

Predicting asthma in preschool children with asthma-like symptoms: Validating and updating the PIAMA risk score

Esther Hafkamp-de Groen, MD,^{a,b} Hester F. Lingsma, PhD,^b Daan Caudri, MD, PhD,^c Deborah Levie, BSc,^{a,b} Alet Wijga, PhD,^d Gerard H. Koppelman, MD, PhD,^e Liesbeth Duijts, MD, PhD,^{c,f,g} Vincent W. V. Jaddoe, MD, PhD,^{a,f,h} Henriëtte A. Smit, PhD,ⁱ Marjan Kerkhof, MD, PhD,^j Henriëtte A. Moll, MD, PhD,^h Albert Hofman, MD, PhD,^f Ewout W. Steyerberg, PhD,^b Johan C. de Jongste, MD, PhD,^c and Hein Raat, MD, PhD^b Rotterdam, Bilthoven, Utrecht, and Groningen, The Netherlands

Background: The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) risk score predicts the probability of having asthma at school age among preschool children with suggestive symptoms.

Objective: We sought to externally validate the PIAMA risk score at different ages and in ethnic and socioeconomic subgroups of children in addition to updating it.

Methods: We studied 2877 children with preschool asthma-like symptoms participating in the multiethnic, prospective, population-based cohort study Generation R. The PIAMA risk score was assessed at preschool age, and asthma was predicted at age 6 years. Discrimination (concordance index [C-index]) and calibration were calculated. The PIAMA risk score was updated, and its performance was similarly analyzed.

Results: At age 6 years, 6% (168/2877) of the children had asthma. The discriminative ability of the original PIAMA risk score to predict asthma in Generation R was similar compared

with that in the PIAMA cohort (C-index = 0.74 vs 0.71). The predicted risks by using the original PIAMA risk score for having asthma at the age of 6 years tended to be slightly higher than the observed risks (8% vs 6%). No differences in discriminative ability were found at different ages or in ethnic and socioeconomic subgroups ($P > .05$). The updated PIAMA risk score had a C-index of 0.75.

Conclusions: The PIAMA risk score showed good external validity. The discriminative ability was similar at different ages and in ethnic and socioeconomic subgroups of preschool children, which suggests good generalizability. Further studies are needed to reproduce the predictive performance of the updated PIAMA risk score in other populations and settings and to assess its clinical relevance. (J Allergy Clin Immunol 2013;■■■:■■■-■■■.)

Key words: Asthma, birth cohort, children, external validation, Prevention and Incidence of Asthma and Mite Allergy risk score, prognosis, prediction, updating, wheeze

From ^athe Generation R Study Group, ^bthe Department of Public Health, and ^cthe Department of Epidemiology, Erasmus Medical Center, Rotterdam; ^dthe Department of Paediatrics, Division of Respiratory Medicine, ^ethe Department of Paediatrics, Division of Neonatology, and ^hthe Department of Paediatrics, Erasmus Medical Center–Sophia Children’s Hospital, Rotterdam; ^fthe Center for Prevention and Health Services Research/National Institute for Public Health and the Environment, Bilthoven; ^gthe Department of Pediatric Pulmonology and the GRIAC Research Institute, University of Groningen, University Medical Center Groningen, Pediatric Allergology, Beatrix Children’s Hospital, Groningen; ⁱJulius Center of Health Sciences and Primary Care, University Medical Center Utrecht, University of Utrecht; and ^jthe University of Groningen, University Medical Center Groningen, GRIAC Research Institute, Groningen.

E.H.-d.G. received funding by means of the Dutch Asthma Foundation (project no. 3.4.12.015). L. Duijts received funding by means of a European Respiratory Society/Marie Curie Joint Research Fellowship (MC 1226-2009) under grant agreement RESPIRE, PCOFUND-GA-2008-229571. V.W.V. Jaddoe received additional grants from the Netherlands Organization for Health Research and Development (ZonMw 90700303 and 916.10159). The Prevention and Incidence of Asthma and Mite Allergy study is supported by the Dutch Lung Foundation (grant no. 3.2.09.081).

Disclosure of potential conflict of interest: E. Hafkamp-de Groen and H. Raat have been supported by one or more grants from the Lung Foundation of the Netherlands. G. H. Koppelman has received one or more grants from or has one or more grants pending with the Netherlands Asthma Foundation and BBMRI-NL. L. Duijts is the recipient of a European Respiratory Society/Marie Curie Joint Research Fellowship–Number MC 1226-2009. The research leading to these results has received funding from the European Respiratory Society and the European Community’s Seventh Framework Programme FP7/2007-2013–Marie Curie Actions under grant agreement RESPIRE, PCOFUND-GA-2008-229571 and from the seventh framework programme, project CHICOS (HEALTH-F2-2009-241504). The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication May 7, 2013; revised July 2, 2013; accepted for publication July 2, 2013.

Corresponding author: Esther Hafkamp-de Groen, MD, PO Box 2040 (Room NA-2919), 3000 CA, Rotterdam, The Netherlands. E-mail: e.hafkamp@erasmusmc.nl.
0091-6749/\$36.00

© 2013 American Academy of Allergy, Asthma & Immunology
<http://dx.doi.org/10.1016/j.jaci.2013.07.007>

Parents of preschool children with asthma-like symptoms, such as wheezing or dry cough, often wonder whether their child will have persistent asthma at a later age. It is known that approximately 30% of preschool wheezing children have asthma at school age.¹ Preschool asthma-like symptoms are nonspecific, and therefore it is difficult to determine which preschool children with asthma-like symptoms actually have or will have asthma at school age.² Most, but not all, asthma starts with respiratory symptoms at preschool age. Several asthma prediction models have been proposed to improve the early diagnosis and management of asthma-like symptoms.^{1,3-9}

Most of these prediction models used information up to a fixed age, irrespective of the age of symptom onset. Some of the prediction models included blood tests.^{3,4,6-9} The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) risk score has been proposed as an instrument to predict asthma at school age in children who present with asthma-like symptoms before age 4 years. The score uses 8 easily obtainable parameters assessed at the time of the first asthma-like symptoms at preschool age. The PIAMA risk score sufficiently discriminated between asthmatic and nonasthmatic children (concordance index [C-index] = 0.71) and might be a suitable tool to distinguish preschool children with asthma-like symptoms at high and low risk of having asthma at school age and thereby help to provide parents a prognosis. External validation is an important step to determine the ability of the PIAMA risk score to reliably predict asthma in other populations and

Abbreviations used

C-index: Concordance index

LR+: Likelihood ratio of a positive test result

LR−: Likelihood ratio of a negative test result

NPV: Negative predictive value

OR: Odds ratio

PIAMA: Prevention and Incidence of Asthma and Mite Allergy

PPV: Positive predictive value

settings before use of a prediction model can be recommended in practice.

The aim of this study was to externally validate the PIAMA risk score in preschool children with asthma-like symptoms in the multiethnic, prospective, population-based cohort study Generation R. Additionally, we will compare the predictive ability of the PIAMA risk score at different ages and in ethnic and socioeconomic subgroups of preschool children. We intend to update the PIAMA risk score in the case that asthma prediction could be improved by more precise definitions and measures of predictors.¹ The prognostic value of the updated PIAMA risk score will then be compared with the prognostic value of the original PIAMA risk score.

METHODS

Development data

The development sample, the PIAMA study, is a Dutch prospective, population-based cohort study. Four thousand one hundred forty-six pregnant women from the general population were included in the development sample in 1996-1997.¹⁰ In total, 3963 children were followed from birth to age 8 years. Baseline information for the PIAMA risk score was assessed from questionnaires at enrollment and at the ages of 3 and 12 months and thereafter on an annual basis up to the age of 8 years, partly based on the International Study of Asthma and Allergies in Childhood core questionnaires.¹¹ In total, 2171 (55%) children reported at least 1 positive response to the following questions in the annual questionnaires at age 1 to 4 years: (1) "Has your child had wheezing in the last 12 months?" and (2) "Has your child had cough during the night, when he/she did not have a cold or a chest infection, in the last 12 months?" Only children with these symptoms were included in the analyses to develop the PIAMA risk score. Of 26 candidate predictors, 8 were eventually selected that predicted asthma at the age of 7 to 8 years. The PIAMA study was approved by the Medical Ethics Committees of the participating hospitals.

Validation data

The validation sample, Generation R, is a Dutch multiethnic, prospective, population-based cohort study. A total of 7295 children born between 2002-2006 gave consent for postnatal follow-up.¹² Details of our study design were published previously.¹³ For this study, the same inclusion criteria were used as in the development study. Children were included when they had an episode of asthma-like symptoms at age 1 to 4 years. Asthma-like symptoms were assessed based on answers to core questions from the International Study of Asthma and Allergies in Childhood.¹¹ The study was conducted in accordance with the guidelines proposed in the Declaration of Helsinki. The Medical Ethical Committee of the Erasmus University Medical Center Rotterdam approved this study. Informed consent was obtained from participating parents.

Outcome

In both the validation and development studies, the aim was to predict active asthma or clinically relevant chronic asthma (see Table E1 in this

article's Online Repository at www.jacionline.org). In the development study an asthma definition was used based on the following: wheezing, inhaled steroids, and/or a doctor's diagnosis of asthma at the ages of 7 and 8 years.⁵ In the validation study data on inhaled steroids were not available, and the definition of asthma was available at age 6 years based on reports by Castro-Rodriguez et al⁴ and Leonardi et al.¹⁴ Children had asthma if they had 1 or more positive score on the following items: (1) doctor's diagnosis of asthma ever and wheezing in the past 12 months or (2) 4 or more episodes of wheezing in the last 12 months. Items were measured by using parent-reported questionnaires. The response rate for the Generation R questionnaire at age 6 years was 68%.

For both validation and updating of the PIAMA risk score, the same asthma definition was used. The outcome data for updating the PIAMA risk score included both PIAMA and Generation R data because in Generation R the definition of asthma was only available at age 6 years and in PIAMA asthma was defined at age 7 years.

Predictors

To validate the PIAMA risk score, the same 8 predictors were used, as described by Caudri et al⁵: (1) male sex, (2) postterm delivery, (3) parental education, (4) parental inhalation medication, (5) wheezing/dyspnea apart from colds, (6) wheezing frequency, (7) respiratory tract infections, and (8) doctor's diagnosis of eczema (ever) and eczematous rash present. We aimed to define predictors in the same way as in the development study. However, data on parental inhalation medication were not available in Generation R, and therefore parental asthma was used as a proxy (see the [Methods](#) section in this article's Online Repository at www.jacionline.org). Data on wheezing/dyspnea apart from colds were not available in Generation R and therefore were imputed based on the total population, including both PIAMA and Generation R.¹⁵

Data analysis

This study consisted of the following phases: *phase I*, external validation (discrimination and calibration) of the PIAMA risk score published by Caudri et al⁵ and in subgroups of age, ethnicity, and socioeconomic status, and *phase II*, improving or updating of the PIAMA risk score.

First, the distribution of characteristics, predictors, and asthma outcome were compared between the development (PIAMA) and validation (Generation R) cohorts. Univariable and multivariable logistic regression analyses were performed, with effects of predictors expressed in odds ratios (ORs) and their CIs.

In phase I discrimination and calibration were calculated to assess the external validity of the PIAMA model. The C-index and 95% CI were used to assess discrimination. Discrimination is not better than chance if the C-index is 0.5, moderate if the C-index is greater than 0.6, good if the C-index is greater than 0.8, and perfect if the C-index is 1.¹⁶ Calibration refers to the agreement between observed and predicted outcomes. The extent of overestimation or underestimation relative to the observed and predicted rates was explored by using graphic validation plots, which show observed outcome by deciles of predictions. Calibration in the large was performed by fitting a logistic regression model with the model predictions as an offset variable. The calibration intercept indicates whether predictions were systematically too low or too high; these should ideally be zero. The calibration slope reflects the average effects of the predictors in the model and was estimated in a logistic regression model, with the logit of the model predictions as the only predictor. For a perfect model, the slope is equal to 1. The validation analyses were performed at different ages and in ethnic/socioeconomic subgroups of preschool children with sufficiently large numbers of children. Ethnicity was defined according to the classification of Statistics Netherlands.¹⁷ Because this definition of a child's ethnicity does not allow for the identification of third-generation migrants, we also externally validated the PIAMA risk score when the children from the Generation R sample were classified according to maternal ethnic background. A 2-sided *t* test was used to test differences between the C-indices of subgroups.

In phase II we analyzed whether the PIAMA risk score could be improved by using both datasets combined and hence make maximal use of all data.¹⁸ Addition of the following variables to the PIAMA risk score was tested: preterm birth, tobacco smoke exposure, sleeping problems caused by asthma-like symptoms, child's allergy, or general health. These variables were selected based on the literature and availability in the validation data.¹⁹⁻²² Furthermore, we assessed whether the predictive performance of the PIAMA risk score remained stable or improved by removing predictors. An updated multivariable logistic regression model was fitted. Eventually, the updated PIAMA risk score was transformed into a score chart to facilitate the computation of the predicted risk of asthma. Test characteristics (ie, sensitivity, specificity, Youden index [indicating the optimal cutoff], likelihood ratio of a positive test result [LR+], likelihood ratio of a negative test result [LR-], positive predictive value [PPVs], and negative predictive value [NPV]) were calculated for different cutoffs of the score. For details, see the [Methods](#) section in this article's Online Repository.

Statistical analyses were performed with SPSS version 20.0 for Windows (SPSS, Chicago, Ill) and the R software environment (version 2.7.1; R Foundation for Statistical Computing, Vienna, Austria).

Missing data analysis

A missing data analysis was conducted to assess how missing values on predictors might affect results (see [Table E2](#) in this article's Online Repository at www.jacionline.org). Of the 20,139 data points (7 available predictors used in 2,877 children), 1,568 (8%) data points were missing. Missing data for the predictors varied between 0% (sex) and 28% (parental asthma, see [Table E2](#)). Children with 1 or more missing values on available predictors (population with incomplete data, $n = 1252$) were more likely than children with complete data ($n = 1625$) to wheeze ($P = .004$) and to have parents with low/medium education ($P \leq .001$). This shows that complete case analyses might lead to selection bias. Missing values on predictors were imputed by using multivariable imputation based on the correlation of the missing variables with other characteristics with SPSS 20.0 software for Windows.^{23,24} The outcome variable was included in the imputation model, but after imputation, cases with imputed asthma outcomes were excluded from the final analysis.²⁵ Analyses were repeated, including imputation of missing data on the asthma outcome, to test the sensitivity of this procedure. We found similar results (data not shown). Because data on wheezing/dyspnea apart from colds were not available in Generation R, only this predictor was imputed based on the total population, including both the PIAMA and Generation R study.¹⁵

RESULTS

Characteristics

Of the 7295 children participating in the postnatal phase of the validation study, 3967 (54%) reported asthma-like symptoms (an episode of wheezing or dry cough at night) in the first 4 years of life. We excluded 1090 (28%) children who were missing the outcome (asthma at age 6 years), leaving 2877 children for the analysis. Child and parental characteristics of both the development and validation studies are shown in [Table I](#).^{5,17} In more than half of the children, first symptoms were reported before the age of 1 year ([Table I](#)). The prevalence of cough at night and wheezing was equally distributed in both the validation and developmental studies (approximately 60%). In the validation study the prevalence of Dutch children was lower (69% vs 94%) and the prevalence of highly educated parents was higher (70% vs 24%) compared with values in the development study. More detail regarding the ethnic subgroups of non-Dutch children is shown in [Table E3](#) in this article's Online Repository at www.jacionline.org. A total of 240 (11%) children had asthma at age 7 to 8 years in the development study,

168 (6%) children had asthma at age 6 years in the validation study, and 276 (6%) had asthma at age 6 to 7 years in the combined PIAMA and Generation R data, which were used for updating of the PIAMA risk score.

Predictors of asthma

The strongest multivariable predictors of asthma at age 6 years assessed at preschool age were the number of wheezing episodes ($OR_{1-3} \text{ wheezing episodes/year, } 2.4 [95\% \text{ CI, } 1.6-3.6]$ and $OR_{\geq 4} \text{ wheezing episodes/year, } 7.2 [95\% \text{ CI, } 4.5-11.6]$) and eczema ($OR, 4.6 [95\% \text{ CI, } 3.1-6.8]$; [Table II](#)).⁵ These effects were stronger in the validation study compared with the development study.⁵ Multivariable effects were only of comparable magnitude in the development and validation study for sex, parental education, and parental asthma. In the validation study postterm delivery, wheezing/dyspnea apart from colds, and respiratory tract infections were not associated with asthma.

Phase I: External validation (in subgroups)

The PIAMA risk score discriminated moderately in the validation sample with a C-index of 0.74 (95% CI, 0.70-0.79). The calibration slope was 1.19 ([Fig 1](#)). [Fig 1](#) shows that the mean predicted risk of asthma at age 6 years was higher than the mean observed risk (calibration intercept = 0.026).

At different ages and in ethnic and socioeconomic subgroups of children, the predictive ability of the original PIAMA risk score for asthma at the age of 6 years varied between 0.72 and 0.78 ([Table III](#)).¹⁷ Validation results were similar between subgroups of the child's ethnicity compared with subgroups of maternal ethnicity (data not shown). To take into account third-generation immigrants, we choose to report validation results between subgroups of maternal ethnicity ([Table III](#)). No differences in discriminative ability were found between different ages, ethnic subgroups, and socioeconomic subgroups of preschool children ($P > .05$).

Phase II: Model update

Including preterm birth (yes, no) instead of the predictor postterm delivery (yes, no) in the updated risk score resulted in a C-index of 0.75 (95% CI, 0.72-0.78), which is higher compared with the performance of the original risk score (C-index = 0.71). The updated PIAMA risk score discriminated moderately in the Generation R sample, with a C-index of 0.77 (95% CI, 0.73-0.81). Addition of tobacco smoke exposure, sleeping problems caused by asthma-like symptoms, allergy, or general health to the PIAMA risk score did not increase the discriminative ability of the original model (data not shown).

The updated PIAMA risk score chart was developed by assigning points for each predictor based on its regression coefficients ([Table IV](#) and see [Table E4](#) in this article's Online Repository at www.jacionline.org). The new score for each child was calculated by using the equation shown in the legend of [Table V](#). The score ranged from 0 to 23 (see [Fig E1](#) in this article's Online Repository at www.jacionline.org).

In [Table V](#) the sensitivity, specificity, Youden index, LR+, LR-, PPV, and NPV are presented, corresponding to ascending cutoff values of the updated PIAMA risk score. The highest Youden index, indicating the optimal cutoff, was found at a score of 8.

TABLE I. Characteristics of the study population in the development and validation studies

	Development study,* N = 2171 (n/N [%])	Validation study, N = 2877 (n/N [%])
Child's characteristics		
Male sex	1196/2171 (55.1)	1467/2877 (51.0)
Ethnicity†		
Dutch	2032/2171 (93.6)	1975/2868 (68.9)
Non-Dutch	139/2171 (6.4)	893/2868 (31.1)
Age of onset of asthma-like symptoms		
First year	1157/2171 (53.3)	1592/2877 (55.3)
Second year	423/2171 (19.5)	686/2877 (23.8)
Third year	366/2171 (16.9)	329/2877 (11.4)
Fourth year	225/2171 (10.4)	270/2877 (9.4)
Cough at night‡§	1314/2171 (60.5)	1790/2856 (62.7)
Wheezing frequency‡		
No wheezing	941/2171 (43.3)	1264/2815 (44.9)
1-3 times/y	860/2171 (39.6)	1261/2815 (44.8)
≥4 times/y	370/2171 (17.0)	290/2815 (10.3)
Low birth weight (<2500 g)	94/2171 (4.3)	150/2875 (5.2)
Delivery		
Term (≥37 and ≤42 wk)	1948/2171 (89.7)	2579/2876 (89.7)
Preterm (<37 wk)	118/2171 (5.4)	158/2876 (5.5)
Postterm (>42 wk)	105/2171 (4.8)	139/2876 (4.8)
Breast-feeding ever	1793/2171 (82.6)	2545/2770 (91.9)
Tobacco smoke exposure at home‡	632/2171 (29.1)	366/2195 (16.7)
Nasal symptoms‡§	908/2171 (41.8)	1267/2844 (44.5)
Respiratory tract infections‡¶		
Never	655/2171 (30.0)	1316/2695 (48.8)
1-3 times/y	993/2171 (46.0)	561/2695 (20.8)
≥4 times/y	523/2171 (24.0)	818/2695 (30.4)
Eczema‡#	349/2171 (16.1)	247/2399 (10.3)
Parental characteristics		
Low/medium education**	1659/2171 (76.4)	864/2842 (30.4)
Smoking during pregnancy††	325/2171 (15.0)	518/2353 (22.0)
Asthma‡‡	389/2171 (17.9)	355/2067 (17.2)
Hay fever§§	885/2171 (40.8)	1103/2110 (52.3)

The development study is the PIAMA study, and the validation study is the Generation R study.

*Data as reported by Caudri et al⁵; numbers refer to the imputed dataset (n = 2171).

†In the Generation R and PIAMA studies, Dutch ethnicity was assigned to a child if both parents were born in The Netherlands.¹⁷

‡At age of report of first asthma-like symptoms.

§In a period without a cold, flu, or chest infection.

||Defined in PIAMA as a parental report of smoking in the child's house more than once a week and defined in Generation R as a parental report of smoking occasionally in the child's home (in the last 12 months; data were only available at the ages of 6 months, 2 years, and 3 years).

¶Defined in both cohorts as a parental report of serious respiratory tract, throat, nose, and/or ear infections, such as flu, infection of the throat, infection of the middle ear, sinusitis, bronchitis, or pneumonia in the last 12 months.

#Defined in both cohorts as a doctor's diagnosis of eczema ever in combination with a parental report of itchy rash in the last 12 months on at least 1 of the following locations: inner elbows, back of the knees, around the ears or eyes, and the upper side of the ankles. Data on rashes in Generation R were only available at age 1 and 2 years.

**Defined in both cohorts as an education less than the level of a bachelor's/master's degree (HBO/University in Dutch system) for 1 parent (in the case that educational level was known for 1 parent) or 2 parents (in the case that educational level was known for both parents).

††Defined in PIAMA as any smoking during 4 weeks after the estimated date of conception and defined in Generation R as smoking after pregnancy was known.

‡‡Defined in both cohorts as a parental report of having asthma ever for at least 1 parent.

§§Defined in both cohorts as a parental report of having hay fever for at least 1 parent.

DISCUSSION

The PIAMA risk score showed acceptable discrimination and good calibration results. Overall, the predicted risks by the original PIAMA risk score for having asthma at the age of 6 years were systematically overestimated. Compared with the development study, the discriminative ability of the original PIAMA risk score was higher in the validation study. No differences in discriminative ability were found at different ages or in ethnic and socioeconomic subgroups of preschool children. The updated PIAMA risk score included preterm birth (instead of postterm), and respiratory tract infections were removed.

Several studies previously developed models to predict asthma at school age.^{1,3-9} Only a few models to predict asthma at

school age among preschool children have been validated.^{4,14,26}

The original PIAMA risk score has only been validated in a population of preschoolers with recurrent wheezing living in a low/middle-income country.²⁶ Compared with this study by Rodriguez-Martinez et al,²⁶ the predictive performance of the updated PIAMA risk score at the optimal cutoff point (highest Youden index) showed high sensitivity (64% in the Generation R study vs 54% in the study by Rodriguez-Martinez et al), similar specificity (74% vs 79%) and LR+ (2.44 vs 2.59), and low PPV (12% vs 75%). The findings of a lower PPV in Generation R are probably due to the lower prevalence of asthma (6% vs 54%).

Recently, the development and use of asthma prediction models was discussed.¹ It was concluded that prediction of asthma can be

TABLE II. Association between PIAMA risk score predictors and asthma at school age

Predictors	Univariable		Multivariable	
	Development study* (n = 2171)	Validation study (n = 2877)	Development study* (n = 2171)	Validation study (n = 2877)
1. Male sex	1.8 (1.4-2.4)	1.8 (1.3-2.5)	1.7 (1.3-2.3)	1.6 (1.1-2.2)
2. Postterm delivery	2.1 (1.3-3.5)	0.5 (0.3-1.1)	2.3 (1.3-4.0)	0.5 (0.2-1.5)
3. Medium/low parental education	1.6 (1.1-2.2)	1.8 (1.3-2.5)	1.6 (1.1-2.3)	1.6 (1.1-2.2)
4. Parental asthma†	2.6 (1.9-3.5)	3.2 (2.3-4.4)	2.4 (1.8-3.3)	2.6 (1.8-3.7)
5. Wheezing/dyspnea apart from colds‡§	2.9 (1.7-4.9)	1.2 (0.6-2.5)	2.3 (1.3-4.1)	1.0 (0.5-2.3)
6. Wheezing frequency‡				
Never	Reference	Reference	Reference	Reference
1-3 times/y	1.8 (1.3-2.5)	2.4 (1.6-3.7)	1.6 (1.1-2.3)	2.4 (1.6-3.6)
≥4 times/y	3.9 (2.7-5.6)	8.4 (5.3-13.2)	2.8 (1.9-4.2)	7.2 (4.5-11.6)
7. Respiratory tract infections‡				
Never	Reference	Reference	Reference	Reference
1-2 times/y	1.8 (1.2-2.6)	0.8 (0.5-1.3)	1.7 (1.3-2.2)	0.7 (0.4-1.2)
≥3 times/y	2.8 (1.9-4.1)	1.8 (1.3-2.5)	2.2 (1.4-3.3)	1.1 (0.8-1.6)
8. Eczema	3.1 (2.3-4.2)	5.5 (3.9-7.9)	2.6 (1.9-3.5)	4.6 (3.1-6.8)

Values are ORs (95% CIs) estimated by using logistic regression models. All numbers refer to the imputed datasets. The development study is the PIAMA study, and the validation study is the Generation R study.

*Data as reported by Caudri et al.⁵

†Defined in the development study as inhalation medication use by at least 1 parent and defined in the validation study as a parental report of having asthma ever for at least 1 parent.

‡At age of report of first asthma-like symptoms.

§In the validation study data on wheezing/dyspnea apart from colds were not available, and therefore multivariable imputation was performed based on the development data.

||Defined in PIAMA as a parental report of number of serious respiratory tract, throat, nose, and/or ear infections, such as flu, infection of the throat, infection of the middle ear, sinusitis, bronchitis, or pneumonia in the last 12 months. In Generation R the number of respiratory tract infections was defined based on parental reports on the number of doctor's office visits caused by child's fever in combination with cough, a runny or blocked nose, or earache in the last 12 months.

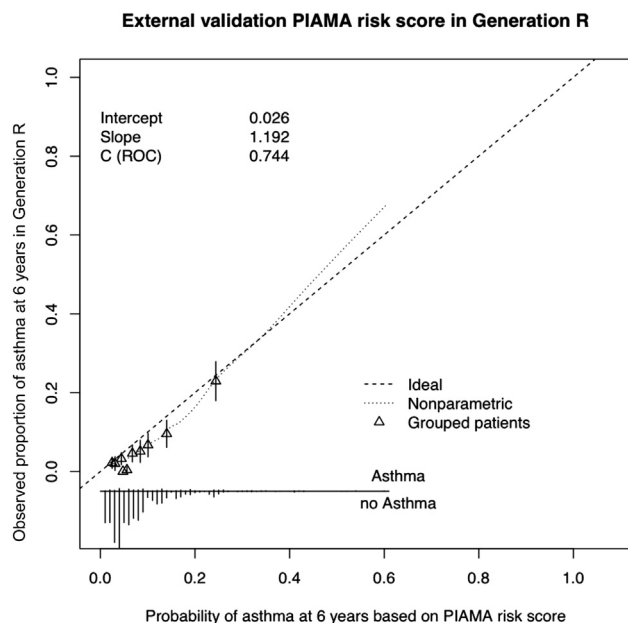


FIG 1. Validation plot of the PIAMA risk score adjusted for calibration in the large. For each percentile of predicted probability, the average predicted probability is plotted against the observed proportion. Distribution of the predicted probabilities is indicated with vertical lines at the bottom. The dashed line is the perfect calibration slope (n = 2877). ROC, Receiver operating characteristic.

improved by more precise definitions of predictors. Our study modified the original PIAMA risk score by replacing the predictor of postterm delivery by preterm birth. The PIAMA study was the first study that reported postterm delivery as an independent

predictor in the asthma prediction model. Caudri et al⁵ emphasized that their finding did not necessarily imply a causal relationship. In our validation study no association was found between postterm delivery and asthma (Table II). Because it is known that children who are born preterm are more likely to have respiratory disease,^{20,27} we included preterm birth as a predictor in the updated PIAMA risk score. Also, no relationship was found between respiratory tract infections and asthma in this study. Although the predictor of chest infection was part of several prediction models in other studies, either the whole prediction model performed poorly³ or only predicted asthma at a fixed age.⁷

This study is carried out within a project to develop an asthma prediction model for use in well-child care.¹³ Compared with other asthma prediction models, the updated PIAMA risk score can be used in this project because it contains 7 easily obtainable parameters assessed at the time of asthma-like symptoms at preschool age. The updated PIAMA risk score was not to be used as a screening tool in a general population because it was developed as a risk assessment tool in preschool children with asthma-like symptoms.

This study presented the predictive performance for a range of scores on the updated PIAMA risk score because different cutoff points might be chosen in different settings (eg, clinical application vs preventive health care). The choice of a cutoff point as a balance between false-positive and false-negative results depends on the benefits and potential harm of the actions that are taken based on predicted risk. For example, when follow-up actions are invasive or costly, false-positive results should be kept as low as possible. Compared with the predictive performance of previously reported models to predict asthma at age 6 to 7 years,^{1,3-9} the predictive probability of the updated PIAMA risk score at a cutoff point of 8 showed a high sensitivity (64% vs 9% to 57%¹) but a low PPV (12% vs 24% to 75%¹).

TABLE III. Prevalence of asthma and C-index in the external validation study stratified by age, ethnicity, and income

	Asthma, n/N (%)	C-index (95% CI)	P value
Overall	168/2877 (5.8)	0.74 (0.70-0.79)	
Subgroups			
Age of onset of asthma-like symptoms			
First or second year	144/2278 (6.3)	0.72 (0.68-0.75)	.78
Third or fourth year	24/599 (4.0)	0.73 (0.66-0.80)	
Maternal ethnicity*			
Non-Western	36/535 (6.7)	0.73 (0.64-0.83)	.87
Other Western	19/418 (4.5)	0.78 (0.67-0.88)	.58
Dutch	113/1924 (5.9)	0.74 (0.69-0.79)	Reference
Net household income†			
<€1600/mo	26/393 (6.6)	0.77 (0.67-0.87)	.43
≥€1600/mo	142/2484 (5.7)	0.73 (0.69-0.76)	

P values were determined by using the 2-sided *t* test. Individual PIAMA risk score is calculated by using the following equation: $0.46 \times \text{Sex (boy = 1, girl = 0)} + 0.73 \times \text{Postterm delivery (yes = 1, no = 0)} + 0.42 \times \text{Medium/low parental education (yes = 1, no = 0)} + 0.77 \times \text{Parental asthma (yes = 1, no = 0)} + 0.42 \times \text{Infrequent wheezing (yes = 1, no = 0)} + 0.91 \times \text{Frequent wheezing (yes = 1, no = 0)} + 0.71 \times \text{Wheezing/dyspnea apart from colds (yes = 1, no = 0)} + 0.46 \times \text{Infrequent serious infections (yes = 1, no = 0)} + 0.69 \times \text{Frequent serious infections (yes = 1, no = 0)} + 0.82 \times \text{Eczema (yes = 1, no = 0)}$.

*Dutch ethnicity was assigned to the mother if both parents were born in The Netherlands.¹⁷

†Less than €1600/mo (ie, less than the modal income).

TABLE IV. Score chart of the modified PIAMA risk score for predicting asthma in preschool children

Male sex	2
Medium/low parental education	1
Parental asthma	4
Preterm birth (<37 wk)	1
Wheezing frequency	
1-3 times/y	4
≥4 times/y	7
Wheezing/dyspnea apart from colds	2
Eczema	6
Range total score	0-23
Total score	Risk on asthma
0-7	≤5%
8-15	6%-22%
16-23	25%-60%

Postterm delivery and respiratory tract infections were deleted from the original PIAMA risk score.

Compared with the LR+ range of previously reported models to predict asthma at age 6 to 7 years (LR+ range, 1-12¹), the LR+ range of the updated PIAMA risk score was similar (1-10, depending on the selected cutoff). The prevalence of asthma at age 6 to 7 years was the lowest in the study population used for updating the PIAMA risk score (6% vs 8% to 54%), as reported by Savenije et al.¹ The different asthma definitions and ages at prediction make it difficult to compare results across studies. The differences between studies might be attributed to different characteristics of the study populations. The overestimation of the predicted risk of asthma might be due to the lower prevalence of asthma in our validation study, which might be lower because of the lack of data on inhaled steroid prescriptions.

Methodological considerations

This study benefits from a longitudinal design, which enabled us to collect repeated measurements of predictors at preschool age. In this way we could identify the age at onset of first symptoms, unlike some earlier studies, which predict asthma at fixed ages.^{3,7,8,28} The ages at which asthma-like symptoms usually appear (0-4 years) are the times that children regularly visit medical professional for well-child care and when prediction of asthma becomes relevant. Other strengths of our study are its size and external validation of the prediction rule in subgroups of younger age, non-Dutch nationality, and low socioeconomic status. With 5048 children included in the update of the PIAMA risk score, this is the largest cohort study used to predict asthma. Although there are differences in design and minor differences in analysis between the development and validation studies, the performance of the model is similar in both cohorts. This gives health care workers more confidence in applying this score in practice.

There are some deficiencies that should be considered when interpreting our results. Below, we will explain why the deficiencies exist and how they were addressed. However, it should be noted that the deficiencies still exist and that the analyses cannot overcome them.

The first deficiency of our study is that we did not have information about 2 predictors used in the original PIAMA risk score, including parental inhalation medication and wheezing apart from colds. Parental asthma was used as a proxy of parental inhalation medication (see the **Methods** section in this article's Online Repository). Data on wheezing/dyspnea apart from colds were not available in Generation R and therefore were imputed based on the total population, including both the PIAMA and Generation R studies.¹⁵ We assumed that the correlation structure of wheezing/dyspnea apart from colds is the same in the original and external validation studies. Another deficiency is that we had to exclude 28% of the cases with asthma-like symptoms because of the lack of outcome data. No large differences in results were observed between analyses with exclusion of children with missing data on the asthma outcome (*n* = 2877) and analyses including imputed asthma outcomes (*n* = 3967, data not shown).

In the validation study we predicted asthma in younger children (5-6 years) compared with those in the development study (7-8 years). In older children asthma can be diagnosed and predicted with more certainty based on spirometry. We recommend to validate the PIAMA prediction model when children in the Generation R validation sample reach age 10 years.

We have to take into account the effect of parental reports on asthma-like symptoms, predictors, and asthma outcomes on observed effects. The fact that our parent-reported predictors will be also parent reported in clinical practice is advantageous for the practical applicability of our results.

In both the validation and development studies, asthma outcome was based on parent-reported questionnaires. In our study misclassification could have taken place because of under-reporting of symptoms or because of a lack of data on inhaled steroid prescriptions. More uniformity of operational asthma definitions seems needed.²⁹ Parental reports of wheezing are widely accepted in epidemiologic studies and reliably reflect the incidence of wheezing in preschool children.³⁰ However, misclassification cannot be excluded. For example, Cane et al³¹

TABLE V. Predictive probability of the updated PIAMA risk score for different cutoff points

Cutoff point	Risk of asthma (%)	No. of positive test results (%)	Sensitivity (%)	Specificity (%)	Youden Index	LR+	LR–	PPV (%)	NPV (%)	OR
≥2	1.8	4227 (83.7)	94.6	16.9	0.11	1.14	0.32	6.2	98.2	3.5
≥4	2.7	3405 (67.5)	89.5	33.8	0.23	1.35	0.31	7.3	98.2	4.4
≥6	4.1	2508 (49.7)	79.7	52.1	0.32	1.66	0.39	8.8	97.8	4.3
≥8	6.1	1423 (28.2)	63.8	73.9	0.38	2.44	0.49	12.4	97.2	5.0
≥10	8.9	891 (17.7)	52.9	84.4	0.37	3.39	0.56	16.5	96.9	6.1
≥12	12.9	470 (9.3)	36.6	92.3	0.29	4.73	0.69	21.6	96.2	6.9
≥14	18.3	238 (4.7)	22.5	96.3	0.19	6.09	0.81	26.2	95.5	7.6
≥16	25.4	122 (2.4)	11.6	98.1	0.10	6.15	0.90	26.4	95.0	6.8
≥18	34.0	45 (0.9)	5.8	99.4	0.05	9.54	0.95	35.7	94.8	10.1
≥20	43.8	20 (0.4)	2.5	99.7	0.02	9.31	0.98	35.1	94.6	9.5
≥22	54.1	5 (0.1)	0.4	99.9	0.00	4.32	1.00	20.1	94.5	4.3

Range in prediction scores was 1 to 23 (n = 5048). The Youden index indicates the optimal cutoff. The individual updated PIAMA risk score was calculated by using the following equation: $2 \times \text{Sex (boy = 1, girl = 0)} + 1 \times \text{Preterm delivery (yes = 1, no = 0)} + 1 \times \text{Medium/low parental education (yes = 1, no = 0)} + 4 \times \text{Parental asthma (yes = 1, no = 0)} + 4 \times \text{Infrequent wheezing (yes = 1, no = 0)} + 7 \times \text{Frequent wheezing (yes = 1, no = 0)} + 2 \times \text{Wheezing/dyspnea apart from colds (yes = 1, no = 0)} + 6 \times \text{Eczema (yes = 1, no = 0)}$.

came to the conclusion that both false-positive and false-negative parental reports of wheeze appeared in their study.

Selection bias cannot be excluded, for example, if nonparticipants (because of nonresponse or lost to follow-up) with preschool asthma-like symptoms more often had asthma at school age compared with participants. The use of multivariable imputation limits the risk of selection bias.^{23,24} As a result, the 95% CIs in our study reflect the uncertainty associated with the missing values.

Because the original study population of the PIAMA birth cohort is a reflection of the general population, our results might be valid for The Netherlands and, perhaps, other Western countries. To improve generalizability, we recommend that future studies will further validate and update the PIAMA risk score in varied other populations and settings, such as in other countries.

The PIAMA risk score is moderately discriminative, which brings into question its clinical utility. We recommend future studies to evaluate whether additional predictors, such as biomarkers and genomic risk profiles, might further improve asthma prediction. In future research, the clinical usefulness of the updated PIAMA risk score should be evaluated, assessing the ability of the model to improve the decision-making process by health care workers in asthma risk assessment and management.

In conclusion, the PIAMA risk score showed good external validity in the population of the Generation R study. The discriminative ability was similar at different ages and in ethnic and socioeconomic subgroups of preschool children, which suggest good generalizability. Future studies are needed to reproduce the predictive performance of the updated PIAMA risk score and to assess its clinical relevance.

The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the School of Law and Faculty of Social Sciences of the Erasmus University Rotterdam; the Municipal Health Service Rotterdam area, Rotterdam; the Rotterdam Homecare Foundation, Rotterdam; and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR-MDC), Rotterdam. We gratefully acknowledge the contribution of the children and parents, general practitioners, hospitals, midwives, and pharmacies in Rotterdam. The general design of the Generation R Study is made possible by financial support from the Erasmus Medical Center, Rotterdam; the Erasmus University, Rotterdam; The Netherlands Organization for Health Research and Development (ZonMw); The Netherlands Organisation for

Scientific Research (NWO); the Ministry of Health, Welfare and Sport; and the Ministry of Youth and Families.

Key messages

- The PIAMA risk score shows good external validity in a multiethnic birth cohort study.
- The discriminative ability of the PIAMA risk score to predict asthma at school age is similar at different ages and in ethnic and socioeconomic subgroups of preschool children, which suggest a good generalizability.

REFERENCES

1. Savenije OE, Kerkhof M, Koppelman GH, Postma DS. Predicting who will have asthma at school age among preschool children. *J Allergy Clin Immunol* 2012;130:325-31.
2. Martinez FD. What have we learned from the Tucson Children's Respiratory Study? *Paediatr Respir Rev* 2002;3:193-7.
3. Balemans WA, van der Ent CK, Schilder AG, Sanders EA, Zielhuis GA, Rovers MM. Prediction of asthma in young adults using childhood characteristics: development of a prediction rule. *J Clin Epidemiol* 2006;59:1207-12.
4. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162:1403-6.
5. Caudri D, Wijga A, Schipper CM, Hoekstra M, Postma DS, Koppelman GH, et al. Predicting the long-term prognosis of children with symptoms suggestive of asthma at preschool age. *J Allergy Clin Immunol* 2009;124:903-10, e1-7.
6. 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. *Br J Gen Pract* 2005;55:125-31.
7. Kurukulaaratchy RJ, Matthews S, Holgate ST, Arshad SH. Predicting persistent disease among children who wheeze during early life. *Eur Respir J* 2003;22:767-71.
8. Matricardi PM, Illi S, Gruber C, Keil T, Nickel R, Wahn U, et al. Wheezing in childhood: incidence, longitudinal patterns and factors predicting persistence. *Eur Respir J* 2008;32:585-92.
9. Wever-Hess J, Kouwenberg JM, Duiverman EJ, Hermans J, Wever AM. Prognostic characteristics of asthma diagnosis in early childhood in clinical practice. *Acta Paediatr* 1999;88:827-34.
10. Brunekreef B, Smit J, de Jongste J, Neijens H, Gerritsen J, Postma D, et al. The prevention and incidence of asthma and mite allergy (PIAMA) birth cohort study: design and first results. *Pediatr Allergy Immunol* 2002;13(Suppl 15):55-60.
11. Sole D, Vanna AT, Yamada E, Rizzo MC, Nasipitz CK. International Study of Asthma and Allergies in Childhood (ISAAC) written questionnaire: validation of the asthma component among Brazilian children. *J Investig Allergol Clin Immunol* 1998;8:376-82.
12. Jaddoe VW, van Duijn CM, Franco OH, van der Heijden AJ, van IJendoorn MH, de Jongste JC, et al. The Generation R Study: design and cohort update 2012. *Eur J Epidemiol* 2012;27:739-56.

13. Hafkamp-de Groen E, Lingsma HF, Caudri D, Wijga A, Jaddoe VW, Steyerberg EW, et al. Predicting asthma in preschool children with asthma symptoms: study rationale and design. *BMC Pulm Med* 2012;12:65.
14. 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. *J Allergy Clin Immunol* 2011;127:1466-72.e6.
15. Janssen KJ, Vergouwe Y, Donders AR, Harrell FE Jr, Chen Q, Grobbee DE, et al. Dealing with missing predictor values when applying clinical prediction models. *Clin Chem* 2009;55:994-1001.
16. Harrell FR Jr, Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modeling strategies for improved prognostic prediction. *Stat Med* 1984;3:143-52.
17. Swertz O, Duimelaar P, Thijssen J. Migrants in the Netherlands 2004. Voorburg/Heerlen: Statistics Netherlands; 2004.
18. 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* 2012;98:691-8.
19. Chugh IM, Khanna P, Shah A. Nocturnal symptoms and sleep disturbances in clinically stable asthmatic children. *Asian Pac J Allergy Immunol* 2006;24:135-42.
20. Jaakkola JJ, Ahmed P, Ieromnimon A, Goepfert P, Laiou E, Quansah R, et al. Preterm delivery and asthma: a systematic review and meta-analysis. *J Allergy Clin Immunol* 2006;118:823-30.
21. Subbarao P, Becker A, Brook JR, Daley D, Mandhane PJ, Miller GE, et al. Epidemiology of asthma: risk factors for development. *Expert Rev Clin Immunol* 2009;5:77-95.
22. Van Gent R, van Essen-Zandvliet EE, Klijn P, Brackel HJ, Kimpen JL, van Der Ent CK. Participation in daily life of children with asthma. *J Asthma* 2008;45: 807-13.
23. Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. *Am J Epidemiol* 1995;142: 1255-64.
24. Van der Heijden GJ, Donders AR, Stijnen T, Moons KG. Imputation of missing values is superior to complete case analysis and the missing-indicator method in multivariable diagnostic research: a clinical example. *J Clin Epidemiol* 2006;59: 1102-9.
25. Von Hippel, Paul T. Regression with missing Y's: an improved strategy for analyzing multiply imputed data. *Sociol Methodol* 2007;37:83-117.
26. 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. *Pediatr Pulmonol* 2011;46: 1175-81.
27. Wang WH, Chen PC, Hsieh WS, Lee YL. Joint effects of birth outcomes and childhood body mass index on respiratory symptoms. *Eur Respir J* 2012;39: 1213-9.
28. Devulapalli CS, Carlsen KC, Haland G, Munthe-Kaas MC, Pettersen M, Mowinkel P, et al. Severity of obstructive airways disease by age 2 years predicts asthma at 10 years of age. *Thorax* 2008;63:8-13.
29. Van Wonderen KE, Van Der Mark LB, Mohrs J, Bindels PJ, Van Aalderen WM, Ter Riet G. Different definitions in childhood asthma: how dependable is the dependent variable? *Eur Respir J* 2010;36:48-56.
30. Jenkins MA, Clarke JR, Carlin JB, Robertson CF, Hopper JL, Dalton MF, et al. Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *Int J Epidemiol* 1996;25:609-16.
31. Cane RS, Ranganathan SC, McKenzie SA. What do parents of wheezy children understand by "wheeze"? *Arch Dis Child* 2000;82:327-32.

METHODS

Predictors

In the validation study data on sex (boy, girl) and gestational age at birth were derived from medical records. Parental education was established at enrollment and defined as an education less than the level of a bachelor's/master's degree (HBO/University in Dutch system) for at least 1 of the parents (in the case that the educational level was known for 1 parent) or for 2 parents (in the case that the educational level was known for both parents).^{E1} Two of 8 predictors (ie, parental inhalation medication and wheezing/dyspnea apart from colds) were not available in the validation study. Because 92% of asthmatic patients use inhalation medication,^{E2} parental asthma (yes, no) was used as a proxy of parental inhalation medication. Child's wheezing frequency and respiratory tract infections were collected at the age of first presentation of asthma-like symptoms to mimic clinical practice. Because wheezing/dyspnea apart from colds was missing in Generation R, multivariable imputation was performed in a combined PIAMA and Generation R dataset ($n = 5048$).^{E3} Parental asthma, wheezing frequency, respiratory tract infections, doctor's diagnosis of eczema (ever), and presence of eczematous rash were measured by using parent-reported questionnaires (based on International Study of Asthma and Allergies in Childhood questionnaires) at child's age of 1, 2, 3, and 4 years.^{E4} In the development study respiratory tract infections were defined as a parental report of the number of serious respiratory tract, throat, nose, and/or ear infections, whereas in the validation study the variable was defined as a parental report of a visit to the doctor because of respiratory tract infections, such as bronchitis, pneumonia, throat, and/or ear infections. In both cohorts it was aimed to select only children with serious respiratory tract infections.

Test characteristics

Sensitivity is the proportion of true-positive results that are correctly identified by using the test; specificity is the proportion of true-negative results that are correctly identified by using the test. The Youden index was used to determine the optimal cutoff point and is calculated as follows: Sensitivity + Specificity - 1.^{E5} To further investigate the correctness of classification, likelihood ratios (LR+ and LR-) were calculated, which are relevant in clinical practice.^{E6} The ratio of the probability of a positive test result if the outcome is positive (true-positive result) to the probability of a positive test result if the outcome is negative (false-positive result) is calculated as follows: $LR+ = \text{Sensitivity} / (1 - \text{Specificity})$. The ratio of the probability of a negative test result if the outcome is positive (false-negative result) to the probability of a negative test result if the outcome is negative (true-negative result) is calculated as follows: $LR- = (1 - \text{Sensitivity}) / \text{Specificity}$. An LR+ of greater

than 5 is considered an informative prediction rule because it generates a large shift from pretest to posttest probability of asthma at school age.^{E7} The positive predictive value, which is calculated as $PPV = (\text{Sensitivity} * \text{Prevalence}) / [(\text{Sensitivity} * \text{Prevalence}) + (1 - \text{Specificity}) * (1 - \text{Prevalence})]$, is the probability that a child with a positive risk score result will have asthma at school age. The negative predictive value, which is calculated as $NPV = [(\text{Specificity}) * (1 - \text{Prevalence})] / [(\text{Specificity}) * (1 - \text{Prevalence}) + (1 - \text{Sensitivity}) * (\text{Prevalence})]$, is the probability that a child with a negative risk score result will not have asthma at school age. The ratio of the odds of a positive test result when having the disorder relative to the odds of a positive test result when not having the disorder is calculated as follows: $OR = \text{Sensitivity} * \text{Specificity} / ((1 - \text{Sensitivity}) * (1 - \text{Specificity})) = LR+ / LR-$. The OR values range from zero to infinity, with higher values indicating better discriminatory test performance.

REFERENCES

- E1. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162:1403-6.
- E2. Heijmans MJWM, Spreeuwenberg P, Rijken PM. Monitor Zorg-en leefsituatie van mensen met astma en COPD. Trends en ontwikkelingen over de periode 2000-2004. Utrecht: NIVEL
- E3. Janssen KJ, Vergouwe Y, Donders AR, Harrell FE Jr, Chen Q, Grobbee DE, et al. Dealing with missing predictor values when applying clinical prediction models. *Clin Chem* 2009;55:994-1001.
- E4. Sole D, Vanna AT, Yamada E, Rizzo MC, Naspitz CK. International Study of Asthma and Allergies in Childhood (ISAAC) written questionnaire: validation of the asthma component among Brazilian children. *J Invest Allergol Clin Immunol* 1998;8:376-82.
- E5. Akobeng AK. Understanding diagnostic tests 3: Receiver operating characteristic curves. *Acta Paediatr* 2007;96:644-7.
- E6. Castro-Rodriguez JA. The Asthma Predictive Index: early diagnosis of asthma. *Curr Opin Allergy Clin Immunol* 2011;11:157-61.
- E7. Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. *JAMA* 1994;271:703-7.
- E8. Caudri D, Wijga A, Schipper CM, Hoekstra M, Postma DS, Koppelman GH, et al. Predicting the long-term prognosis of children with symptoms suggestive of asthma at preschool age. *J Allergy Clin Immunol* 2009;124:903-10, e1-7.
- E9. 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. *J Allergy Clin Immunol* 2011;127:1466-72.e6.
- E10. Swertz O, Duimelaar P, Thijssen J. Migrants in the Netherlands 2004. Voorburg/Heerlen: Statistics Netherlands; 2004.

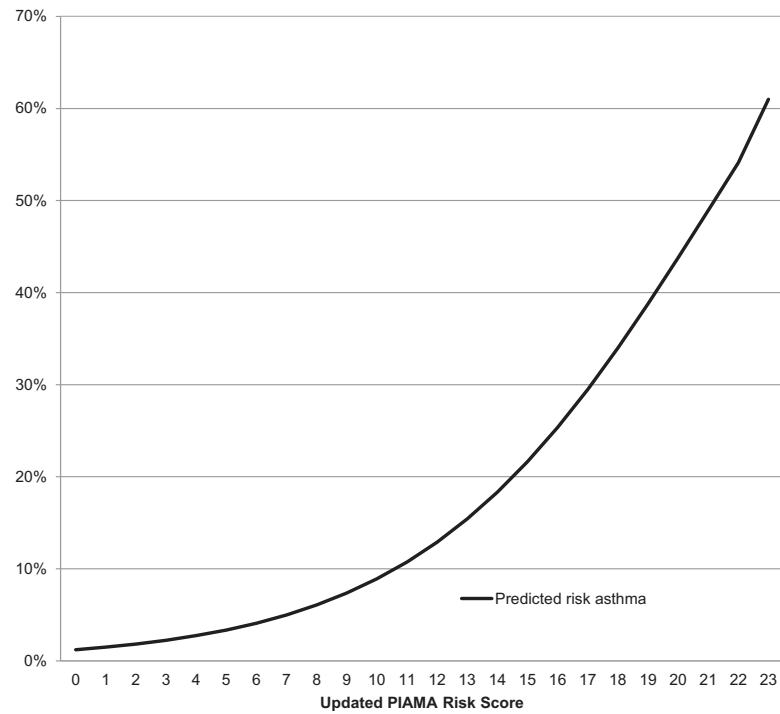


FIG E1. Predicted risk of asthma development at school age by updated prediction score.

TABLE E1. Definitions of asthma used in development, validation, and updating of the PIAMA risk score

Asthma definition	Study	Step in prediction modeling	Total population, no.	Asthma, no. (%)
At least 1 of the following items scored positive at age 7 y AND ≥ 1 item scored positive at age 8 y ^{E8}	PIAMA	Development	2171	240 (11.1)
Wheezing at least once				
Inhaled steroid prescriptions				
Doctor's diagnosis of asthma ever and asthma in the last 12 mo				
Doctor's diagnosis of asthma ever AND ≥ 1 episode of wheezing in the last 12 mo OR ≥ 4 episodes of wheezing in the last 12 mo: at age 6 y	Generation R	External validation	2877	168 (5.8)
Doctor's diagnosis of asthma ever AND ≥ 1 episode of wheezing in the last 12 mo OR ≥ 4 episodes of wheezing in the last 12 mo: at age 6 y in Generation R and at age 7 y in PIAMA	Combined data: PIAMA and Generation R	Updating	5048	276 (5.5)

All numbers refer to the imputed datasets. Asthma outcome data were collected by using parent-reported questionnaires and sent to the child's home. Asthma definition was based on reports by Castro-Rodriguez et al.^{E1} and Leonardi et al.^{E9}

TABLE E2. Missing data analyses within the validation study (n = 2877)

	Population with incomplete data* (n = 1252)	Population with complete data (n = 1625)	P value†	Multivariable imputation
Male sex	633 (51%)	834 (51%)	.684	0%
Delivery				
Preterm	74 (6%)	84 (5%)	.730	0%
Term	1117 (89%)	1462 (90%)		
Postterm	60 (5%)	79 (5%)		
Medium/low parental education	475 (39%)	389 (24%)	<.001	1%
Parental asthma	85 (19%)	270 (17%)	.196	28%
Wheezing frequency‡				
Never	497 (42%)	767 (47%)	.004	2%
1-3 times/y	561 (47%)	700 (43%)		
≥4 times/y	132 (11%)	158 (10%)		
Respiratory tract infections‡				
Never	528 (49%)	788 (49%)	.326	6%
1-2 times/y	190 (18%)	371 (23%)		
≥3 times/y	352 (33%)	466 (29%)		
Eczema‡	75 (10%)	172 (11%)	.500	17%

*Data on 1 or more available predictors are missing.

† χ^2 Test.

‡At age of report of first symptoms.

TABLE E3. Ethnicity of children participating in Generation R
(n = 2877)

Child's ethnicity	n (%)
Dutch	1975 (68.9)
Non-Dutch	
Other Western	258 (9.0)
Non-Western	
Surinamese	140 (4.9)
Moroccan	85 (3.0)
Turkish	167 (5.8)
Antillean	39 (1.4)
Cape Verdean	45 (1.6)
Other non-Western	159 (5.5)

Values are absolute numbers (percentages). Ethnicity was defined according to the classification of Statistics Netherlands.^{E10}

TABLE E4. Points in prediction score of the updated model compared with the original PIAMA risk score

Predictors	Points in prediction score, Caudri et al ^{E8}	Points in predict on score, updated model	SE*	OR (95% CI)*
1. Male sex	4.6	3.7	0.13	1.5 (1.1-1.9)
2. Postterm delivery (only included in original model) [†]	7.3	—	—	—
Preterm delivery (only included in updated model)	—	2.0	0.26	1.2 (0.7-2.0)
3. Medium/low parental education	4.2	2.5	0.13	1.0 (1.0-1.7)
4. Parental asthma	7.7	8.1	0.14	2.2 (1.7-2.9)
5. Wheezing/dyspnea apart from colds	7.1	4.5	0.26	1.6 (0.9-2.6)
6. Wheezing frequency				
Never	Reference	Reference	—	Reference
1-3 times/y	4.2	7.7	0.16	2.2 (1.6-3.0)
≥4 times/y	9.1	15.4	0.18	4.6 (3.3-6.6)
7. Respiratory tract infections				
Never	Reference	—	—	—
1-2 times/y	4.6	—	—	—
≥3 times/y	6.9	—	—	—
8. Eczema	8.2	12.0	0.14	3.3 (2.5-4.4)
Intercept	-39.1	-43.7	0.17	—

Points were calculated based on regression coefficients (log[OR] multiplied by a factor 10). All numbers refer to the combined datasets (PIAMA and Generation R, n = 5048). Gestational age at birth is included in the updated model instead of postterm delivery.

—, Not applicable.

*Calculated for the regression coefficient for the updated model.

[†]In the original model postterm delivery (yes, no) is included. In the updated model preterm delivery (yes, no) is included as a predictor, and respiratory tract infection is removed as a predictor.