

# The simple 10-item PARC tool to predict childhood asthma – an external validation

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## Background

External validation of prediction models is important to assess generalisability 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 and outcomes in ALSPAC to match those used in LRC. We assessed performance of PARC by calculating sensitivity, specificity, predictive values, likelihood ratios, area under the curve (AUC), Brier score and Nagelkerke's R-squared. Sensitivity analyses varied inclusion criteria, scoring items and outcomes.

## Results

The validation population included 2690 children with preschool respiratory symptoms of which 373 (14%) had asthma at school age. Discriminative performance of PARC was equally good in ALSPAC (AUC=0.77, Brier score 0.13) as in LRC (0.78, 0.22). The score cut-off of 4 showed the highest sum of sensitivity (69%) and specificity (76%). Changes to inclusion criteria, scoring items or outcome definitions barely altered the prediction performance.

## Conclusion

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.

**Keywords:**

Asthma, Wheeze, Prediction, External Validation, PARC, Leicestershire Respiratory Cohorts, ALSPAC

## Introduction

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 (1-3). 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 (4). Prediction models must be carefully developed using sound methodology for selecting prediction variables and examine discriminative performance and assess calibration (5). 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 generalisability (6, 7).

Several models to predict later asthma in preschool children have been developed (8). Most use a combination of demographic information, symptoms and results of clinical tests (e.g. lung function or allergic sensitisation) (9-16). These models are useful for specialised clinical settings, where spirometry, body plethysmography and skin prick test can be done. Two other 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 (17, 18). 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, a population-based cohort study from the United Kingdom (18).

Four childhood asthma prediction models have been externally validated. The Asthma Predictive Index (API) (9) was validated in four external cohorts (10, 14, 19, 20), the PIAMA risk score (17) was validated in two external cohorts (20, 21), the Isle of Wight was validated in one external cohort (22) and the PARC tool was validated in a German asthma cohort, where it showed good predictive properties (23).

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 (TRIPOD) guidelines to report this external validation study (24).

### **Predicting Asthma Risk in Children (PARC)**

The PARC tool was developed as a simple, low-cost, and non-invasive method to predict the risk of later asthma in symptomatic preschool children (18). It uses parental information about respiratory symptoms in 1-3 year old children to predict asthma five 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 model was developed using the least absolute shrinkage and selection operator (LASSO) penalised 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 (18).

#### **Development cohort, LCR**

We used the Leicestershire Respiratory Cohort study (LRC) to develop PARC. The LRC is a longitudinal population-based study from Leicestershire, United Kingdom (25). 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 and at follow-up in 2003 when the children were aged 6-8 years. The Leicestershire Health Authority Research Ethics Committee approved the study.

#### **External validation cohort, ALSPAC**

ALSPAC is a longitudinal birth cohort that recruited 14541 pregnant women from Avon, United Kingdom, with expected delivery between April 1991 and December 1992, resulting in 14062 live born children. The study has been described in detail previously (26). 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.

### **Inclusion criteria**

We defined inclusion criteria for ALSPAC that resembled the inclusion criteria used in the LRC (**table 1**). 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 information on asthma at age 7.5 years.

### **Calculation of prediction scores**

Items used for the prediction score are presented in **Table 3** 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. In order 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 year for 28% of the study population, at age 2.5 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 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 3**).

### **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 the ‘asthma’ as ‘yes’ to 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 the predictive performance of PARC 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) (7). To assess discrimination, we calculated sensitivity, specificity, positive predictive value, negative predictive value, and positive and negative likelihood ratios for each possible cut-off value of the score. We also plotted receiver operator curves (ROC) 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. (18). Based on these predicted probabilities, we first calculated maximum rescaled Brier score and Nagelkerke’s  $R^2$  as overall performance measures (7). These measures can be interpreted as “goodness-of-fit measures” showing how well the predicted probability approximates the binary outcome (1 indicating later asthma and 0 no asthma) on a scale between 0 and 1, with 1 indicating perfect prediction. We plotted predicted probabilities calculated in the LRC and recalibrated predicted probabilities calculated in ALSPAC (recalibration was done by taking the fitted values from a generalized linear model with asthma as outcome and calculated score as linear predictor) for each score point. 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 (27). We calibrated the model by fitting a logistic regression of the outcome on the PARC score (as a linear term) in the ALSPAC data. We also examined prediction performance measures and calibration of this recalibrated model. In the main analysis, 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'. 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 (**supplementary table E1**). Firstly, we restricted age at baseline by including children aged 1.5 only, 2.5 only 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 definitions: 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).

## 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 due to missing information in one 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 1**). **Table 2** shows similarities and differences between the two studies including location in the UK and the gender and age distribution. The two cohorts differed considerably in ethnicity composition (98% whites in ALSPAC, 81% whites and 19% south Asians in LRC).

### Distribution of PARC score

For most items of PARC we were able to use similar questions in ALSPAC as in the LRC (**table 3**). 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 2**).

### 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 cut-off maximizing the sum of sensitivity (69%) and specificity (76%) was 4, in LRC the best cut-off was 5 (sensitivity 72%, specificity 71%). Overall performance in ALSPAC was comparable to that in LRC. The max-scaled Brier score was 0.13 in ALSPAC and 0.22 in LRC, the Nagelkerke's R-squared 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 (**figure 3 and figure 4**). After recalibrating the predicted probabilities in ALSPAC (**figure 4B**), our calibration plot showed good calibration of PARC in ALSPAC (Brier score = 0.17 for 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 4**). PARC performed better in children aged 3.5 years (AUC = 0.78, Brier score = 0.21), compared with 1.5 year-olds (AUC = 0.71, Brier score = 0.06). Prediction was slightly worse in a population including only children who wheezed (AUC=0.73, Brier

score = 0.08) compared with those who also saw a doctor or only children who coughed with or without seeing a doctor (AUC = 0.76, Brier score = 0.07). 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 to 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 cut-off 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 cut-off 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 question about cough. These relaxed inclusion criteria has led to 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 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 were collected. Thirdly, less than 5% of the information in the single variables used for scoring (apart from 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 change our main results. Fourthly, for the primary outcome, we had perfectly 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 compared with the original cohort (23). The study used information from the German Multicentre 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, 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, three have been externally validated. The Asthma Predictive Index developed using the Tucson Children's Respiratory Study in 2000 (9) was externally validated in 3 separate studies (14, 19, 20), showing generally higher sensitivity, but lower specificity than in the development cohort, which could partly be explained by differences in inclusion criteria. Caudri et al. developed an asthma prediction model using the Prevalence and Incidence of Asthma and Mite Allergy birth cohort (PIAMA) (17), which was externally validated in a Colombian clinical cohort of children with wheeze (20) and in the Dutch population-based Generation R study (21) and showed similar performance compared with the development cohort. The calibration assessment showed that the PIAMA risk score systematically overestimated asthma risk at age 7 years. Kurukulaaratchy et al. developed a prediction model in the Isle of Wight birth cohort (12), which was applied in the British Multicentre Allergy Study (MAS) birth cohort, where calibration showed different predictive properties compared with 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 API are the models most easily applied in practice as they require no specific physiological measurements or blood investigations.

### **Interpretation**

PARC predicted asthma better in children who were older at the baseline survey. A reason for this could be that the aetiology of wheeze in children age 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 al. (28) investigated wheezing phenotypes over time and found a majority of children with the phenotype *transient early wheeze* begin wheezing in the first two years of life. In our data we saw that more children fulfilled our inclusion criteria early in life (3583 1.5-year-olds compared to 2238 3.5-year-olds), but the proportion of children that 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 characterised by persistence of symptoms from an early age (3, 28, 29). Children with 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 (30), 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 two 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 the 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 to 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.

## **Conclusion**

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 pre-school children and its use in clinical practice is ready to be tested.

**List of abbreviations**

PARC – Predicting Asthma Risk in Children

ALSPAC – Avon Longitudinal Study of Parents And Children

LRC – Leicestershire Respiratory Cohort study

ROC – Receiver Operator Curves

AUC – Area Under the Curve

PIAMA – Prevalence and Incidence of Asthma and Mite Allergy

MAS-90 - Multicentre Allergy Study

**Ethics approval and consent to participate**

The ALSPAC study was approved by the ALSPAC Ethics and Law Committee and from Local Research Ethics Committees. The Leicestershire Health Authority Research Ethics Committee approved the Leicestershire Respiratory Cohort study.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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### **Authors' contributions**

EP, BS, and CK made substantial contributions to the study conception and design and were involved in the drafting of the manuscript. AR contributed to the study management and data preparation. EP, BS and FH were responsible for the statistical analyses. JH and RG were involved in data collection and preparation of ALSPAC. EP, BS, FH, CJ, AR, EG, JH, RG and CK critically revised and approved the manuscript.

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### **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/](http://www.bristol.ac.uk/alspac/researchers/access/))

1. Brooke AM, Lambert PC, Burton PR, Clarke C, Luyt DK, Simpson H. The natural history of respiratory symptoms in preschool children. *American journal of respiratory and critical care medicine*. 1995;152(6 Pt 1):1872-8.
2. Granell R, Henderson AJ, Sterne JA. Associations of wheezing phenotypes with late asthma outcomes in the Avon Longitudinal Study of Parents and Children: A population-based birth cohort. *The Journal of allergy and clinical immunology*. 2016.
3. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *The New England journal of medicine*. 1995;332(3):133-8.
4. Hemingway H, Croft P, Perel P, Hayden JA, Abrams K, Timmis A, et al. Prognosis research strategy (PROGRESS) 1: a framework for researching clinical outcomes. *BMJ (Clinical research ed)*. 2013;346:e5595.
5. Altman DG. Prognostic models: a methodological framework and review of models for breast cancer. *Cancer investigation*. 2009;27(3):235-43.
6. Moons KG, Kengne AP, Grobbee DE, Royston P, Vergouwe Y, Altman DG, et al. Risk prediction models: II. External validation, model updating, and impact assessment. *Heart (British Cardiac Society)*. 2012;98(9):691-8.
7. Steyerberg E. *Clinical prediction models: a practical approach to development, validation, and updating*. . Berlin: Springer-Verlag; 2009.
8. Smit HA, Pinart M, Anto JM, Keil T, Bousquet J, Carlsen KH, et al. Childhood asthma prediction models: a systematic review. *The Lancet Respiratory medicine*. 2015;3(12):973-84.
9. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *American journal of respiratory and critical care medicine*. 2000;162(4 Pt 1):1403-6.
10. Chang TS, Lemanske RF, Jr., Guilbert TW, Gern JE, Coen MH, Evans MD, et al. Evaluation of the modified asthma predictive index in high-risk preschool children. *The journal of allergy and clinical immunology In practice*. 2013;1(2):152-6.
11. Eysink PE, ter Riet G, Aalberse RC, van Aalderen WM, Roos CM, van der Zee JS, et al. Accuracy of specific IgE in the prediction of asthma: development of a scoring formula for general practice. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2005;55(511):125-31.
12. Kurukulaaratchy RJ, Matthews S, Holgate ST, Arshad SH. Predicting persistent disease among children who wheeze during early life. *The European respiratory journal*. 2003;22(5):767-71.
13. Lodrup Carlsen KC, Soderstrom L, Mowinckel P, Haland G, Pettersen M, Munthe Kaas MC, et al. Asthma prediction in school children; the value of combined IgE-antibodies and obstructive airways disease severity score. *Allergy*. 2010;65(9):1134-40.

14. Singer F, Luchsinger I, Inci D, Knauer N, Latzin P, Wildhaber JH, et al. Exhaled nitric oxide in symptomatic children at preschool age predicts later asthma. *Allergy*. 2013;68(4):531-8.
15. van der Mark LB, van Wonderen KE, Mohrs J, van Aalderen WM, ter Riet G, Bindels PJ. Predicting asthma in preschool children at high risk presenting in primary care: development of a clinical asthma prediction score. *Primary care respiratory journal : journal of the General Practice Airways Group*. 2014;23(1):52-9.
16. Vial Dupuy A, Amat F, Pereira B, Labbe A, Just J. A simple tool to identify infants at high risk of mild to severe childhood asthma: the persistent asthma predictive score. *The Journal of asthma : official journal of the Association for the Care of Asthma*. 2011;48(10):1015-21.
17. Caudri D, Wijga A, CM AS, Hoekstra M, Postma DS, Koppelman GH, et al. Predicting the long-term prognosis of children with symptoms suggestive of asthma at preschool age. *The Journal of allergy and clinical immunology*. 2009;124(5):903-10.e1-7.
18. Pescatore AM, Dogaru CM, Duembgen L, Silverman M, Gaillard EA, Spycher BD, et al. A simple asthma prediction tool for preschool children with wheeze or cough. *The Journal of allergy and clinical immunology*. 2014;133(1):111-8.e1-13.
19. Leonardi NA, Spycher BD, Strippoli MP, Frey U, Silverman M, Kuehni CE. Validation of the Asthma Predictive Index and comparison with simpler clinical prediction rules. *The Journal of allergy and clinical immunology*. 2011;127(6):1466-72.e6.
20. Rodriguez-Martinez CE, Sossa-Briceno MP, Castro-Rodriguez JA. Discriminative properties of two predictive indices for asthma diagnosis in a sample of preschoolers with recurrent wheezing. *Pediatric pulmonology*. 2011;46(12):1175-81.
21. Hafkamp-de Groen E, Lingsma HF, Caudri D, Levie D, Wijga A, Koppelman GH, et al. Predicting asthma in preschool children with asthma-like symptoms: validating and updating the PIAMA risk score. *The Journal of allergy and clinical immunology*. 2013;132(6):1303-10.
22. Matricardi PM, Illi S, Keil T, Wagner P, Wahn U, Lau S. Predicting persistence of wheezing: one algorithm does not fit all. *The European respiratory journal*. 2010;35(3):701-3.
23. Grabenhenrich LB, Reich A, Fischer F, Zepp F, Forster J, Schuster A, et al. The novel 10-item asthma prediction tool: external validation in the German MAS birth cohort. *PloS one*. 2014;9(12):e115852.
24. Moons KG, Altman DG, Reitsma JB, Collins GS. New Guideline for the Reporting of Studies Developing, Validating, or Updating a Multivariable Clinical Prediction Model: The TRIPOD Statement. *Advances in anatomic pathology*. 2015;22(5):303-5.
25. Kuehni CE, Brooke AM, Strippoli MP, Spycher BD, Davis A, Silverman M. Cohort profile: the Leicester respiratory cohorts. *International journal of epidemiology*. 2007;36(5):977-85.
26. Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, et al. Cohort Profile: the 'children of the 90s'--the index offspring of the Avon Longitudinal Study of Parents and Children. *International journal of epidemiology*. 2013;42(1):111-27.

27. Van Calster B, Nieboer D, Vergouwe Y, De Cock B, Pencina MJ, Steyerberg EW. A calibration hierarchy for risk models was defined: from utopia to empirical data. *Journal of clinical epidemiology*. 2016;74:167-76.
28. Henderson J, Granell R, Heron J, Sherriff A, Simpson A, Woodcock A, et al. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax*. 2008;63(11):974-80.
29. Spycher BD, Silverman M, Pescatore AM, Beardsmore CS, Kuehni CE. Comparison of phenotypes of childhood wheeze and cough in 2 independent cohorts. *The Journal of allergy and clinical immunology*. 2013;132(5):1058-67.
30. Lee SY, Kim HB, Yu J, Hong SJ. Exercise-induced asthma in children. *Expert review of clinical immunology*. 2009;5(2):193-207.