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External Validation of the Predicting Asthma Risk in Children (PARC) tool in a clinical cohort

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Take home message

This external validation demonstrates that the PARC tool may be useful in ruling out
future asthma development in preschool aged children presenting to paediatric

pulmonology clinics and that new prediction tools should be developed for clinical settings.

Running title: External Validation of PARC in a clinical cohort

Abstract

Introduction

The Predicting Asthma Risk in Children (PARC) tool uses questionnaire-based respiratory symptoms collected from preschool children to predict asthma risk 5 years later. The tool was developed and validated in population cohorts but not validated using a clinical cohort. We aimed to externally validate the PARC tool in a paediatric pulmonology clinic setting.

Methods

The Swiss Paediatric Airway Cohort (SPAC) is a prospective cohort of children seen in paediatric pulmonology clinics across Switzerland. We included children aged 1-6 years with cough or wheeze at baseline who completed the 2-year follow up questionnaire. The outcome was defined as current wheeze plus use of asthma medication. We assessed performance using: sensitivity, specificity, negative and positive predictive value (NPV, PPV), area under the curve (AUC), scaled Brier's score and Nagelkerke's R^2 scores. We compared performance in SPAC to that in the original population, the Leicester Respiratory Cohort (LRC).

Results

Among 346 children included, 125 (36%) reported the outcome after 2 years. At a PARC score of 4: sensitivity was higher (95% vs 79%), specificity lower (14% vs 57%), and NPV and PPV comparable (0.84 vs. 0.87 and 0.37 vs. 0.42) in SPAC versus LRC. AUC (0.71 vs 0.78), R^2 (0.18 vs 0.28) and Brier's scores (0.13 vs 0.22) were lower in SPAC.

Conclusions

The PARC tool shows some clinical utility, particularly for ruling out the development of asthma in young children, but performance limitations highlight the need for new prediction tools to be developed specifically for the clinical setting.

Abbreviations

ALSPAC: Avon Longitudinal Study of Parents and Children

API: Asthma Predictive Index

AUC: Area under the curve

FeNO: Fractional exhaled nitric oxide

IgE: Immunoglobulin E

IoW: Isle of Wight

IQR: inter-quartile range

ISAAC: International Study of Asthma and Allergies in Childhood

LASSO: least absolute shrinkage and selection operator

LR: Likelihood Ratio

LRC: Leicester Respiratory Cohort

MAS: Multi-centre Allergy Study

PAPS: Persistent Asthma Predicting Score

PARC: Predicting Asthma Risk in Children

PIAMA: Prevalence and Incidence of Asthma and Mite Allergy

ROC: Receiver operator curves

SPAC: Swiss Paediatric Airway Cohort

Introduction

Symptoms such as cough and wheeze in preschool aged children can be an early sign of asthma and cause a high burden of morbidity and health-care utilisation.¹⁻⁴ Asthma also remains an important cause of morbidity later in childhood.^{5,6} To reduce childhood asthma morbidity and overtreatment, it is important for clinicians to identify children with asthma early. For this, they require tools that help distinguish preschool children who are at risk of developing asthma from those who cough or wheeze for other reasons and will possibly outgrow their symptoms.

Several asthma prediction tools have been developed to help identify preschool children at risk of developing asthma. These prediction tools vary in their target

population, geography, predictors used and applicable settings. Most use validated questions on respiratory symptoms and some include invasively measured traits such as atopy, fractional exhaled nitric oxide (FeNO), lung function and genetic markers⁷⁻¹⁵.

The PARC tool has the advantage that it predicts asthma risk in preschool children by using questions asked in routine clinical care and avoids the use of invasive measures that may not be available in primary care or resource-poor settings. The tool was developed by Pescatore et. al. using data of preschool children from the population-based Leicester Respiratory Cohort (LRC) who had seen their doctor at age 1-3 years with symptoms of cough or wheeze, and aimed to predict whether they would have asthma 5 years later (Supplementary table 1).¹⁶ The outcome of asthma was defined as wheeze and asthma medication use in the preceding 12 months. In internal validation in the LRC, the PARC tool demonstrated good discriminatory performance (area under the curve AUC of 0.78).¹⁶ In external validation in community-based settings, the PARC tool demonstrated a good discriminatory performance in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort (area under the curve AUC 0.77)¹⁷ and very good discriminatory performance in the Multi-centre Allergy Study (MAS) cohort (AUC 0.83)¹⁸. The PARC tool has yet to be externally validated in clinical settings where preschool children are seen for wheeze or cough. We therefore aimed to perform an external validation of the PARC tool in a prospective cohort of children with respiratory symptoms presenting to paediatric pulmonology outpatient clinics and assess its performance in predicting asthma 2 years later.

Methods

We used the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines to report this external validation study.^{19,20}

The External Validation Cohort: Swiss Paediatric Airway Cohort (SPAC)

This external validation was performed using data from SPAC, a multi-centre prospective cohort embedded in routine paediatric pulmonology care across Switzerland. SPAC includes children referred for respiratory symptoms such as wheeze, cough and dyspnoea.²¹ As of 28th February 2022, SPAC includes 3547 children aged 0-16 years of whom 1079 have already completed 2 years of follow up (Figure 1). The SPAC study was approved by the Bern Cantonal Ethics Committee (Kantonale Ethikkommission Bern 2016-02176).

The PARC Tool

The PARC tool includes 10-items in its prediction score. These include: age, sex, occurrence of wheeze episodes not associated with a cold, number of episodes of wheeze, impact of wheezing on daily activities, dyspnoea, wheeze or cough triggered by exercise, laughing, crying or excitement, wheeze or cough triggered by dust, grass, pets or other animals, history of eczema in the child and history of asthma, bronchitis or wheeze in the parents. Each item is assigned a score with the overall sum ranging from 0 to 15.

Inclusion Criteria

Inclusion criteria for this external validation were selected to resemble original LRC inclusion criteria as closely as possible (Supplementary table 1). In order to achieve a larger sample size the inclusion age range was expanded from 1-3 to 1-6 years.

Children were included if at the baseline visit they responded “yes” to the question: “In the past 12 months, has your child ever had a dry cough at night, apart from a cough associated with a cold or chest infection?” or “Has your child had wheezing or whistling in the chest in the past 12 months?” and if they had responded to the 2-year follow up questionnaire.

Outcome Criteria

Outcome criteria were selected to resemble original LRC outcome criteria (Supplementary table 1). Time to the development of the outcome was shortened from 5 years to 2 years due to current study limitations, as we do not yet have 5 years of follow-up. We defined the outcome as children who responded “yes” to the question: “Has your child reported wheeze in the past 12 months” at the 2-year follow up questionnaire and who also reported having used an asthma medication in the previous 12-months.

Sample Size

As a rule of thumb, a sample used for external validation should include at least 100 outcome events and 100 non-outcome events.²³ This external validation is based on 125 events and 221 non-events.

Missing Data

The data used to assess PARC score predictors was complete for the majority of predictors. For the remainder, the proportion of missing values was <2% for 3 predictors, 9% for 2 predictors, and 29% for 1 predictor. The predictor with the most missing values was derived from the question: “In the last 12 months, which of the following have caused the child to cough or wheeze: dust, grass or animals?” We decided to recode these missing values to “no”, assuming that if the parents had not decisively answered with “yes” the symptom was absent, borderline or mild.

Statistical Analysis

We assessed predictive performance of the PARC tool in SPAC using measures of discrimination and calibration. We assessed overall performance in terms of “goodness-of-fit” using maximum-scaled Brier’s score and Nagelkerke’s R^2 scores. For these scores 1 indicates perfect prediction and 0 non-informative prediction. The Brier Score evaluates mean square error of prediction while Nagelkerke’s R^2 compares likelihoods between the prediction and a non-informative models. We assessed discrimination using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratios (LR+, LR-) and AUC. We used an AUC definition of good if > 0.7, very good if > 0.8 and excellent if >0.9.²⁴ We assessed calibration by assigning original probabilities derived from the developmental model by Pescatore et. al. of the outcome of asthma to each PARC score. We then recalibrated PARC scores in SPAC by fitting a logistic regression of the outcome on the calculated scores as a linear term and calculating predicted probabilities for each score from the fitted model. We then compared

calibration performance of the recalibrated SPAC scores with the original scores. 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 children in SPAC with that score value, using the function `calibrate.plot` and `val.prob.ci.2` from the `gbm` package in R (R Foundation, Vienna, Austria). We used STATA 17 for data preparation, descriptive analysis and logistic regression and RStudio 2021.09.0 to assess model performance.

Sensitivity Analysis

To further examine the performance of the PARC tool in SPAC we undertook sensitivity analyses using alternative definitions for inclusion and outcome criteria. First, we modified inclusion criteria by age group. For outcome sensitivity analysis we modified the timing of the outcome to 1-year and 3-year follow-up so that we could assess the role of different follow up time frames on the performance of the model. As in the development cohort, LRC, and another external validation cohort, ALSPAC, we also did a sensitivity analysis assessing performance for a more severe definition of asthma.

Results

In the SPAC study, 346 of 1079 children (32%) satisfied the inclusion criteria (response yes to wheeze or cough in the past 12 months at baseline), were aged 1-6 years and completed the 2-year follow up (Supplementary figure 1). 125 (36% of the 346 children) had the defined outcome. In contrast, in LRC 1226 of 8700 children (14%) satisfied inclusion criteria and 345 (28%) had the outcome. Notable differences between the cohorts include: geographical area, study years (2017-2020 versus 1998-

1999) and study setting (clinical cohort versus population-based cohort)

(Supplementary table 1). Follow up time was 2 years in SPAC and 5 years in LRC.²²

The median PARC score was higher in SPAC (median 8, inter-quartile range (IQR) 5 – 8) than in LRC (median 4, IQR 2-6) (Figure 1). At a PARC score of 4, sensitivity was higher (95% versus 79%) and specificity lower (14% versus 57%) in SPAC compared to LRC. The positive and negative predictive values were comparable (37% versus 42%) and (84% versus 87%) in SPAC and LRC respectively. The positive and negative likelihood ratios were also comparable (1.1 versus 1.83 and 0.38 versus 0.38) in SPAC and LRC respectively (Table 3). The PARC tool's ability to discriminate between those children with and without the outcome was modest in SPAC (AUC 0.71) and lower than in LRC (AUC 0.78) (Figure 3). The tool also showed poorer overall performance in SPAC than LRC with scaled Brier's score 0.13 versus 0.22 and Nagelkerke's R^2 0.18 versus 0.28 (Table 2).

Sensitivity analysis with changes to inclusion and outcome criteria in SPAC resulted in modest adjustments to performance indicators (Table 2). Altering inclusion criteria to 1-3 year-olds only as per LRC inclusion criteria resulted in AUC of 0.71. Altering the outcome criteria to a higher severity defined as > 4 episodes of wheeze in the past 12 months plus asthma medication use improved the AUC to 0.74. This same sensitivity analysis resulted in an AUC of 0.84 when performed in the LRC.¹⁷ Altering outcome criteria to follow up 1 year or 3 years later increased the AUC marginally to 0.72.

Assessment of performance at a PARC score of 7 showed higher sensitivity (79% versus 46%), lower specificity (51% versus 91%), comparable PPV and NPV (45%

versus 44% and 83% versus 91%), lower positive likelihood ratio (1.6 versus 4.95) and comparable negative likelihood ratio (0.42 versus 0.59) in SPAC versus LRC (Figure 2). The maximum predicted probability of developing the outcome in SPAC was 76% compared to 95% in LRC (Figure 3). The Loess smoothed calibration plot demonstrated c statistic of 0.71 (CI 0.65 to 0.77), slope of 1 (CI 0.69 - 1.31) and intercept of 0 (-0.24 to 0.24) (Figure 4).

Discussion

This is the first external validation of the PARC tool in a clinical cohort. The tool showed reduced predictive ability for asthma development in young children aged 1-6 years old in the clinical validation cohort (SPAC) than in the original population-based cohort (LRC). Discrimination, though modest in both cohorts, was somewhat reduced in SPAC (AUC 0.71) compared to LRC (0.78). The PARC tool had a higher sensitivity (95% versus 79%) at a score of 4 in the clinical setting of SPAC compared to the community-setting of LRC, and a similarly high negative predictive value (84% vs 87%). However, all other indicators suggested reduced performance. The mean PARC score was higher in SPAC than LRC and AUC improved to 0.74 when the outcome was defined as moderately severe asthma (more than 4 attacks in the past year and use of asthma medication).

Strengths and limitations

This study has several strengths. It is the first external validation of the tool in a clinical setting where children with respiratory problems are treated. In addition, SPAC is a longitudinal study embedded in routine pulmonology care across German-speaking parts of Switzerland, which represents a real-world setting. Questionnaire

items used in SPAC are identical to those used in LRC. A strength of the PARC tool is, that it used state-of the art modelling strategies and selected predictors using a method (least absolute shrinkage and selection operator (LASSO) regression) that minimises the risk of over-fitting the data. The main limitation of this external validation is the small sample size currently available in this clinical setting and the limited follow-up time. However, due to the longitudinal and ongoing nature of SPAC, there is scope to perform further external validations in future when the participant number and follow up time has increased.

Interpretation and Comparison with Previous Studies

There are several differences between SPAC and LRC which must be considered when interpreting the performance of the PARC tool in this external validation setting. Firstly, the broader age range (1-6 years versus 1-3 years) and shorter follow up time (2 years versus 5 years) in SPAC compared to LRC. Secondly, this analysis used information collected from parent-reported questionnaires written in German. The specific terms for “wheeze” are not easily interchangeable between the German and English languages. However, a previous external validation of the PARC tool in the German MAS population-based cohort showed very good discriminatory performance with an AUC of 0.83, suggesting that differences in language are not a likely explanation for the poorer performance of PARC in SPAC.¹⁸ Thirdly, SPAC represents a group of children with a high burden of respiratory disease in a clinical setting. A higher burden of respiratory disease results in a more homogenous case-mix which has been shown in external validations to reduce discriminative ability of prediction models²⁵ and application of a prediction tool from a population or primary

care setting to a tertiary setting has also been shown to demonstrate reduced spectrum transportability²⁶.

Other asthma predictive tools have been developed for preschool children in clinical settings. A retrospective study by Boersma et. al. that aimed to examine how sensitisation to inhalant allergens among wheezing toddlers in secondary healthcare predicted asthma development, demonstrated an improvement in the AUC from 0.70 to 0.79 when it included invasive sensitisation measures compared to when they used only International Study of Asthma and Allergies in Childhood (ISAAC) questions.²⁷ Vial Dupuy et. al developed and independently validated the Persistent Asthma Predicting Score (PAPS) in a clinical setting. They defined the outcome as “persistent” asthma. Predictors included: family history of asthma, personal history of atopic dermatitis and IgE sensitisation. Their analysis demonstrated an AUC of 0.66 in the development population and 0.65 in the internal validation population demonstrating low overall discrimination of the tool.¹⁴ In a clinical setting including corticosteroid-naïve 3-47 month old children in Zürich, Switzerland, Singer et. al. performed an external validation of a modified Asthma Predictive Index (API) tool. They used an outcome of physician diagnosed asthma and included FeNO as a predictor. Their analysis showed good discrimination with AUC of 0.76 when FeNO was used instead of blood eosinophilia, as per the original API tool.²⁸ Rodriguez-Martinez et. al. implemented the loose API and modified Prevalence and Incidence of Asthma and Mite Allergy (PIAMA) tools in a clinical setting in Bogota, Columbia. They reported a sensitivity and specificity for predicting asthma at age 5-6 years in pre-schoolers with recurrent wheeze of 71.4% and 33.3% (loose API) and 54.5% and 78.9% (modified PIAMA) for ideal ROC cut off points. The authors suggested that

these prediction tools could therefore be applicable in clinical practice.²⁹ In our external validation, the PARC tool had an NPV of 83%, PPV of 46%, and sensitivity and specificity of 79% and 50% respectively at a PARC score of 7, which suggests that it also has scope for clinical application.

Implications for Clinical Care and Future Research

The PARC tool has now undergone external validation in two population-based and one clinical cohort. The tool shows good to very-good discriminative ability in community settings and good discriminative ability in the clinical setting. However, it has a higher sensitivity of 95% and an NPV of 84% in SPAC, indicating a possible role for assisting clinicians to accurately identify children with a low risk of developing. For example, paediatric pulmonologists in Switzerland could use the PARC tool to reassure parents with children with a score of 4 or less that their child's risk of having asthma in 2 years' time is only 5%. The proportion of children in our analysis with a PARC score 4 or less was 10%. The tool could also have potential applications for triaging patients for follow up. Furthermore, by narrowing the definition of asthma to a more severe spectrum the tool performs better in SPAC. This suggests that, in a clinical context, the PARC tool may be able predict severe asthma better and that any adaptation of the PARC tool in the future should use different outcome definitions such as "severe asthma" or "asthma persistence". Previous applications of prediction tools to clinical settings have demonstrated a role for invasive measures such as blood eosinophils, IgE sensitisation and FeNO with variable success.^{14, 26, 27} Future prediction model development for asthma risk in preschool children attending respiratory clinics could include these invasive measures to improve their discriminatory performance.

Conclusion

This external validation of the PARC tool in a clinical cohort embedded in routine paediatric pulmonology care suggested that the tool has a role for application in this setting. Currently, it can be used to help identify 1-6 year old children who are at low risk of having asthma at 2-years of follow up, due to its negative predictive value and sensitivity at a cut-off of 4. Discrimination of the PARC tool between children who will and will not have asthma 2 years later was borderline good highlighting the need for new childhood asthma prediction tools in the clinical setting. We suggest that future efforts to improve asthma prediction in this setting should explore the added value of biomarkers of physiological asthma-related traits available in pulmonology clinics, such as FeNO, allergy tests and lung function measurements.

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Availability of data and material

The SPAC dataset is available on reasonable request by contacting Claudia Kuehni by email: Claudia.kuehni@ispm.unibe.ch.

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Figures

Figure 1: Distribution (relative frequency %) of PARC Score in the external validation population (Swiss Paediatric Airway Cohort, SPAC, N = 346) versus original development population (Leicester Respiratory Cohort, LRC, N = 1226). Mean PARC scores of 7.4 for SPAC and 4.6 for LRC indicated by dashed vertical red lines.

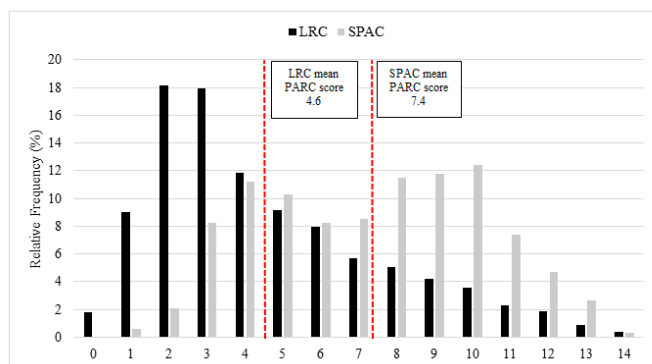


Figure 2: Receiver operating characteristic from external validation (SPAC in black with PARC scores marked in red) and development cohort (LRC in grey) including area under the curve. Table shows sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio for each score in SPAC. SPAC, Swiss Paediatric Airway Cohort; LRC, Leicester Respiratory Cohort.

Score Cut-Off	Sensitivity	Specificity	PPV	NPV	LR+	LR-
1	1	0	0.34	-	1.00	-
2	1	0	0.35	1	1.01	0.00
3	0.99	0.04	0.35	0.89	1.03	0.24
4	0.95	0.14	0.37	0.84	1.10	0.37
5	0.93	0.30	0.41	0.89	1.33	0.22
6	0.87	0.42	0.44	0.86	1.52	0.30
7	0.79	0.60	0.46	0.83	1.59	0.42
8	0.71	0.59	0.48	0.79	1.73	0.50
9	0.56	0.69	0.49	0.75	1.84	0.63
10	0.45	0.81	0.56	0.74	2.40	0.68
11	0.29	0.92	0.67	0.71	3.91	0.76
12	0.18	0.98	0.85	0.70	10.46	0.83
13	0.07	1	0.90	0.67	17.10	0.93
14	0.01	1	1	0.66	-	0.99

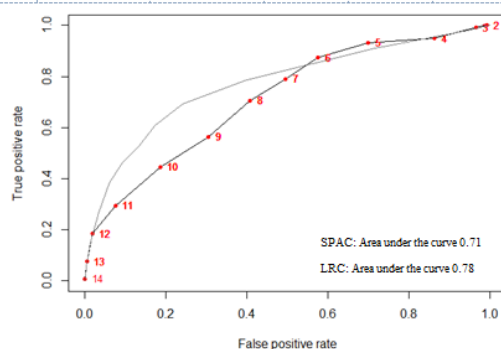


Figure 3: Predicted probability of developing asthma at follow-up in the LRC (grey line) and probability of developing asthma in recalibrated model in SPAC (black line). SPAC, Swiss Paediatric Airway Cohort; LRC Leicester Respiratory Cohort.

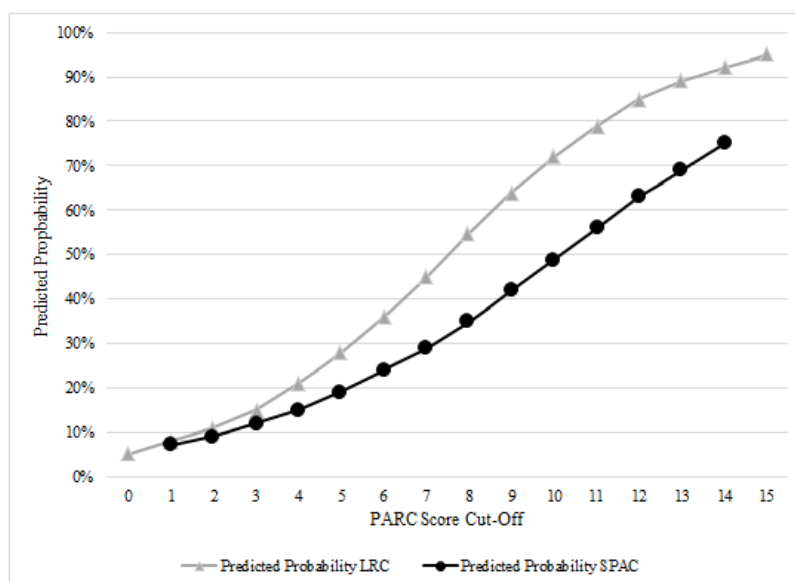


Figure 4: Calibration assessment of predicted probabilities in SPAC. SPAC, Swiss Paediatric Airway Cohort; LRC Leicester Respiratory Cohort.

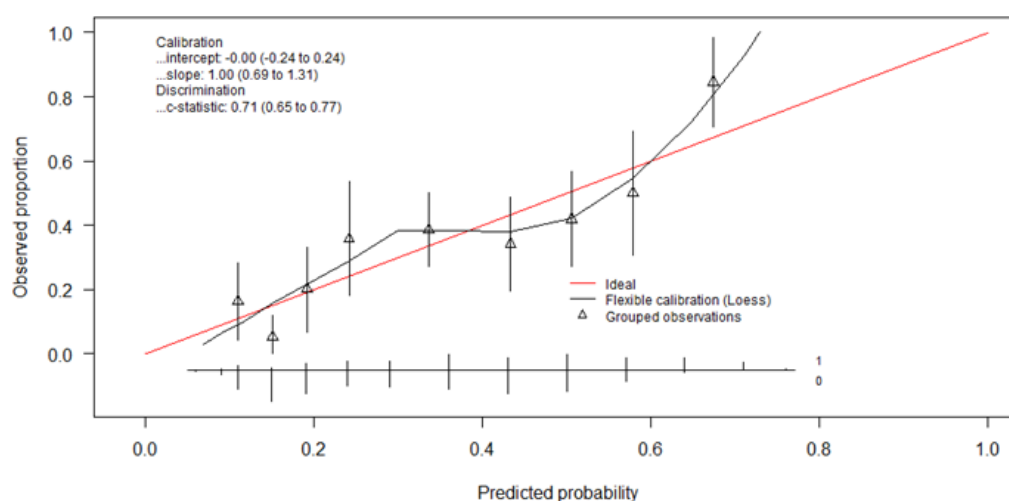


Table 1: Questions used for each PARC score item at baseline in SPAC and LRC. SPAC, Swiss Paediatric Airway Cohort; LRC Leicester Respiratory Cohort.

Question in asthma prediction score		LRC (%)	Questionnaire item in SPAC		SPAC (%)	Comparability
1 What is the child's sex	Female = 0	(45)	Gender	Female = 0	(34)	Perfect
	Male = 1	(55)		Male = 1	(66)	
2 How old is the child? (in years)	1 years = 0	(27)	Age	0– 1 years = 0	(11)	Very good
	2 = 1	(57)		2 – 6 years = 1	(89)	
	3 = 1	(15)				
3 In the last 12 months, has the child had wheezing or whistling in the chest even without having a cold or flu?	No = 0	(82)	In the last 12 months has the child had wheezing or whistling in the chest even without having a cold or flu?	No = 0	(25)	Perfect
	Yes = 1	(18)		Yes = 1	(75)	
4 How many attacks of wheeze has the child had during the last 12 months?	0-3=0	(77)	How many attacks of wheeze has the child had in the last 12 months?	0 or 1- 3= 0	(57)	Perfect
	>3 = 2	(23)		>3 = 2	(43)	
5 In the last 12 months, how much did wheezing interfere with the child's daily activities?	Never = 0	(64)	In the last 12 months, how much did wheezing or shortness of breath interfere with the child's daily activities?	Never = 0	(19)	Very good
	A little = 1	(26)		A little = 1 Moderately = 1	(53)	
	A lot = 2	(10)		A lot = 2	(28)	
6 Do these wheezing attacks cause the child to be short	Never = 0	(65)	Did the child have wheeze or shortness of breath during these episodes (i.e. wheezing	Never = 0	(47)	Perfect

of breath?	Sometimes = 2	(29)	attacks)?	Sometimes = 2	(35)	
	Always = 3	(6)		Always = 3	(18)	
7 In the last 12 months, did exercise (playing, running) or laughing, crying or excitement cause wheezing or coughing in the child?	No = 0	(61)	In the last 12 months, which of the following have caused the child to cough or wheeze: exertion, laughing, crying loudly	Never = 0	(27)	Excellent
	Yes = 1	(39)			(73)	
				Sometimes = 1		
				Often = 1		
8 In the last 12 months, did contact with dust, grass, pets or other animals cause wheezing or coughing in the child?	No = 0	(93)	In the last 12 months, which of the following have caused the child to cough or wheeze: dust, grass or animals	Never = 0	(59)	Perfect
	Yes = 1	(7)		Sometimes = 1	(41)	
				Often = 1		
9 Has the child ever had eczema?	No = 0	(71)	Has your doctor ever told you that the child has eczema or dermatitis?	No = 0	(76)	Excellent
	Yes = 1	(29)		Yes = 1	(24)	
10 Have the child's parents ever suffered from wheezing, asthma or bronchitis?	None = 0	(65)	Have the child's parents ever suffered from wheezing, asthma or bronchitis?	None = 0	(59)	Excellent
	Mother = 1	(31)		Mother = 1	(35)	
	Father = 1			Father = 1		
	Both = 2	(4)		Both = 2	(6)	

Table 2: Sensitivity analysis of SPAC versus LRC at a PARC Score of 4

	N	Cases N(%)	Sensitivi- ty	Specificali- ty	PP V	NP V	LR +	LR- -	AU C	R ²	Brier
SPAC											
Main analysis	346	125 (36)	0.95	0.14	0.37	0.84	1.10	0.37	0.71	0.18	0.13
Altered inclusion criteria											
Only children aged 1-3 years	146	45(36)	0.90	0.18	0.38	0.77	1.10	0.53	0.71	0.17	0.14
Altered outcome definition											
Follow up 1 year later	509	233 (46)	0.93	0.25	0.51	0.80	1.23	0.30	0.72	0.19	0.14
Follow up 3 years later	180	50 (28)	0.94	0.23	0.32	0.91	1.22	0.26	0.72	0.16	0.12
Severity: wheeze in the past 12 months with more than 4 episodes and use of asthma medication	346	37 (11)	0.97	0.22	0.13	0.99	1.24	0.12	0.74	0.15	0.09
LRC											

Main analysis	122 6	345 (28)	0.79	0.57	0.42	0.87	1.83	0.3 8	0.78	0.2 8	0.22
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Altered outcome definition

Severity: wheeze in the past 12 months with more than 4 episodes and use of asthma medica- tion	103 0	86 (8)	0.86	0.61	0.17	0.98	2.19	0.2 3	0.84	0.3 2	- 0.15
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