23)	How many separate times has this happened	>3 = 2	(18)	
5	In the last 12 mo, how much did wheezing interfere with your child's daily activities?	Never = 0	(64)	Proxy: "how many days altogether would you say he had wheezed in the past 12 mo?"	0-3 d = 0	(77)	Poor. Different question.
		A little = 1	(26)		4-19 d = 1	(16)	
		A lot = 2	(10)		20 or more days = 2	(7)	
6	Do these wheezing attacks cause him/her to be short of breath?	Never = 0	(65)	Because she was 6/18/30* mo old, has she had any periods when there was wheezing with whistling on her chest when she breathed?	No for all = 0	(84)	Very good
		Sometimes = 2	(29)	Was he breathless (struggling for breath) during any of these times?	Yes for some = 2	(15)	
		Always = 3	(6)		Yes for all = 3	(1)	
7	In the last 12 mo, did exercise (playing, running) or laughing, crying, or excitement cause wheezing or coughing in the child?	No = 0	(61)	Has your baby ever had wheezing with whistling on her chest when she breathed?	No = 0	(99)	Moderate. Optional free text field—few answers
		Yes = 1	(39)	What do you think brings them on? (exercise, emotion)	Yes = 1	(1)	
8	In the last 12 mo, did contact with dust, grass, pets or other animals cause wheezing or coughing in the child?	No = 0	(93)	Has your baby ever had wheezing with whistling on her chest when she breathed?	No = 0	(99)	Moderate. Optional free text field—few answers
		Yes = 1	(7)	What do you think brings them on? (allergy)	Yes = 1	(1)	

9	Has the child ever had eczema?	No = 0	(57)	Has the baby had a rash in the joints and creases of her body (eg, behind the knees, under the arms)?	No = 0	(71)	Good. Asking about rash instead of eczema
		Yes = 1	(43)		Yes = 1	(29)	
10	Has the child's parents ever suffered from wheezing, asthma, or bronchitis?	None = 0	(52)	Have you ever had any of the following problems: asthma/ wheezing past 2 y	None = 0	(65)	Moderate. Information asked from partner instead of father
		Mother = 1	(17)	Have you had wheeze or bronchitis since the child was born (8 mo after birth)	Mother or father = 1		
		Father = 1	(22)		Both = 1	(31)	
		Both = 1	(9)			(4)	

ALSPAC, Avon Longitudinal Study of Parents and Children; LRC, Leicestershire Respiratory Cohort.

*Ages correspond to age 12 mo before questionnaire mailing.

and calculated area under the curve (AUC). To assess calibration, we assigned the probabilities of later asthma to each score value as proposed in the original article by Pescatore et al.¹⁹ On the basis of these predicted probabilities, we first calculated the maximum rescaled Brier score and Nagelkerke's R^2 as overall performance measures.⁸ These measures can be interpreted as "goodness-of-fit measures" showing how well the predicted probability approximates the outcome on a scale between 0 and 1, with 1 indicating perfect prediction and 0 representing a noninformative model, in which a constant probability equaling the prevalence of the outcome is predicted for each child. Details on how to compute these measures are provided in this article's Online Repository at www.jaci-inpractice.org. We examined calibration of the PARC tool graphically by plotting the predicted probability for each value of the score against the observed frequency of asthma among ALSPAC children with that score value, using the function `calibrate.plot` and `val.prob.ci.2` from the "gbm" package in R (R Foundation, Vienna, Austria).²⁹ We excluded children if they had missing information in any of the scoring variables (8%) apart from the item "partner's history of wheeze, asthma, and bronchitis," for which 25% had missing information. For these children, we set missing information about the partner to "no history."

In a separate analysis, we recalibrated the PARC scores in the ALSPAC cohort, by fitting a logistic regression of the outcome on the calculated scores (as a linear term) used in the main analysis above. For each child, we then calculated recalibrated scores as the value of the linear predictor from this regression. We then compared calibration performance of these scores with that of the original scores.

We used STATA 14 for data preparation and descriptive analysis and R version 2.1 to study model performance and model fit.

Sensitivity analyses

To test the robustness of PARC, we performed sensitivity analyses in ALSPAC and LRC datasets using alternative definitions of the included population, prediction score items, and outcome definitions (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). First, we restricted age at baseline by including children aged 1.5, 2.5, and 3.5 years only (only ALSPAC). Secondly, we altered the inclusion criteria to: (1) any wheeze in the past 12 months, and (2) any cough in the past 12 months (only in ALSPAC). Thirdly, we changed items in the prediction score by: (1) excluding "wheeze triggered by exercise or allergy," as triggers of wheeze were measured differently in ALSPAC (open question) compared with LRC (specific response categories), and (2) exchanging "wheeze without colds" with "current wheeze" (only in LRC), (3) setting missing information in the prediction score items to the lowest value instead of excluding children with missing values in the analysis. Fourthly, we used an alternative outcome definition: severe asthma (ALSPAC: current wheeze and use of asthma medication on at least 3 episodes, LRC: wheeze on at least 4 episodes and use of asthma inhalers).

Sample size

There are no guidelines for the adequate sample size needed for external validations of the prediction model, but according to a simulation study by Collins et al,³⁰ ideally 200 events are required. We had more than 300 events (asthma at age 7.5 years) in any of our analyses.

TABLE III. Comparison of study characteristics and demographic factors in development cohort (LRC) and external validation cohort (ALSPAC)

Variable	Development cohort (LRC) N = 1226	Validation cohort (ALSPAC) N = 2690
Location	Leicestershire (United Kingdom)	Bristol (United Kingdom)
Study design	Prospective cohort (from birth)	Prospective cohort (from pregnancy)
Recruitment	General population random sample	General population random sample
Year of birth	1995-1997	1991-1992
Sex		
Male	678 (55)	1433 (54)
Ethnicity		
White	797 (69)	2580 (98)
South Asian	305 (26)	—
Other	57 (5)	52 (2)
Baseline assessment		
Age*		
1 y	336 (27)	763 (28)
2 y	702 (57)	1516 (56)
3 y	188 (15)	411 (15)
Wheeze† prevalence	766 (62)	791 (29)
Cough† prevalence	1085 (89)	2654 (99)
Follow-up assessment		
Age		
6 y	336 (27)	
7 y	702 (57)	2690 (100)
8 y	188 (15)	
Wheeze† prevalence	427 (35)	451 (17)
Use of asthma medication†	345 (28)	586 (22)
Wheeze† + use of asthma medication†	345 (28)	373 (14)

ALSPAC, Avon Longitudinal Study of Parents and Children; LRC, Leicestershire Respiratory Cohort.

This table is displayed using n (%) unless otherwise stated.

*The age distribution at baseline in ALSPAC was matched to the baseline age distribution in LRC.

†In the past 12 months. Prevalence of wheeze and cough is so high, because only children with lower respiratory symptoms were included.

RESULTS

Of the 14,541 children originally recruited in ALSPAC, 7200 children responded to the questionnaires at 1, 2, 3, and 7 years. Of these, 2921 fulfilled the inclusion criteria (saw a doctor for wheeze or cough in the past 12 months) and 2690 were included in our main analysis (231 were excluded because of missing information in 1 or more prediction score items). Not all questions used to specify inclusion criteria in the LRC were available in ALSPAC resulting in less restrictive inclusion criteria (Table I). Table III shows similarities and differences between the 2 studies including location in the United Kingdom and the gender and age distribution. The 2 cohorts differed considerably in ethnicity composition (98% whites in ALSPAC, 81% whites, and 19% south Asians in LRC).

Distribution of the PARC score

For most items of PARC, we were able to use similar questions in ALSPAC as in the LRC (Table II). There were some differences for “wheeze without colds,” questions on triggers for wheeze, and parental history of wheeze and bronchitis. Assigning scores to ALSPAC children resulted in a more left skewed distribution of the PARC score in ALSPAC compared with the LRC (Figure 1). The maximum and median values were lower in the ALSPAC cohort (max = 13, median = 2, interquartile range:

2-4) compared with the LRC cohort (max = 14, median = 4, interquartile range: 2-6).

Frequency of asthma at follow-up

In ALSPAC, 373 (14%) of the included children had the primary outcome at age 7.5 years compared with 345 (28%) in LRC (Table III).

Performance of PARC main analysis

The discriminative ability of PARC was similar in ALSPAC and LRC (Figure 2). ROC curves from ALSPAC and LRC were almost identical, AUC of 0.77 in ALSPAC and 0.78 in LRC. In ALSPAC, the score cutoff maximizing the sum of sensitivity (69%) and specificity (76%) was 4, and in LRC, the best cutoff was 5 (sensitivity 72%, specificity 71%). The validation analysis showed positive and negative predictive values of 0.32 and 0.94 and positive and negative LR of 2.87 and 0.41, respectively, all at the score cutoff 4 (discriminative values for all cutoff points in Figure 2). Overall performance in ALSPAC was comparable with that in LRC. The max-scaled Brier score was 0.13 in ALSPAC and 0.22 in LRC, and Nagelkerke's R^2 was 0.23 in ALSPAC and 0.28 in LRC. The calibration assessment showed that PARC scores from the ALSPAC population were associated with a lower frequency of later asthma than predicted from the LRC (Figures 3 and 4). After recalibrating the predicted probabilities

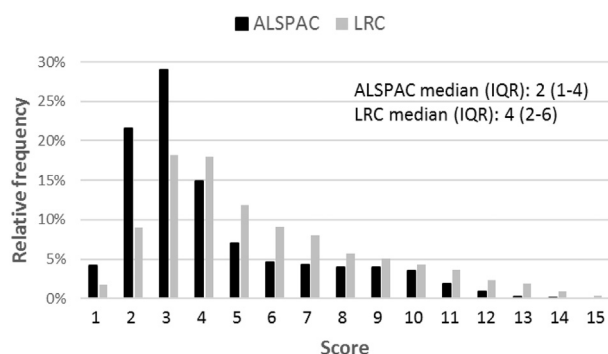


FIGURE 1. *Score based on items described in table 3 for ALSPAC and LRC, respectively. Distribution of the PARC scores* (relative frequency) in the external validation population (ALSPAC, $n = 2690$, black) and original development population (LRC, $n = 1226$, grey). *ALSPAC*, Avon Longitudinal Study of Parents and Children; *IQR*, Interquartile range; *LRC*, Leicestershire Respiratory Cohort; *PARC*, Predicting Asthma Risk in Children.

in ALSPAC (Figure 4, B), our calibration plot showed good calibration of PARC in ALSPAC (Brier score = 0.17 for the recalibrated main model).

Sensitivity analyses

Changes in inclusion criteria, prediction score items, and definition of outcome resulted only in minor changes for most performance measures (Table IV). In sensitivity analyses, PARC performed better in children aged 3.5 years ($AUC = 0.78$, $R^2 = 0.26$), compared with 1.5-year-olds ($AUC = 0.71$, $R^2 = 0.13$). Prediction was slightly worse in a population including only children who wheezed ($AUC = 0.73$, $R^2 = 0.18$) compared with those who also saw a doctor or only children who coughed with or without seeing a doctor ($AUC = 0.76$, $R^2 = 0.20$). The exclusion of trigger variables in ALSPAC barely altered the performance. PARC performed better when the main outcome was severe asthma ($AUC = 0.78$, $R^2 = 0.23$). Sensitivity analysis where results excluding missing information were compared with results where missing information was set to zero showed no difference in the performance of PARC (data not shown).

DISCUSSION

We found that PARC predicted asthma at school age equally well in the validation cohort, ALSPAC ($AUC = 0.77$), compared with the development cohort, LRC ($AUC = 0.78$). Using a cutoff score value of 4, PARC predicted asthma with a sensitivity of 69% and specificity of 76%, which was similar to what was found in LRC for a cutoff score of 5 (sensitivity = 72% and specificity = 71%). The calibration assessment showed that the observed frequency of asthma was generally lower in ALSPAC than predicted by the PARC score, but when we recalibrated the predicted probabilities to the ALSPAC population, agreement between predicted and observed asthma frequency was good.

Limitations and strengths

The information used to define the included population was not the same in ALSPAC as in LRC. Specifically, the ALSPAC cohort had insufficient information on night cough and cough without colds, so we replaced this information with a general

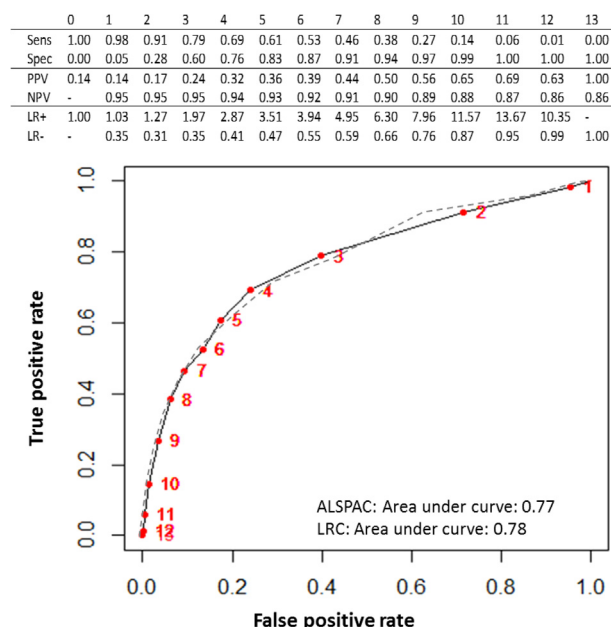


FIGURE 2. Receiver operating characteristic from validation population ALSPAC (solid line) and the original development population LRC (dashed line). Numbers (1-13) indicate asthma prediction score values and their corresponding positions (indicated in red in the figure). The area under the curve corresponds to the primary outcome in both cohorts. The table above the figure shows sensitivity (Sens), specificity (Spec), positive and negative predictive values (PPV, NPV) and likelihood ratios (LR+, LR-) for each score point in ALSPAC. *ALSPAC*, Avon Longitudinal Study of Parents And Children; *LRC*, Leicestershire Respiratory Cohort.

question about cough. These relaxed inclusion criteria have led to the inclusion of less severely affected children than the LRC population, which in turn explains the lower prevalence of asthma at school age (14% in ALSPAC compared with 28% in LRC). This did not affect the discriminative ability of PARC, but it affected calibration and the overall performance measures such as the Brier score. Furthermore, we lacked perfectly matched information on items needed to compute the PARC score. Key information for the score such as wheeze without colds and triggers of wheeze were not available in the same detail. However, our sensitivity analysis in ALSPAC suggested that exclusion of triggers of wheeze did not affect the performance much ($AUC = 0.77$, same as the main analysis).

A strength of our study was that we had full access to all data from the development and the validation cohort, which made it possible to compare the populations and assess discriminative performance and calibration of PARC directly. Secondly, the cohort used for the external validation was large and had collected questionnaire information yearly between birth and the age of 8 years. This enabled us to match and vary the age at which baseline and outcome information was collected. Thirdly, less than 5% of the information in the single variables used for scoring (apart from the partner's history of asthma and wheeze) was missing and we therefore excluded only a small number of the children satisfying the inclusion criteria (8%). Sensitivity analysis, in which missing information was set to zero, did not

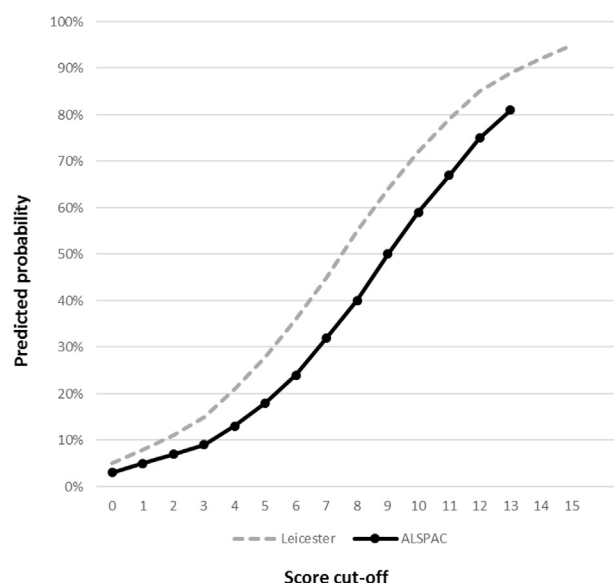


FIGURE 3. Predicted probability of developing asthma at follow-up in LRC (dashed gray line) and probabilities predicted by the recalibrated model in ALSPAC (black line). *ALSPAC*, Avon Longitudinal Study of Parents And Children; *LRC*, Leicestershire Respiratory Cohort.

change our main results. Fourthly, for the primary outcome, we had a perfect matching on current wheeze and use of asthma medication at the age of 7.5 years, and we could therefore rule out that differences in performance of the PARC tool in ALSPAC and LRC cohorts were caused by different outcome definitions.

Comparison with other studies

One other study has investigated the external validity of PARC and found similar performance to the original cohort.²⁵ The study used information from the German Multicenter Allergy Study (MAS-90) birth cohort with an overrepresentation of children from allergic parents. The authors included 140 children in their validation population. The authors found that PARC predicted asthma with AUC = 0.83 and a sensitivity of 0.82 and a specificity of 0.69 at a score of 5. The calibration assessment showed good agreement between predicted probabilities of asthma and observed frequency.

Of the other models developed to predict asthma in children, 3 have been externally validated (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). The API developed using the Tucson Children's Respiratory Study in 2000¹⁰ was externally validated in 5 separate studies,^{11,15,20-22} showing generally higher sensitivity, but lower specificity than in the development cohort, which could partly be explained by differences in inclusion criteria. Caudri et al¹⁸ developed an asthma prediction model using the PIAMA,¹⁸ which was externally validated in a Colombian clinical cohort of children with wheeze²¹ and in the Dutch population-based Generation R study²³ and showed similar performance to the development cohort. The calibration assessment showed that the PIAMA risk score systematically overestimated asthma risk at age 7 years. Kurukulaaratchy et al¹³ developed a prediction model in the Isle of Wight

birth cohort, which was applied in the British MAS birth cohort, where calibration showed different predictive properties from the development cohort. The evidence from these external validation studies and the present study suggests that these prediction models are generally robust in different populations and discriminate asthma from no asthma well in different settings, but calibration must be assessed for the models to accurately predict asthma risk. Among the existing prediction models that have been externally validated, PARC and the PIAMA risk score are the models most easily applied in practice as they require no specific physiological measurements or blood investigations as does, for example, the API (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). In addition, PARC predicts as well or better than other existing asthma prediction tools when comparing the combined sensitivity and specificity using the Youden index³¹ (sensitivity + specificity – 1, calculated based on the maximal sum of sensitivity and specificity), which ranges from 0 to 1, with 1 indicating perfect prediction. The reported values of the Youden index are 0.43 for PARC compared with 0.32 for the API, 0.36 for the PIAMA risk score, and 0.38 for the Isle of Wight score.¹⁹ PARC has a similar positive LR (true positives/false positives) (+LR = 2.5) to the PIAMA risk score (+LR = 2.5) but lower than the API (+LR = 7.8) and the Isle of Wight (+LR = 3.4) (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). These differences could be due to different inclusion criteria used for the study populations in which the prediction scores were developed. The API was developed in a general population sample including mostly healthy children. Such a population has a low baseline risk of asthma at follow-up, whereas the populations used for PARC and the PIAMA score included only children visiting doctors for wheeze or chronic cough who thus had a higher baseline risk of asthma at follow-up. In a population with low baseline risk, it may be easier to correctly identify those who will not develop asthma, which increases specificity and, assuming the same sensitivity, increases the positive LR. Also, the positive LR can be interpreted as the ratio of posterior odds (after a model predicts that a child will have asthma based on baseline information) of having later asthma to the prior odds (ignoring baseline information). A higher positive LR is needed to achieve the same posterior likelihood of asthma if the baseline risk is low compared with when it is high.

Interpretation

PARC predicted asthma better in children who were older at the baseline survey. A reason for this could be that the etiology of wheeze in children aged less than 2 years is more heterogeneous and only a small proportion will eventually have asthma. In a study using data from ALSPAC, Henderson et al³² investigated wheezing phenotypes over time and found a majority of children with the phenotype transient early wheeze begin wheezing in the first 2 years of life. In our data, we saw that more children fulfilled our inclusion criteria early in life (3583 1.5-year-olds compared with 2238 3.5-year-olds), but the proportion of children who had asthma at school age was lower among children aged 1.5 years initially (12%) than in children aged 3.5 years at baseline (19%). This may explain the poorer prediction, particularly poorer calibration, among 1.5-year-olds.

The different phenotypes of wheeze might also explain why the predictive performance of PARC was better for severe asthma. Several studies have identified a phenotype characterized by persistence of symptoms from an early age.^{3,32,33} Children with

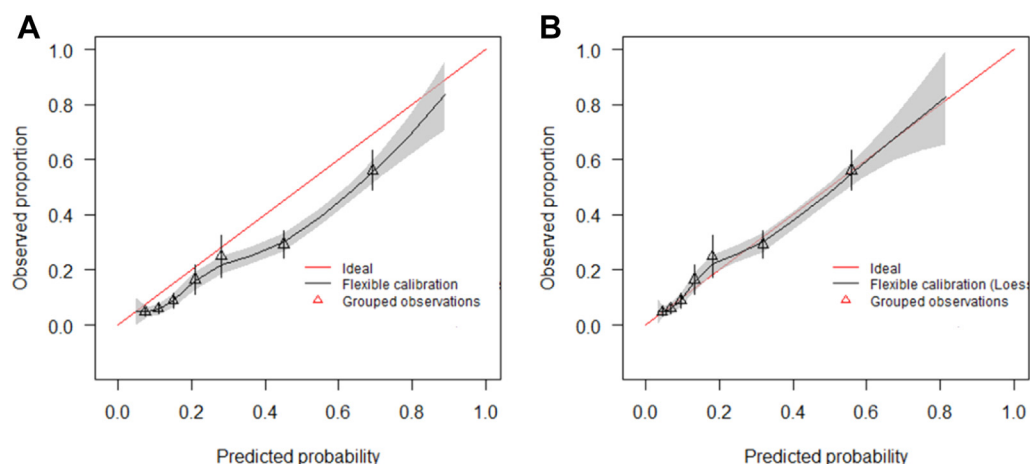


FIGURE 4. Calibration assessment of predicted probabilities versus observed asthma frequencies in 7 equally sized groups. **A,** The calibration assessment for the predicted probabilities calculated in LRC. **B,** The probabilities predicted by the recalibrated model in ALSPAC. The shaded areas represent exact pointwise 95% CI for asthma frequency. The diagonal red line represents perfect calibration. ALSPAC, Avon Longitudinal Study of Parents And Children; CI, confidence interval; LRC, Leicestershire Respiratory Cohort.

TABLE IV. Predictive performance of PARC for main analysis and sensitivity analyses in ALSPAC and LRC (definitions of main and sensitivity analyses in Table E1, available in this article's Online Repository at www.jaci-inpractice.org)

		N	Cases (%)	Sens	Spec	PPV	NPV	LR+	LR–	AUC	R ²	Brier score
<i>ALSPAC</i>												
A1	Main analysis	2690	373 (14)	0.69	0.76	0.32	0.94	2.87	0.41	0.77	0.23	0.13
A2	Altered inclusion criteria											
A2.1	Only children aged 1 y	3583	439 (12)	0.51	0.80	0.26	0.92	2.53	0.61	0.71	0.13	0.06
A2.2	Only children aged 2 y	2817	410 (14)	0.69	0.72	0.29	0.93	2.42	0.44	0.76	0.21	0.07
A2.3	Only children aged 3 y	2238	396 (19)	0.62	0.82	0.43	0.91	3.46	0.46	0.78	0.26	0.21
A2.4	Wheeze past 12 mo	1423	326 (23)	0.81	0.46	0.31	0.89	1.49	0.42	0.73	0.18	0.08
A2.5	Cough past 12 mo	6351	554 (9)	0.52	0.87	0.28	0.95	4.11	0.55	0.76	0.20	0.07
A3	Altered scoring variables											
A3.1	Exclude trigger variables	2690	373 (14)	0.69	0.76	0.32	0.94	2.89	0.41	0.77	0.23	0.13
A4	Altered outcome definition											
A4.1	Severity: wheeze past 12 mo and use of asthma medication at 3 or more episodes	2688	307 (11)	0.70	0.75	0.26	0.95	2.78	0.40	0.78	0.23	0.06
<i>LRC</i>												
L1	Main analysis	1226	345 (28)	0.79	0.57	0.42	0.87	1.83	0.38	0.78	0.28	0.22
L2	Altered inclusion criteria											
L2.1	Wheeze past 12 mo	1033	330 (32)	0.72	0.53	0.42	0.80	1.52	0.53	0.69	0.17	0.14
L3	Altered scoring variables											
L3.1	Exclude trigger variables	1226	345 (28)	0.74	0.63	0.44	0.86	2.04	0.40	0.77	0.28	0.22
L3.2	Exchange wheeze without colds with current wheeze	1226	345 (28)	0.82	0.53	0.40	0.88	1.73	0.34	0.77	0.28	0.21
L4	Altered outcome definition											
L4.1	Severity: wheeze past 12 mo more than 4 episodes and use of asthma medication	1030	86 (8)	0.86	0.61	0.17	0.98	2.19	0.23	0.84	0.32	–0.15*

ALSPAC, Avon Longitudinal Study of Parents and Children; AUC, area under the curve; LR, negative likelihood ratio; LR+, positive likelihood ratio; LRC, Leicestershire Respiratory Cohort; NPV, negative predictive value; PARC, Predicting Asthma Risk in Children; PPV, positive predictive value; R², Nagelkerke's; Sens, sensitivity; Spec, specificity.

Sens, Spec, PPV, NPV, LR+, LR– are all presented for the PARC score = 4.

*The negative scaled Brier score is due to the large difference in the prevalence of the outcome in main analysis and the corresponding sensitivity analysis.

this phenotype tend to have more wheezing episodes, more often use bronchodilators, and cough without colds compared with wheeze phenotypes with late onset transient or viral wheeze. Because severity tends to track,³⁴ PARC identifies those with more severe disease at school age because these children often had already severe symptoms early in life. As disease burden is greater in children with severe asthma, they are the main target group for interventions.

The discriminative ability of PARC appears robust to changes in item and population definitions. Although different questions were used in the 2 cohorts, they probably measure similar concepts. This makes PARC useful also in settings with misclassification of information. Outcome prevalence appears to be the more critical factors affecting predictive performance. Therefore, if PARC is to be used in a population with outcome prevalence very different from that in LRC, we recommend simple recalibration of PARC, which allows obtaining risk probabilities that are closer to the observed frequencies. Practically, one approach for calibration could be to examine the prevalence of school-age asthma in the population in question and compare it with LRC or ALSPAC. If the observed frequencies are similar to those in LRC or ALSPAC, the predicted probabilities calculated in the original study or this validation study can be used. If the prevalence is much higher or much lower, it might be necessary to collect (possibly retrospectively from medical records) information from a subsample of children to fill in the PARC tool and thereby calculate new predicted probabilities.

The ALSPAC cohort did not offer the possibility of validating the PARC tool in different ethnic groups as the ALSPAC included 98% whites. The PARC tool would need to be externally validated in a sample with a larger ethnic diversity to determine the generalizability of PARC in different ethnic settings.

The sample size in the original development of the PARC prediction model was estimated to be sufficient according to the one-variable-per-ten-events rule with 24 potential predictor variables (represented by 38 binary variables) and 345 events.³⁵ However, the appropriateness of this rule has been questioned.³⁶ It is possible that our original study did not have sufficient statistical power to identify some important predictors among the 38 predictors considered, although 10 of these were retained in the final model and are used in the PARC tool. That the PARC tool includes irrelevant predictors as a result of overfitting is less likely as we used penalized logistic regression to build the tool. Furthermore, almost all predictors included in PARC are either recognized risk factors (male sex, parental history) or are indicators of atopy or symptom severity, which are both known to be associated with persistence. The only exception is older age (≥ 1 year), which is a plausible predictor, as wheeze or cough in infancy is more transient and usually associated with respiratory infections.

CONCLUSIONS

This validation study showed that PARC has the same ability to identify preschool children who are likely to develop asthma at 7.5 years in a population different from the development cohort. The discriminative ability of the tool appears to be robust to changes in inclusion criteria, scoring variables, and outcome definitions suggesting that PARC is robust to misclassification of information. Our study suggests that the tool may need recalibration when applied to populations, in which the outcome

prevalence differs greatly from the development cohort. PARC is a valid tool for predicting asthma in preschool children and its use in clinical practice is ready to be tested.

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ONLINE REPOSITORY

Definition of the Scaled Brier Score and Nagelkerke's R^2

In the following, let y_i represent the outcome for child i taking on the value 1 if the child has later asthma and 0 otherwise, and p_i the predicted probability based on the baseline information of that child using the Predicting Asthma Risk in Children (PARC) tool. Let n be the total number of children in the cohort and $\bar{y} = \frac{1}{n} \sum_{i=1}^n y_i$ be the prevalence of the outcome.

Scaled Brier Score

The Brier score evaluates the mean squared error of prediction^{E1}:

$$\text{Brier} = \frac{1}{n} \sum_{i=1}^n (p_i - y_i)^2$$

This score takes on the minimum value of 0 when p_i predicts y_i perfectly. To obtain a similar interpretation for this statistic as for R^2 in linear regression models, we rescale this score as

$$\text{Brier}_{\text{scaled}} = 1 - \frac{\text{Brier}}{\text{Brier}_{\text{max}}}$$

where $\text{Brier}_{\text{max}}$ is the Brier score evaluated with $\bar{y}$ replacing p_i in the formula above. $\text{Brier}_{\text{scaled}}$ takes on values between 0 and 1 with 1 representing perfect

prediction and 0 a noninformative prediction model in which the outcome for each child is predicted with a constant equal to the prevalence $\bar{y}$.

Nagelkerke's R^2

Nagelkerke's R^2 compares the likelihood of the prediction model with that of a noninformative model in which the outcome for each child is predicted with a constant equal to the prevalence $\bar{y}$. It is calculated as follows:^{E1,E2}

$$R_{\text{NK}}^2 = \frac{1 - (L_0/L_1)^{2/n}}{1 - (L_0)^{2/n}}$$

where L_1 and L_0 are the likelihood of PARC and the noninformative models, respectively. The denominator of this equation is simply used for rescaling and represents the maximum value that the numerator can attain (in a perfect model $L_1 = 1$). As $\text{Brier}_{\text{scaled}}$, the statistic R_{NK}^2 thus takes on values between 0 and 1 with 1 representing perfect prediction and 0 the noninformative model. The likelihood function evaluated for the predictions of the PARC tool is given by

$$L_1 = \prod_{i=1}^n p_1^{y_i} (1 - p_i)^{(1-y_i)}$$

L_0 is calculated by replacing p_i with $\bar{y}$ in this formula.

TABLE E1. Overview of the definitions of main analysis and sensitivity analyses in ALSPAC and LRC.

Analysis		Definition changed	Definition
<i>ALSPAC</i>			
A1	Main analysis	—	Inclusion criteria: wheeze or cough in the past 12 mo and saw a doctor for this. Scoring variables: (1) sex, (2) age, (3) wheeze past 12 mo, (4) number of wheeze attacks, (5) number of days wheezed, (6) breathless due to wheeze, (7) exercise as trigger for wheeze, (8) allergy as trigger for wheeze, (9) rash in the joints, and (10) family history of asthma or bronchitis. Outcome definition: wheeze past 12 mo and use of asthma medication
A2	Altered inclusion criteria		
A2.1	Only children aged 1 y	Inclusion criteria	Age excluded as a prediction variable
A2.2	Only children aged 2 y	Inclusion criteria	Age excluded as a prediction variable
A2.3	Only children aged 3 y	Inclusion criteria	Age excluded as a prediction variable
A2.4	Wheeze past 12 mo	Inclusion criteria	Past 12 mo: “Has he/she had periods when there was wheezing with whistling on his/her chest?” or “Has he/she had wheeze?”
A2.5	Cough past 12 mo	Inclusion criteria	Past 12 mo: “Has he/she ever had a time when he has coughed on and off for at least 2 d?” or “Has he/she had cough?”
A3	Altered scoring variables		
A3.1	Exclude trigger variables	Scoring variables	Exclude items 7 and 8: exercise and allergy as triggers for wheeze
A4	Altered outcome definition		
A4.1	Severity: wheeze past 12 mo and use of asthma medication at 3 or more episodes	Outcome	“Has he had wheeze in the past 12 mo?” and “Please indicate which of the following have been given to your child in the past 12 mo” (answer category: asthma medication, on 3 or more episodes)
<i>LRC</i>			
L1	Main analysis	—	Inclusion criteria: wheeze or cough apart from colds in the past 12 mo and saw a doctor for wheeze or cough. Scoring variables: (1) sex, (2) age, (3) wheeze apart from colds, (4) number of wheeze attacks, (5) wheeze interference with daily life, (6) shortness of breath due to wheeze, (7) exercise or emotion as trigger for wheeze, (8) allergy as trigger for wheeze, (9) child ever had eczema, and (10) family history of wheeze, asthma, or bronchitis. Outcome: wheezing or whistling in the chest in the last 12 mo, and use of asthma medication
L2	Altered inclusion criteria		
L2.1	Wheeze past 12 mo	Inclusion criteria	“Has your child has wheezing or whistling in the chest in the last 12 mo?”
L3	Altered scoring variables		
L3.1	Exclude trigger variables	Scoring variables	Exclude items 7 and 8: exercise and allergy as triggers for wheeze
L3.2	Exchange wheeze without colds with current wheeze	Scoring variables	Exchange item 3 “wheeze without colds” with “wheezing or whistling in the chest in the last 12 mo”
L4	Altered outcome		
L4.1	Severity: Wheeze past 12 mo more than 4 episodes and use of asthma medication	Outcome	More than 4 episodes of wheeze past 12 mo and use of asthma medication past 12 mo

ALSPAC, Avon Longitudinal Study of Parents and Children; LRC, Leicestershire Respiratory Cohort.

TABLE E2. Comparison of 4 asthma prediction tools for preschool children

	PARC	API*	Isle of Wight	PIAMA
No. (included in analysis)	1226	776	336	2054
Inclusion criteria				
Age (y)	1-3	2-3	4	1-4
Symptoms	Health care visit because of respiratory problems plus ≥ 1 of the following: wheeze, cough without colds, cough at night	Entire cohort (including a majority of children without symptoms)	Wheeze at ages 1, 2, and 4 y	Wheeze or cough at night without colds in the past 12 mo
Outcome definition				
Age (y)	6-8	8	10	7-8
Prediction interval (y)	5	5	6	3-7
Criteria	Wheeze plus asthma medication (past 12 mo)	Doctor's diagnosis of asthma plus current wheeze or >3 episodes of wheeze (past 3 mo)	Current wheeze	At ages 7 and 8 y: current wheeze or prescription of inhaled corticosteroids or doctor's diagnosis of asthma (past 12 mo)
Outcome prevalence	28%	14%	37%	12%
Predictor variables included in tool	Male sex, age, wheeze without colds, frequent wheeze, activity disturbance, shortness of breath, exercise-related wheeze/cough, aeroallergen-related wheeze/cough, eczema, parental asthma, or bronchitis	Wheeze, frequent wheeze, wheeze without colds, eczema, parental asthma, blood eosinophilia, allergic rhinitis	Family history of asthma, recurrent chest infections (at 2 y), skin prick test positive (at 4 y), nasal symptoms (at 1 y)	Male sex, post term delivery, wheeze/dyspnea without colds, frequent wheeze, eczema, respiratory infections, inhalation medication (parents), parental education
Method used to derive tool	Penalized logistic regression	Combination of predictors was chosen that yielded the highest PPV and specificity	Stepwise backward logistic regression	Stepwise backward logistic regression
Performance measures	Score cutoff ≥ 5	Loose API	Score cutoff ≥ 3	Score cutoff ≥ 20
Youden index	0.43	0.32	0.38	0.36
Sensitivity (%)	72	51	53	60
Specificity (%)	71	81	85	76
PPV (%)	49	29	68	23
NPV (%)	86	91	74	94
LR+	2.48	7.43	3.41	2.50
LR-	0.39	0.75	0.56	0.53

API, Asthma Predictive Index; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NPV, negative predictive value; PARC, Predicting Asthma Risk in Children; PIAMA, Prevalence and Incidence of Asthma and Mite Allergy; PPV, positive predictive value.

PARC,^{E3} API,^{E4} Isle of Wight risk score,^{E5} PIAMA risk score,^{E6} and Youden index reported for cutoff where the sum of sensitivity and specificity was maximal. It is possible that a higher sum of sensitivity and specificity exists at a cutoff point that was not reported in the respective studies.

*To have a prediction interval comparable with the one in our tool, we focused here on the API for prediction at 8 y.

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