A simple asthma prediction tool for pre-school children with wheeze or cough

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Asthma, wheeze, cough, children, prediction, prognosis, persistence, longitudinal, cohort study

Clinical Implications

The proposed asthma prediction tool is simple and uses information that is non-invasive and easy to assess. This makes it an ideal instrument for use in clinical practice and research.

Capsule summary

We have developed a simple tool to predict later asthma in preschool children suffering from wheeze or cough. Its simplicity and internal validity facilitate use in clinical practice and epidemiological research.

Abbreviations

ROC curve: receiver operating characteristic curve

AUC: area under the ROC curve

HL test: Hosmer-Lemeshow goodness-of-fit-test

OR: odds ratio

Abstract

Background: Many preschool children suffer from wheeze or cough, but only some have asthma later. Existing prediction tools are difficult to apply in clinical practice or exhibit methodological weaknesses.

Objective: To develop a simple and robust tool for predicting asthma at school-age in pre-school children with wheeze or cough.

Methods: From a population-based cohort in Leicestershire, UK, we included 1-3 year-olds seeing a doctor for wheeze or cough, and assessed prevalence of asthma five years later. We considered only non-invasive predictors that are easy to assess in primary care: demographic and perinatal data, eczema, various upper and lower respiratory symptoms and family history of atopy. We developed a model using logistic regression, avoided over-fitting with a LASSO-penalty, and then simplified it to a practical tool. We performed internal validation and assessed its predictive performance using the scaled Brier score and the area under receiver operating characteristic curve (AUC).

Results: Of 1226 symptomatic children with follow-up information, 345 (28%) had asthma 5 years later. The tool is based on 10 predictors yielding a total score between 0 and 15: sex, age, wheeze without colds, wheeze frequency, activity disturbance, shortness of breath, exercise-related and aeroallergen-related wheeze/cough, eczema, and parental history of asthma/bronchitis. The scaled Brier scores for the internally validated model and tool were 0.20 and 0.16, and the AUCs were 0.76 and 0.74, respectively.

Conclusion:

This simple, low-cost and non-invasive tool has good potential for identifying pre-school children at risk for later asthma and should be tested in other populations.

Introduction

Many preschool children present to primary care with recurrent wheeze or cough. These symptoms are a burden to families and lead to treatment with inhalers, antibiotics or cough mixtures, hospitalizations and considerable health care costs.[1] In this age-group, wheezing illness is, heterogeneous and includes different phenotypes with varying prognoses.[2-5] Fortunately, only some children will have persistent problems till school-age. The ability to predict persistence of wheeze up to school-age would allow preventative and therapeutic efforts to be directed to those most in need[6] and would reassure parents of children with transient problems. It would also help to select children for intervention studies aiming to alter the course of disease.[7]

Several groups have presented tools for prediction of later asthma in preschool children[8-16], but their use for primary care is limited.[17] Some tools were developed in study populations untypical for primary care. For instance, they included asymptomatic children,[8, 10, 14, 16] children with mild symptoms, who never visited their doctor,[13, 15] or only high-risk children hospitalized for bronchiolitis.[12] Several studies excluded children with chronic cough,[13, 15] who might actually suffer from a variant of asthma.[4, 18] Some tools included predictors, such as parental education, that are not easily generalizable to other populations.[9] Other tools involve invasive measurements (blood tests or skin prick tests) that might not be accepted by all families in primary care.[8, 11, 13, 14] Finally, the methods commonly used to develop the prediction tools are prone to over-fitting the data.[9, 11, 13] Over-fitting leads to reduced performance when tools are applied to other populations.[19, 20]

In this study we aimed to develop a simple tool to predict asthma at school-age in preschool children with wheeze or chronic cough. We designed the tool for

application in clinical practice, particularly primary care, by: a) studying a population of symptomatic children, who had presented to the doctor for wheeze or cough; b) defining a clinically relevant outcome; c) considering only predictive factors easily assessed during a single consultation (a detailed symptom history, but no blood or skin prick tests and no repeated observations); d) developing a robust model that performs well in internal validation and relevant sensitivity analyses but does not over-fit the data and is therefore likely to be transferable to other populations.

Methods

Study population

We analyzed data from a population-based childhood cohort from Leicestershire, UK, described in detail elsewhere.[21, 22, 23] In brief, we recruited a representative population-based sample of 6808 children of white and south Asian ethnic origin, born in 1993-97. Perinatal data were collected at birth; data on growth and development were acquired prospectively during childhood. Upper and lower respiratory morbidity, treatments and health care utilization, family history of atopic disease and individual and family-related exposures were assessed by repeated questionnaires (1998, 1999, 2001, 2003, 2006, 2010). The study was approved by the Leicestershire Health Authority Research Ethics Committee.

Presentation at baseline (inclusion criteria)

Our analysis included all cohort children aged 1-3 years at baseline with parent-reported wheeze or chronic cough (cough without colds or cough at night) with one or more visits to the doctor for wheeze or cough during the past 12 months (Fig 1, highlighted in grey). The original questions are provided in the online repository. We included chronic cough, because some children with chronic cough might suffer from

a variant of asthma and be at risk for asthma later in life.[4, 18] Information on symptoms at baseline was taken from the 1998 or the 1999 questionnaire, favoring the questionnaire when children were closest to age 2.0 years.

Any asthma at school-age (definition of outcome)

We defined a clinically relevant outcome as the combination of current wheeze *plus* use of asthma medication during the past 12 months at the age of 6-8 years, i.e. 5 years later (see online repository for original questions). Asthma medication included short- or long-acting beta-2-agonists, inhaled corticosteroids, leukotriene receptor antagonists or oral corticosteroids.

Choice of potential predictive factors

We used the following approach to compile the list of potential predictors. First, we reviewed the literature to identify relevant risk factors for incidence or persistence of childhood asthma.[3, 24-31] From these, we only selected factors that are readily available in primary care and do not require repeated observations or additional investigations like blood or skin prick tests. The final list contained 24 potential predictors (Table E1): demographic and perinatal data; eczema; upper and lower respiratory symptoms, particularly those reflecting triggers and severity of wheeze; and parental history of wheeze, asthma, bronchitis or hay fever (see online repository for original questions). We did not include environmental or socioeconomic information, because their prevalence and interpretation is likely to vary between populations and, thus, their inclusion might reduce the generalizability of the tool.

Model development

We used LASSO-penalized logistic regression to develop the prediction model.[32, 33]

153 This approach allows to identify important predictors and to estimate their influence
154 on later asthma without over-fitting the data. Traditional methods used for selecting
155 predictors, such as stepwise backward or forward selection, tend to over-fit the data,
156 resulting in models that predict outcomes in the current dataset well, but become
157 unreliable in other datasets.[20] For our analysis, we recoded all potential predictors
158 with >2 response categories into multiple binary variables. Thus, 38 binary variables
159 derived from the 24 questions entered the variable selection process (see online
160 repository for details). LASSO regression selects predictors in the order of their
161 predictive importance. The final prediction model allows calculation of a prediction
162 score and the probability of later asthma for each child.

163 *Model performance*

164 We assessed our prediction model in terms of overall performance, discrimination
165 and calibration. To assess *overall performance* we calculated the scaled Brier
166 score,[20] a measure of the discrepancy between the predicted probability and the
167 actual outcome. A scaled Brier score with a value of zero means that the model
168 predicts later asthma in an individual not better than if it had been informed only by
169 the average prevalence of asthma at school-age; the maximal value of one indicates
170 perfect prediction. To determine the *discriminative ability* of the model (i.e. its ability
171 to distinguish between children with and without later asthma) we plotted the receiver
172 operating characteristics (ROC) curve and calculated the area under this curve
173 (AUC), also known as c-statistic.[20, 34] The AUC can take on values from 0 to 1, with 1
174 being a perfectly discriminating model. Discrimination is considered not better than
175 chance if AUC=0.5, moderate if AUC is 0.6 to 0.8, and good if AUC>0.8.[34]
176 *Calibration* of the model (how well the predicted probabilities agree with the
177 prevalence of the outcome in subgroups of children) was tested using the Hosmer-

Lemeshow goodness-of-fit-test (HL test)[20, 35] and visualized using a calibration plot.[20] An HL test result of less than 0.05 indicates that the predicted probabilities and the actual outcome agree poorly. In the calibration plot, a perfect calibration curve would lie exactly on the diagonal line.

Internal validity

A prediction model can be validated internally to provide a more accurate estimate of model performance in other populations. As an internal validation of our model, we used the leave-one-out cross-validation method[20, 34] assessing overall performance (Brier), discrimination (AUC), and calibration (see online repository for further explanations).

Sensitivity analyses

To test the robustness of the model developed in our original study population (P0), we performed sensitivity analyses using modified inclusion criteria at baseline or modified definitions of the outcome, resulting in slight changes of the study populations (P1 to P4, described in more detail in Tables E3 and E4 of the online repository).

We first applied our existing prediction model to these modified populations and calculated the scaled Brier score and AUC (Sensitivity analysis I). Second, we developed new models within the slightly modified study populations P1 to P4, and assessed their performance (Sensitivity analysis II).

Clinical prediction tool

To simplify our model to a practical tool, we considered three different approaches: a) multiplying regression coefficients by factors 10, 5 and 3 and rounding them to the nearest integer;[20] b) setting the penalty of the LASSO-penalized logistic regression so that only a few important predictors (5 or 3) were retained, and c) considering a

model with frequency of wheeze as the only predictor.[19] All these approaches aimed to reduce the number of variables while maintaining a comparable predictive performance.

Results

Study population

At the baseline survey, 5878 of 6808 children were aged 1-3 years. Of these, 3050 (52%) reported episodes of wheeze, cough without colds or cough at night in the past 12 months from which 2444 reported visits to a doctor, making them eligible for the study (Fig 1). For 1226 we had information on any asthma five years later. Their characteristics are shown in Table I for the variables selected by the main model and in Table E1 (online repository) for all potential predictors considered. At baseline, 336 children (27.4%) were aged one year, 702 (57.3%) two years and 188 (15.3%) three years. The mean prediction interval from baseline to outcome was 4.5 (± SD 0.5) years. At school-age, 345 (28.1%) had any asthma.

Table E2 in the online repository compares eligible children with and without follow-up information. The groups were comparable in many aspects (chronic cough, upper respiratory infections, eczema and parental history), but those with follow-up information were more likely to be of white ethnicity and less likely to have wheeze at baseline.

Main prediction model

Of the 38 binary predictors that entered variable selection, the LASSO-penalized logistic regression retained 22 (Table II). The 5 most important predictors were, in order of importance, shortness of breath, frequent wheeze, wheeze without colds, activity disturbance by wheeze and wheeze/cough triggered by exercise. In addition,

the model included aeroallergen-related wheeze/cough, male sex, age, birth weight, gestational age, eczema, upper respiratory symptoms, and parental history of wheeze, asthma, bronchitis or hay fever.

In the original study population, the overall performance of the main model measured by the scaled Brier score was 0.23 and its discriminative ability (AUC) was 0.78. In internal validation, these measures were comparable, 0.20 and 0.76 respectively. The calibration plot (Fig 2) shows good agreement between the predicted probabilities of later asthma and the observed frequencies in internal validation. The same was indicated by the Hosmer-Lemeshow test (p=0.6).

Sensitivity analyses

Sensitivity analyses I: The main model was robust to changes in baseline criteria (P1, P2 in Table E3). When the outcome definition was changed to wheeze plus a doctor's diagnosis of asthma (P3) or to moderately severe asthma (≥4 attacks plus inhaled corticosteroids; P4), the AUC improved to 0.80 and 0.87 respectively (P3 and P4 in Table E3). Sensitivity analyses II: The performance of new models developed in these alternative study populations was comparable to the main model for P1-P3 and slightly improved for P4 (Table E4). The selected predictors and estimated coefficients in the newly developed models (Table E5) were comparable to those of the main model. Severity-related predictors (wheeze without colds, frequent attacks, shortness of breath, activity disturbance) gained comparatively more weight when predicting moderately severe asthma (P4).

Clinical prediction tool

We then simplified the model using the three planned approaches. Our preferred simplification includes 10 variables (13 binary predictors), each of which contributes

with one of 3 values (1, 2 or 3) to the prediction score (Fig 3; an online version of the prediction tool is available on www.leicestercohorts.org).

This tool was derived from the original model by multiplying all regression coefficients with 3 and rounding them to the nearest integer, dropping variables with coefficients rounded to zero.[20] It had almost the same discriminative ability (AUC=0.775) as the main model (AUC=0.782) (Fig.4). Other approaches to simplification retained more predictors (making the tool complicated with little benefit) or had reduced discriminative ability (Table E6), particularly the model with frequency of wheeze only.

In internal validation, the prediction tool showed only a minor decrease in performance compared to the main model: the scaled Brier score was 0.16 and the AUC 0.74.

The maximum score a child can attain using the prediction tool is 15, corresponding to a 95% probability of having any asthma 5 years later (Fig 3). Sensitivity and specificity of the tool are 0.72 and 0.71 for a score of 5, and 0.22 and 0.98 for a score of 10 (additional performance measures are reported in Table E7). In our study sample, 840 (69%) children were at low risk (score ≤5), 288 (23%) at medium risk (score ≥6 and ≤9) and 98 (8%) at high risk (score ≥10) of any asthma 5 years later. The percentage of children with any asthma at school age was 16%, 48% and 79% in the low, medium and high risk groups respectively.

Discussion

Summary of findings

We have developed a new tool for predicting asthma at school-age in preschool children who see a doctor for wheeze or cough. Our tool includes 10 predictors

277 representing wheeze severity and triggers, male sex, age, eczema and parental
278 respiratory history. It showed good internal validity and is distinguished by ease of
279 use in primary care and epidemiological studies.

280 *Comparison with previous prediction models*

281 Several prediction models have been proposed for estimating the risk of persistent
282 asthma in preschool children.[8-16] Table III summarizes inclusion criteria, outcome,
283 methods used to derive the tool, predictors and performance for three tools that used
284 a similar prediction interval as ours and had a sample size of >300. In short, Castro-
285 Rodriguez (Tucson Children's Respiratory Study) used data from 2-3 year-olds with
286 and without respiratory symptoms to develop two prediction tools for asthma at
287 school-age (loose and stringent asthma predictive index, API; Table III).[8]
288 Kurukulaaratchy (Isle of Wight birth cohort) proposed a score for persistence of early
289 wheeze up to age 10.[13] Caudri (PIAMA birth cohort), developed a clinical risk score
290 for 0-4 year-olds with wheeze or cough to predict asthma at age 7-8.[9]
291 The performance of these tools was comparable or slightly less than ours (Table III),
292 with a Youden index[36] (sensitivity + specificity -1) varying from 0.32[8] to 0.38[13]
293 (calculated based on the maximal sum of sensitivity and specificity reported in the
294 respective studies) compared to 0.43 in our study. The Youden index ranges
295 between 0 and 1. Values close to 1 indicate large predictive effectiveness and values
296 close to 0 limited effectiveness.
297 The method used to derive the APIs is difficult to replicate,[8] while methods used for
298 the other tools [9, 13] (logistic regression with stepwise variable selection) tend to over-
299 fit the data, i.e. the models might be overly influenced by the random variation in the
300 data used to develop them. This limits the application of the models to other
301 populations.

Only Caudri et al. performed an internal validation of their prediction model and reported a similar AUC (0.72) to the one we obtained (0.74). They included 8 predictors with exact regression coefficients, while our model includes 10 predictors with simplified regression coefficients that facilitate calculation of individual risks in a clinical setting. The PIAMA risk score and the API have been tested in a small external population.[19, 37]

In comparison to our tool, previous asthma prediction rules included at most two descriptors of wheeze (out of frequency, duration or wheeze without colds).[8-10, 14] In addition, they relied on blood or skin prick tests,[8, 11-13, 15] which are more time consuming, costly and cumbersome than a detailed symptom history.

Socioeconomic position is a proxy measure for a variety of exposures and health care access and might have a variable impact in different populations. [9]

Strengths and limitations

The main strengths of our tool are the objective approach used for its development and its clinical applicability. We used a population-based sample of an adequate size to develop the model. We included only children with health care visits for wheeze or cough, assuring that the sample represents a clinically relevant population. We defined a clinically relevant outcome measure (wheeze needing treatment). When defining a more severe outcome (moderately severe asthma, defined as ≥4 attacks per year and inhaled corticosteroid treatment) the tool performed even better. All predictors are easy to assess in one short primary care consultation or in a questionnaire survey. We used a method that minimizes over-fitting and is less affected by sampling variability compared to stepwise variable selection procedures,[38] and we did an internal validation. Finally, our model predicts a range of probabilities rather than predicting only a low or high risk as the API.[8]

Like other studies,[8, 9, 11, 13] ours relies on parent-reported questionnaire data. However, it uses standardized questions, mostly from the ISAAC-study[39] and reflects to some extent the clinical situation, where parents report respiratory symptoms. The applied questionnaire showed good repeatability[40]. Children with and without follow-up information were comparable (Table E2), although we cannot exclude that selection bias has affected the composition of the final model. Finally, we interpreted missing values in potential predictor variables as an absence of the respective risk factor, which may also have affected the results. However, the number of missing values did not exceed 5.8% in any of the potential predictor variables.

Meaning of the study

Our model was robust and results changed little with modifications of the inclusion criteria and outcomes. In fact, the performance improved (AUC 0.89 vs. 0.78) when we predicted moderately severe asthma, rather than any asthma. After internal validation, the AUC of main model and tool were similar to the ones before validation, suggesting that there was little over-fitting.

Our tool used only information on symptoms that can be gathered in a simple anamnesis. Despite that, it had a similar or better predictive performance than previous tools including more complex measurements.[8, 11, 13-15] This suggests that a detailed description of presented symptoms might predict later asthma equally well as more invasive methods, including blood eosinophilia or skin prick tests.[8, 11, 13-15]

Seven of 10 predictors (including the 5 strongest) describe the symptoms: frequency of attacks, activity disturbance, shortness of breath, triggers (wheeze apart from colds, exercise, aeroallergens) and eczema. This is consistent with the old knowledge that frequent wheeze strongly predicts asthma persistence, [10, 41] and with our previous report, showing that frequency of wheeze predicted asthma nearly as

352 well as the complicated API rule.[19] In our tool, adding more symptoms (in addition to
353 wheeze frequency) improved the performance (AUC after internal validation 0.74 for
354 the tool vs. 0.57 for wheeze frequency only; Table E6). This shows that more
355 detailed assessment of symptoms in pre-school children improves prediction of later
356 asthma.

357 *Future research*

358 To further evaluate the predictive performance of the proposed tool and assess its
359 generalizability to other populations, external validation in independent samples is
360 necessary.[34] We therefore encourage the application and validation of this tool in
361 ongoing epidemiological studies and clinical care (particularly primary care) is. Some
362 earlier prediction models[8, 9, 13] performed similarly in external populations, but their
363 performance remained modest.[15, 19, 37]

364 Compared to other prediction rules, our tool includes detailed description of symptom
365 severity and pattern. This raises the possibility that further refinement in the
366 description of preschool wheeze phenotype might improve precision of prediction of
367 later asthma. Additional gains might be made by detailed assessment of age-related
368 changes, physiological measurements (lung function, bronchial
369 hyperresponsiveness, exhaled nitric oxide, atopy), environmental, socioeconomic
370 and genetic risk factors.[17] All this could, however, compromise the tool's simplicity.

371 *Conclusions*

372 This simple, low-cost and non-invasive tool has good potential for identifying pre-
373 school children at risk for later asthma and should be tested in other populations.

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Table I. Characteristics of the study population (N=1226) at baseline, by development of asthma 5 years later*

		5 yrs later: **Asthma (n=345)**		5 yrs later: **No Asthma (n=881)**		
		n	**(%)**	**n**	**(%)**	**p-value†**
Demographic and perinatal data						
Male		224	(64.9)	454	(51.5)	<0.001
Age (years):	1	85	(24.6)	251	(28.5)	0.388
	2	204	(59.1)	498	(56.5)	
	3	56	(16.2)	132	(15.0)	
Gestational age <37 weeks		35	(10.1)	49	(5.6)	0.006
Birth weight <2500 g		41	(11.9)	68	(7.7)	0.025
Wheeze-related symptoms‡						
Current wheeze		272	(78.8)	425	(48.2)	<0.001
Wheeze without colds		127	(36.8)	95	(10.8)	<0.001
Frequency of attacks:	0	81	(23.5)	476	(54.0)	<0.001
	1-3	111	(32.2)	281	(31.9)	
	4-12	117	(33.9)	106	(12.0)	
	>12	36	(10.4)	18	(2.0)	
Activity disturbance:	no	141	(40.9)	649	(73.7)	<0.001
	little	129	(37.4)	185	(21.0)	
	moderate	57	(16.5)	39	(4.4)	
	a lot	18	(5.2)	8	(0.9)	
Shortness of breath:	never	129	(37.4)	668	(75.8)	<0.001
	sometimes	166	(48.1)	190	(21.6)	
	always	50	(14.5)	23	(2.6)	
Exercise-related wheeze/cough§		196	(56.8)	286	(32.5)	<0.001
Aeroallergen-related wheeze/cough		52	(15.1)	37	(4.2)	<0.001
Other symptoms‡						
Cough without colds		233	(67.5)	536	(60.8)	0.030
Duration of colds (weeks):	<1	75	(21.7)	203	(23.0)	0.194
	1-2	198	(57.4)	533	(60.5)	
	>2	72	(20.9)	145	(16.5)	
Nasal symptoms		186	(53.9)	350	(39.7)	<0.001
Eczema (ever)		190	(55.1)	343	(38.9)	<0.001
Parental history						
Wheeze, asthma or bronchitis:	none	142	(41.2)	499	(56.6)	<0.001
	father	68	(19.7)	136	(15.4)	
	mother	85	(24.6)	182	(20.7)	
	both	50	(14.5)	64	(7.3)	
Hay fever:	none	152	(44.1)	474	(53.8)	0.001
	father	56	(16.2)	144	(16.3)	
	mother	93	(27.0)	203	(23.0)	
	both	44	(12.8)	60	(6.8)	

* This table includes all predictors that were selected for the main model

† Fisher's exact test

‡ During the last 12 months

§ Wheeze or cough with running, playing, laughing or crying

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Table II. Important factors for prediction of asthma at school age in symptomatic preschool children (selected by penalized logistic regression)

		OR	Regression coefficient (RC)	Simplified RC*	Order of inclusion
			Main model	Tool	
Demographic and perinatal data					
Male		1.48	0.394	1	9
Age: >1 year		1.19	0.171	1	16
Gestational age <37 weeks		1.11	0.108		18
Birth weight <2500g		1.17	0.154		17
Wheeze-related symptoms†					
Current wheeze		1.18	0.163		13
Wheeze without colds		1.40	0.337	1	3
Frequency of attacks: >3		1.65	0.500	2	2
Activity disturbance:	any	1.28	0.243	1	4
	moderate or a lot	1.16	0.144		7
	a lot	1.63	0.491	1	13
Shortness of breath:	sometimes or always	1.98	0.684	2	1
	always	1.56	0.442	1	6
Exercise-related wheeze/cough‡		1.26	0.233	1	5
Aeroallergen-related wheeze/cough		1.22	0.198	1	10
Other symptoms†					
Cough without colds		1.09	0.086		18
Duration of colds: at least 1week		0.97	-0.031		22
Nasal symptoms		1.17	0.157		12
Eczema (ever)		1.52	0.420	1	7
Parental history					
Wheeze, asthma or bronchitis:	mother or father	1.23	0.203	1	10
	both parents	1.26	0.235	1	13
Hay fever:	mother or father	1.03	0.025		21
	both parents	1.12	0.110		18

* RC of the main model multiplied by 3 and rounded to the nearest integer (simplification approach where the number of variables was substantially reduced without relevant decrease in predictive performance)

† During the last 12 months

‡ Wheeze or cough with running, playing, laughing or crying

497

Table III. Comparison of four asthma prediction tools for preschool children

	Leicester (present study) (Leicestershire Respiratory Cohort Studies)	**Tucson (API)[8]*** Tucson Children's Respiratory Study	**IoWBC[13]** Isle of White Birth Cohort	**PIAMA[9]** Prevention and Incidence of Asthma and Mite Allergy
N (included in analysis)	1226	776	336	2054
Inclusion criteria				
Age (y)	1-3	2-3	4	1-4
Symptoms	Health care visit due to respiratory problems plus at least one of the following symptoms in the past 12 months: Wheeze, cough without colds, cough at night	Entire cohort (including a majority of children without symptoms)	Wheeze at ages 1,2 and 4 yrs	Wheeze or cough at night without colds (or both) in the past 12 months
Outcome definition				
Age (y)	6-8	8	10	7-8
Prediction interval (y)	4-5	5	6	3-7
Criteria	Wheeze plus asthma medication (past 12 mo)	Doctor's diagnosis of asthma plus current wheeze, or more than 3 wheeze episodes (past 12 mo)	Current wheeze	At ages 7 and 8y: Current wheeze or prescription of inhaled corticosteroids or doctor's diagnosis of asthma (past 12 mo)
Outcome prevalence	28.1 %	13.7%	37.2%	11.7%
Predictor variables included in tool	Male sex, Age: >1y, wheeze without colds, frequent wheeze, activity disturbance, shortness of breath, exercise-related wheeze/cough†, aeroallergen-related wheeze/cough, eczema, parental asthma or wheeze bronchitis	Wheeze, frequent wheeze‡ , wheeze without colds, eczema, parental asthma, blood eosinophilia, allergic rhinitis	Family history of asthma, recurrent chest infections (at 2yrs), skin prick test positivity (at 4yrs), nasal symptoms (at 1yr)	Male sex, post term delivery, wheeze/dyspnea without colds, frequent wheeze, eczema, respiratory infections, inhalation medication (parents), parental education
Method used to derive tool	Penalized logistic regression	The combination of predictors was chosen that yielded the highest PPV and specificity	Stepwise backward logistic regression	Stepwise backward logistic regression
Performance measures§	Score-cutoff: ≥5	Loose API	Score-cutoff: ≥3	Score-cutoff: ≥20
Youden index[36]	0.43	0.32	0.38	0.36
Sensitivity (%)	72	51	53	60
Specificity (%)	71	81	85	76
PPV (%)	49	29	68	23
NPV (%)	86	91	74	94

API, Asthma Predictive Index; *PPV*, positive predictive value; *NPV*, negative predictive value.

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

† Wheeze or cough with running, playing, laughing or crying

‡ This variable is only part of the stringent API, but not of the loose API

§ Reported for cut-off where sum of sensitivity and specificity pair was maximal. It is possible that a higher sum of sensitivity and specificity exists at a cut-off point that was not reported in the respective studies.

505 **Figure legends**

506

507 **Fig 1. Wheeze, cough and health care visits in 1 to 3 year-old children.**

508 Proportional Venn diagram for children aged 1 to 3 years, showing frequency of

509 health care visits due to wheeze or cough, current wheeze and chronic cough (cough

510 without colds or cough at night). The shaded grey represents our study population.

511

512 **Fig 2. Calibration plot of main model (assessed in leave-one out cross-**

513 **validation).** Children are grouped into deciles of their predicted probability. The

514 average predicted probability for later asthma among children within each decile is

515 plotted against the actual observed frequency (prevalence) of asthma in that group.

516 The straight line represents perfect calibration.

517

518 **Fig 3. Asthma prediction tool.** For any 1-3-year-old child seeking health care due

519 to wheeze or cough the applicable predictors are summed to a total score in the

520 upper part of the figure. The estimated probability of having asthma 5 years later is

521 given below for different total scores.

522

523 **Fig 4. Receiver operating characteristic (ROC) curves for the main asthma**

524 **prediction model and for the prediction tool.**

525 The dots represent sensitivity and specificity for different cutoff-values of the

526 prediction tool.

527

Figure No.1

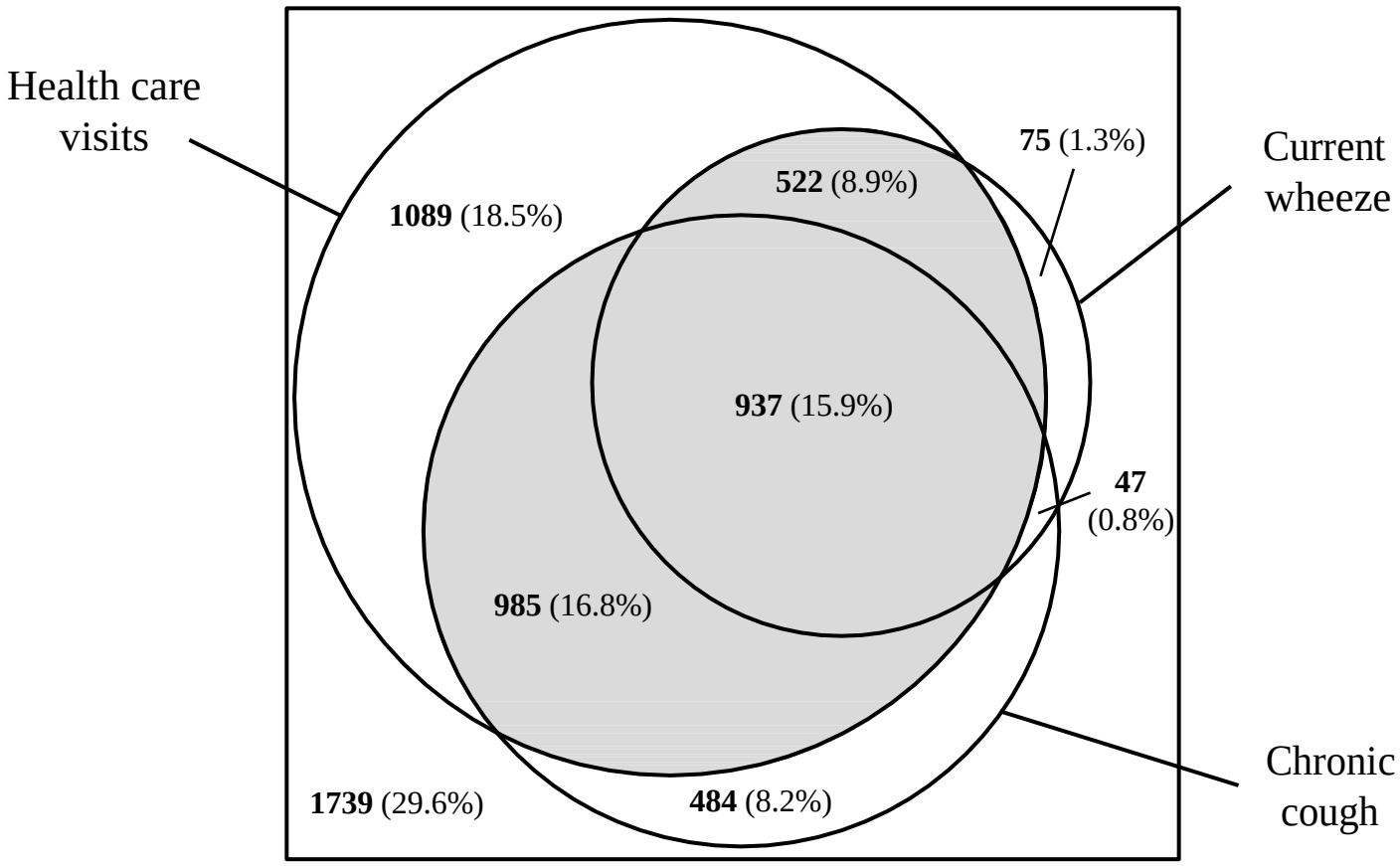

Health care visits
Current wheeze
Chronic cough
1089 (18.5%)
522 (8.9%)
75 (1.3%)
937 (15.9%)
47 (0.8%)
985 (16.8%)
1739 (29.6%)
484 (8.2%)

Figure No.2

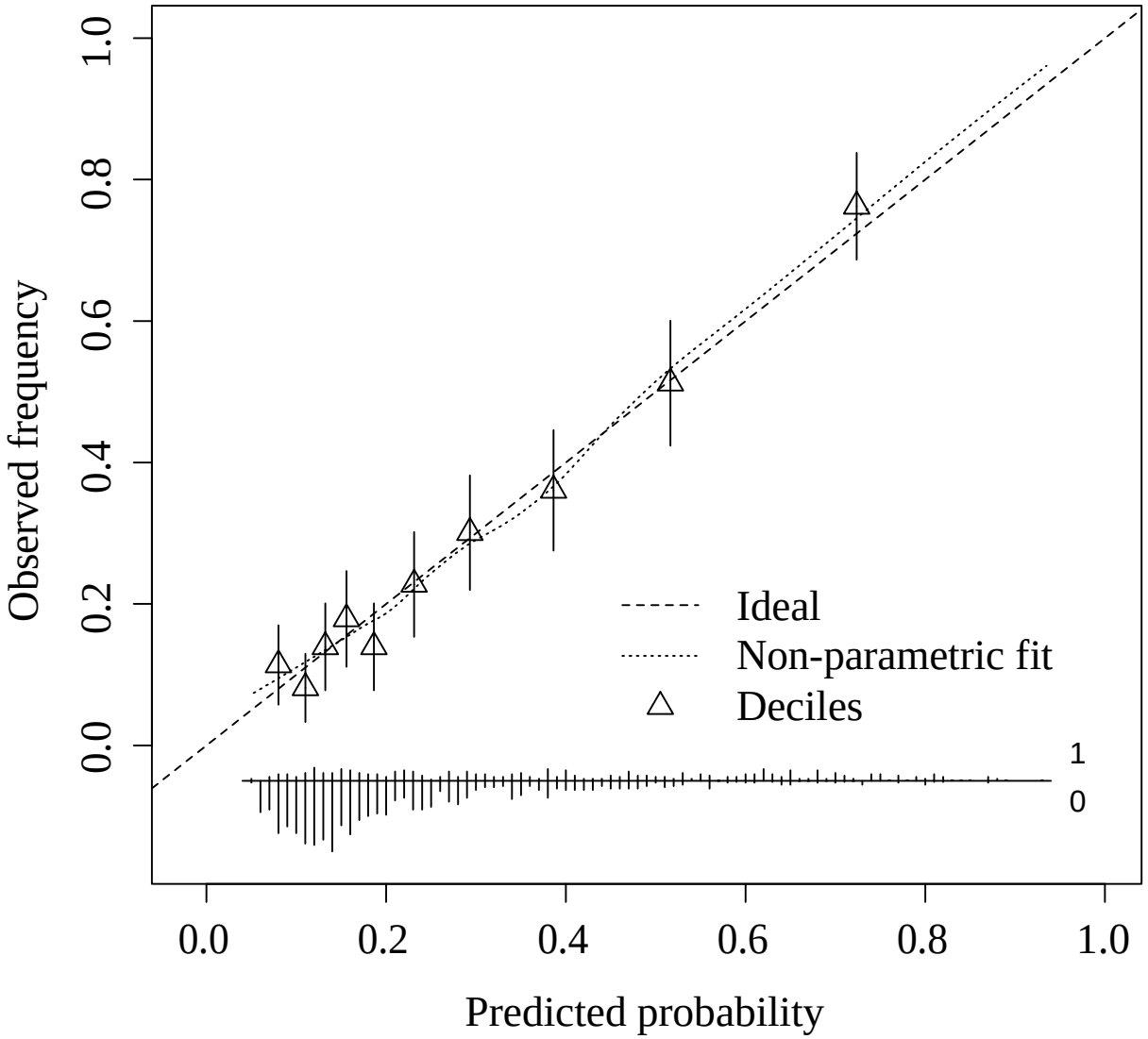

Observed frequency
0.0
0.2
0.4
0.6
0.8
1.0
Predicted probability
0.0
0.2
0.4
0.6
0.8
1.0
Ideal
Non-parametric fit
Deciles
1
0

Figure No.3

Asthma Prediction Tool

1.	What is the child's sex?	Female ☐ 0 Male ☐ 1
2.	How old is the child? (in years)	1 ☐ 0 2 ☐ 1 3 ☐ 1
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 Yes ☐ 1
4.	How many attacks of wheeze has the child had during the last 12 months?	0-3 ☐ 0 >3 ☐ 2
5.	In the last 12 months, how much did wheezing interfere with the child's daily activities?	No ☐ 0 A little ☐ 1 A lot ☐ 2
6.	Do these wheezing attacks cause him/her to be short of breath?	Never ☐ 0 Sometimes ☐ 2 Always ☐ 3
7.	In the last 12 months, did exercise (playing, running) or emotions (laughing, crying or excitement) cause wheezing or coughing in the child?	No ☐ 0 Yes ☐ 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 Yes ☐ 1
9.	Has the child ever had eczema?	No ☐ 0 Yes ☐ 1
10.	Have the child's parents ever suffered from wheezing, asthma or bronchitis?	None ☐ 0 Mother ☐ 1 Father ☐ 1

Total Score = SUM= _____

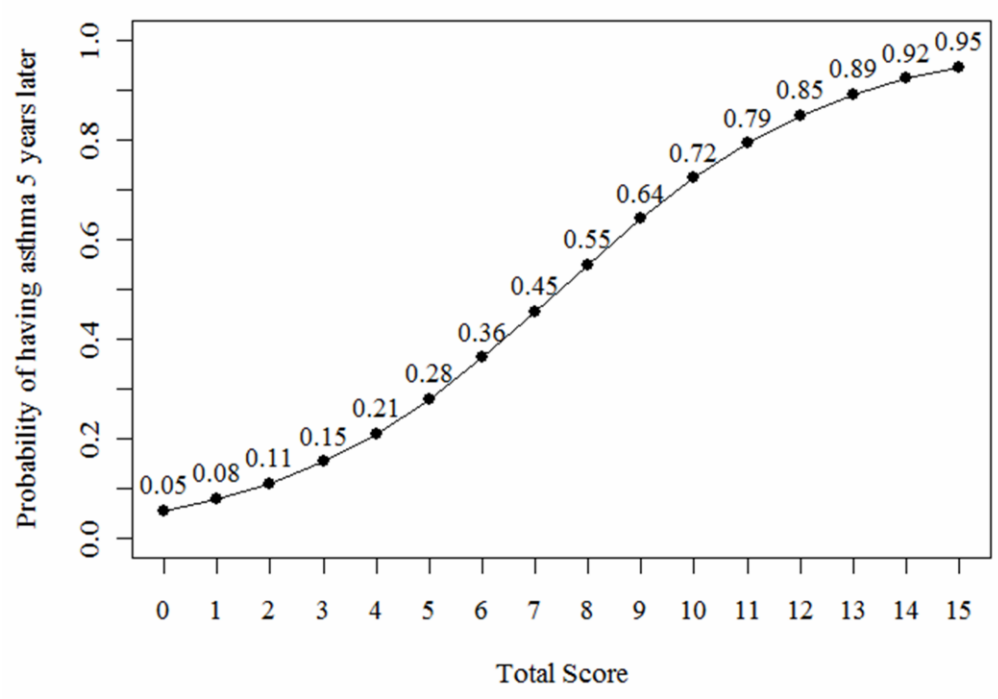
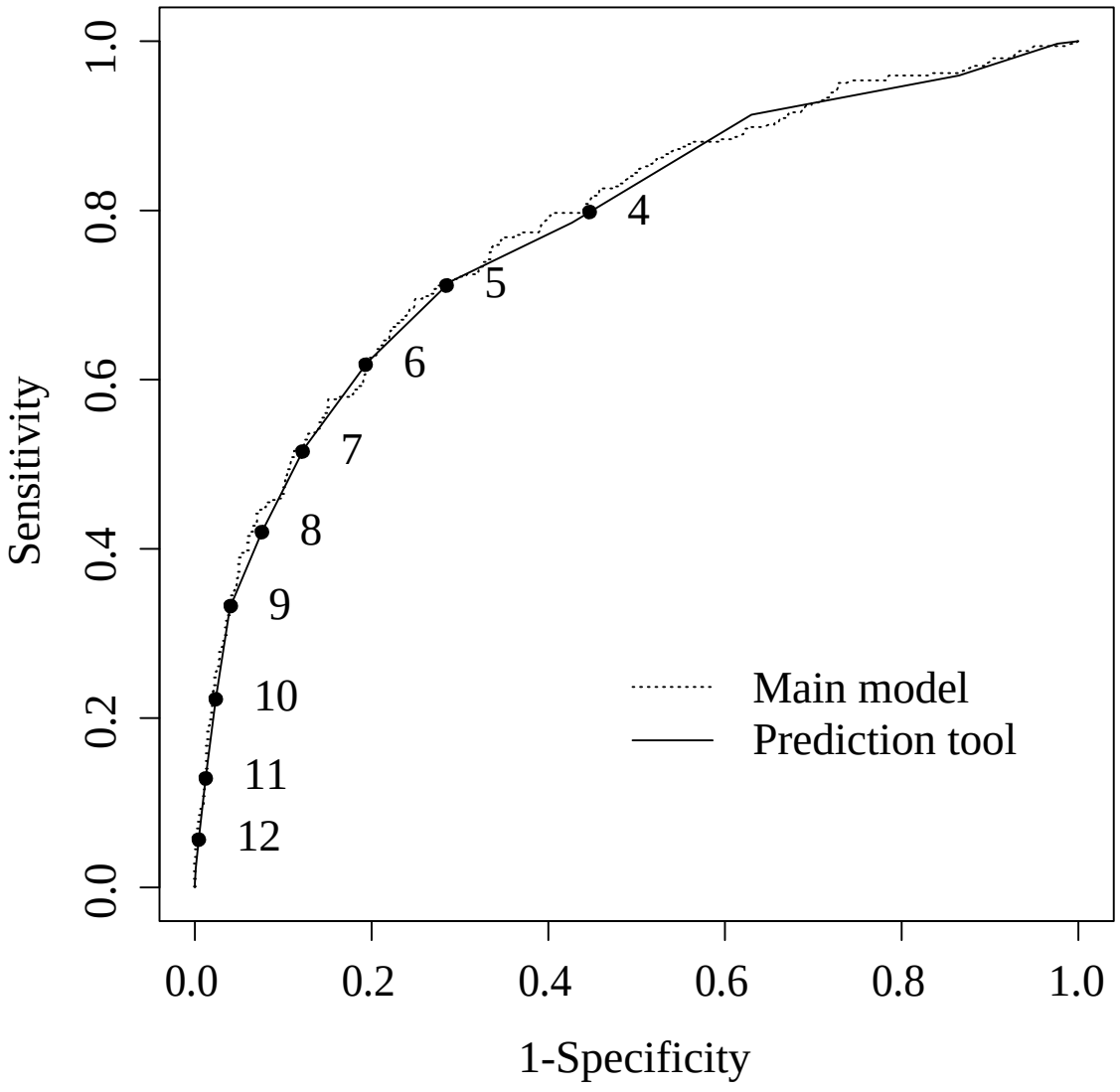


Figure No.4


Sensitivity
1-Specificity
0.0
0.2
0.4
0.6
0.8
1.0
4
5
6
7
8
9
10
11
12
Main model
Prediction tool

A simple asthma prediction tool for pre-school children with wheeze or cough

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* Shared last authorship

Online Repository

Original questions used in questionnaires

Questions used to define inclusion criteria at baseline

1. Has your child had **wheezing or whistling in the chest** in the last 12 months? yes ☐ no ☐

2. Does your child usually have **a cough apart from colds?** yes ☐ no ☐

3. In the last 12 months, has your child had a **dry cough at night**, apart from a cough associated with a cold or a chest infection? yes ☐ no ☐

4. **How often did your child see the GP for coughing or wheezing** during the last 12 months?
   never ☐ once ☐ 2 - 3 times ☐ 4 - 6 times ☐ 7 or more times ☐

5. In the last 12 months, **has wheezing or asthma resulted in your child**:
   - being referred to a consultant in hospital yes ☐ no ☐
   - being admitted to hospital yes ☐ no ☐
   - attending the casualty (A and E) department yes ☐ no ☐
   - attending (or calling) the GP in an emergency yes ☐ no ☐

Questions used to assess outcome at follow-up

7. **Did your child take any of the following** during the last 12 months?
   - **a blue inhaler** (Salbutamol, Ventolin, Bricanyl or other) yes ☐ no ☐ don't know ☐
   - **a brown or orange inhaler** (Pulmicort, Flixotide, Becotide, Beclovent or other) yes ☐ no ☐ don't know ☐
   - **a green inhaler** (Serevent or Oxis) yes ☐ no ☐ don't know ☐
   - **Singulair tablets** (Montelukast) yes ☐ no ☐ don't know ☐
   - **Steroid tablets** (prednisolone) for attacks yes ☐ no ☐ don't know ☐

Questions used as potential predictive factors

8. Has your child had **wheezing or whistling in the chest** in the last 12 months? yes ☐ no ☐

9. In the last 12 months, has your child had wheezing or whistling in the chest even **without** having a cold or flu? yes ☐ no ☐

10. **How many attacks of wheezing** has your child had during the last 12 months?
None ☐ 1 to 3 ☐ 4 to 12 ☐ more than 12 ☐

11. In the last 12 months, how much did **wheezing interfere with your child's daily activities?** not at all ☐ a little ☐ a moderate amount ☐ a lot ☐

12. Do these attacks cause him/her to be **short of breath?**
yes, always ☐ yes, occasionally ☐ no, never ☐

13. In the last 12 months, how often, on average, has your child's **sleep been disturbed due to wheezing**?
Never woken with wheezing ☐ less than one night per week ☐ one or more nights per week ☐

14. In the last 12 months **did the following things cause wheezing in your child**?
- exercise (playing or running) yes ☐ no ☐ don't know ☐
- laughing, crying or excitement yes ☐ no ☐ don't know ☐
- contact with pets or other animals yes ☐ no ☐ don't know ☐
- food or drinks yes ☐ no ☐ don't know ☐

15. Does your child usually have **a cough apart from colds?** yes ☐ no ☐

16. In the last 12 months, has your child had a **dry cough at night**, apart from a cough associated with a cold or a chest infection? yes ☐ no ☐

17. In the last 12 months, **how many times** has your child had a **cold or flu?**
never ☐ 1 - 3 times ☐ 4 - 6 times ☐ 7 -10 times ☐ more than 10 times ☐

18. **How long does a cold** usually **last** in your child?
less than 1 week ☐ 1 to 2 weeks ☐ 2 to 4 weeks ☐ more than 4 weeks ☐

19. In the past 12 months, has your child had **ear infections**?
no, never ☐ yes, once ☐ yes, more than once ☐

20. In the past 12 months, has your child had a problem with **sneezing, or a runny, or blocked nose when he/she did NOT have a cold or the flu?** yes ☐ no ☐

21. Over the past 12 months, has your child **snored** at night? yes ☐ no ☐

22. Has your child ever had **eczema?** (an itchy dry rash on arms, face and legs) yes ☐ no ☐

In the past 12 months, has your child had **eczema**? yes ☐ no ☐

23. Has the **child's father** ever suffered from any of the following conditions?
- **wheezing**? yes ☐ no ☐ don't know ☐
- **asthma**? yes ☐ no ☐ don't know ☐
- **bronchitis**? yes ☐ no ☐ don't know ☐
- **hayfever**? yes ☐ no ☐ don't know ☐

24. Has the **child's mother** ever suffered from any of the following conditions?
- **wheezing**? yes ☐ no ☐ don't know ☐
- **asthma**? yes ☐ no ☐ don't know ☐
- **bronchitis**? yes ☐ no ☐ don't know ☐
- **hayfever**? yes ☐ no ☐ don't know ☐

Details of statistical methods

Development of the main prediction model

We used the R package glmnet to fit the penalized logistic regression. The parameter alpha was set to 1 so that only a LASSO type penalty was included. This tends to retain only the most influential predictors. The parameter lambda, which determines the magnitude of the penalty was set to a value that maximized the area under the receiver operating characteristic curve of resulting predictions in 10-fold cross-validation[1]. All potential predictors with more than 2 response categories were coded as binary variables. If the original categories were ordered, these dichotomous variables represented all possible cut-off points separating lower from higher categories. For instance, frequency of wheezing episodes in the past 12 months (0, 1-3, 4-12, >12) was coded into 3 binary variables indicating >0, >3, and >12 episodes respectively. This procedure resulted in 38 binary variables entering variable selection. Data were prepared using Stata 11.0 and analysed using R version 2.12.2. We used the R package ROCR to assess discrimination and the functions hosmerlem and val.prob.ci to assess calibration[2].

Clinical prediction tool

To simplify our model to a practical tool, we considered three different approaches: a) multiplying regression coefficients by factors 10, 5 and 3 and rounding them to the nearest integer;[20] b) setting the penalty of the LASSO-penalized logistic regression so that only a few important predictors (5 or 3) were retained, and c) considering a model with frequency of wheeze as the only predictor.[19] All these approaches aimed to reduce the number of variables while maintaining a comparable predictive performance.

In Table E7 the performance of these tools are compared with the main model in sample (sample used for model development) and by internal validation (see below). In a final step, we recalibrated the probabilities for later asthma of the preferred tool by re-running a logistic regression of the outcome on simplified scores.

Internal validation

To assess the reliability of our result of model performance within our study sample (i.e. to test its repeatability within our development sample) we tested our model in leave-one-out cross-validation. The first step in this technique is to omit the first of total n observations and to use the remaining n-1 observations from the entire study sample to develop a new model. Using this new model, the probability for later asthma is estimated for the one observation left out before. In total, this procedure is repeated n times, each time omitting an observation that has not previously been left out. In the end, internal validity of the model is tested based on these estimated probabilities.

Because the purpose was to test the main model's predictive performance and not how the method performs (including variable selection), we chose leave-one-out cross-validation as an internal validation technique that aims to fit models which are very similar to the main model. Other approaches, such as bootstrapping, would result in fitting models that are less similar to the main model, and thus would have tested the repeatability of the method (variable selection approach and estimation of regression coefficients) rather than have validated the main model itself.

References

1. Friedman J, Hastie T, Tibshirani R. Regularization Paths for Generalized Linear Models via Coordinate Descent. J Stat Softw 2010; 33:1-22.
2. Homepage for clinical prediction models. [Cited 2011 November 9.] Available from http://survey.erasmusmc.nl/wiki/mgz-clinpred/doku.php?id=rcode_and_data:chapter15.

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Table E1. Characteristics of the study population (N=1226) at baseline by development of asthma 5 years later (all potential predictors considered in the analysis)

Question number*			Total study population (N=1226)		5 yrs later: Asthma (N=345)		5 yrs later: No Asthma (N=881)		
			n	(%)	n	(%)	n	(%)	p-value†
	Demographic and perinatal data								
	Male		678	(55.3)	224	(64.9)	454	(51.5)	<0.001
	Age (years)	1	336	(27.4)	85	(24.6)	251	(28.5)	0.388
		2	702	(57.3)	204	(59.1)	498	(56.5)	
		3	188	(15.3)	56	(16.2)	132	(15.0)	
	Gestational age <37 weeks		84	(6.9)	35	(10.1)	49	(5.6)	0.006
	Birth weight <2500 g		109	(8.9)	41	(11.9)	68	(7.7)	0.025
	South Asian ethnicity (versus white)		316	(25.8)	78	(22.6)	238	(27.0)	0.127
	Wheeze-related symptoms‡								
8	Current wheeze		697	(56.9)	272	(78.8)	425	(48.2)	<0.001
9	Wheeze without colds		222	(18.1)	127	(36.8)	95	(10.8)	<0.001
10	Frequency of attacks:	0	557	(45.4)	81	(23.5)	476	(54.0)	<0.001
		1-3	392	(32.0)	111	(32.2)	281	(31.9)	
		4-12	223	(18.2)	117	(33.9)	106	(12.0)	
		>12	54	(4.4)	36	(10.4)	18	(2.0)	
11	Activity disturbance:	no	790	(64.4)	141	(40.9)	649	(73.7)	<0.001
		little	314	(25.6)	129	(37.4)	185	(21.0)	
		moderate	96	(7.8)	57	(16.5)	39	(4.4)	
		a lot	26	(2.1)	18	(5.2)	8	(0.9)	
12	Shortness of breath:	never	797	(65.0)	129	(37.4)	668	(75.8)	<0.001
		sometimes	356	(29.0)	166	(48.1)	190	(21.6)	
		always	73	(6.0)	50	(14.5)	23	(2.6)	
13	Sleep disturbance:	never	790	(64.4)	148	(42.9)	642	(72.9)	<0.001
		<1	269	(21.9)	122	(35.4)	147	(16.7)	
		>=1	167	(13.6)	75	(21.7)	92	(10.4)	
14	Exercise-related wheeze/cough§		482	(39.3)	196	(56.8)	286	(32.5)	<0.001
14	Aeroallergen-related wheeze/cough		89	(7.3)	52	(15.1)	37	(4.2)	<0.001
14	Food-related wheeze/cough		186	(15.2)	54	(15.7)	132	(15.0)	0.791
	Other symptoms‡								
15	Cough without colds		769	(62.7)	233	(67.5)	536	(60.8)	0.030
16	Cough at night		631	(51.5)	190	(55.1)	441	(50.1)	0.127
17	Frequency of colds:	<4	447	(36.5)	101	(29.3)	346	(39.3)	0.001
		4-6	461	(37.6)	134	(38.8)	327	(37.1)	
		>6	318	(25.9)	110	(31.9)	208	(23.6)	
18	Duration of colds (weeks):	<1	278	(22.7)	75	(21.7)	203	(23.0)	0.194
		1-2	731	(59.6)	198	(57.4)	533	(60.5)	
		>2	217	(17.7)	72	(20.9)	145	(16.5)	
19	Ear infection(s):	0	599	(48.9)	151	(43.8)	448	(50.9)	0.020
		1	351	(28.6)	99	(28.7)	252	(28.6)	
		>1	276	(22.5)	95	(27.5)	181	(20.5)	
20	Nasal symptoms		536	(43.7)	186	(53.9)	350	(39.7)	<0.001
21	Snoring		880	(71.8)	267	(77.4)	613	(69.6)	0.006
22	Eczema (ever)		533	(43.5)	190	(55.1)	343	(38.9)	<0.001

	Parental history								
23/24	Wheeze, asthma or bronchitis:	none	641	(52.3)	142	(41.2)	499	(56.6)	<0.001
		father	204	(16.6)	68	(19.7)	136	(15.4)	
		mother	267	(21.8)	85	(24.6)	182	(20.7)	
		both	114	(9.3)	50	(14.5)	64	(7.3)	
23/24	Hay fever:	none	626	(51.1)	152	(44.1)	474	(53.8)	0.001
		father	200	(16.3)	56	(16.2)	144	(16.3)	
		mother	296	(24.1)	93	(27.0)	203	(23.0)	
		both	104	(8.5)	44	(12.8)	60	(6.8)	

* See Online Repository: Original questions used in questionnaires

† Fisher's exact test

‡ During the last 12 months

§ Wheeze or cough with running, playing, laughing or crying

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Table E2. Characteristics of children at baseline, by availability of follow-up information (N=2444)

		Follow-up information available (N=1226)		Follow-up information not available (N=1218)		
		n	**(%)**	**n**	**(%)**	**p-value***
Demographic and perinatal data						
Male		678	(55.3)	633	(52.0)	0.105
Gestational age <37 weeks		84	(6.9)	86	(7.1)	0.874
Birth weight <2500 g		109	(8.9)	86	(7.1)	0.101
South Asian ethnicity (versus white)		316	(25.8)	386	(31.7)	0.001
Wheeze-related symptoms†						
Current wheeze		697	(56.9)	762	(62.6)	0.004
Wheeze without colds		222	(18.1)	272	(22.3)	0.010
Frequency of attacks:	0	557	(45.4)	482	(39.6)	0.012
	1-3	392	(32.0)	419	(34.4)	
	4-12	223	(18.2)	269	(22.1)	
	>12	54	(4.4)	48	(3.9)	
Activity disturbance:	no	790	(64.4)	725	(59.5)	0.044
	little	314	(25.6)	371	(30.5)	
	moderate	96	(7.8)	91	(7.5)	
	a lot	26	(2.1)	31	(2.5)	
Shortness of breath:	never	797	(65.0)	749	(61.5)	0.193
	sometimes	356	(29.0)	387	(31.8)	
	always	73	(6.0)	82	(6.7)	
Sleep disturbance:	never	790	(64.4)	728	(59.8)	0.059
	<1	269	(21.9)	304	(25.0)	
	>=1	167	(13.6)	186	(15.3)	
Exercise-related wheeze/cough‡		482	(39.3)	531	(43.6)	0.033
Aeroallergen-related wheeze/cough		89	(7.3)	104	(8.5)	0.261
Food-related wheeze/cough		186	(15.2)	196	(16.1)	0.540
Other symptoms†						
Cough without colds		769	(62.7)	798	(65.5)	0.152
Cough at night		631	(51.5)	612	(50.2)	0.571
Frequency of colds:	<4	447	(36.5)	420	(34.5)	0.498
	4-6	461	(37.6)	484	(39.7)	
	>6	318	(25.9)	314	(25.8)	
Duration of colds (weeks):	<1	278	(22.7)	268	(22.0)	0.897
	1-2	731	(59.6)	737	(60.5)	
	>2	217	(17.7)	213	(17.5)	
Ear infection(s):	0	599	(48.9)	613	(50.3)	0.481
	1	351	(28.6)	322	(26.4)	

	>1	276	(22.5)	283	(23.2)	
Nasal symptoms		536	(43.7)	569	(46.7)	0.143
Snoring		880	(71.8)	877	(72.0)	0.928
Eczema (ever)		533	(43.5)	548	(45.0)	0.464
Parental history						
Wheeze, asthma or bronchitis:	none	641	(52.3)	647	(53.1)	0.581
	father	204	(16.6)	178	(14.6)	
	mother	267	(21.8)	276	(22.7)	
	both	114	(9.3)	117	(9.6)	
Hay fever:	none	626	(51.1)	646	(53.0)	0.702
	father	200	(16.3)	199	(16.3)	
	mother	296	(24.1)	271	(22.2)	
	both	104	(8.5)	102	(8.4)	

* Fisher's exact test

† During the last 12 months

‡ Wheeze or cough with running, playing, laughing or crying

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Table E3. **Sensitivity analysis I**: Testing performance of *main asthma prediction model* in alternative study populations

	Baseline criteria 1-3 year-olds			**Outcome definition** 5 yrs later							
Study population	Health care visit and any wheeze or chronic cough	Health care visit and any wheeze	Any wheeze	Any wheeze and asthma medication	Any wheeze and ever doctor-diagnosed asthma	>4 episodes of wheeze and inhaled corticosteroids	**N** Total	**n** Outcome	**(%)**	**Brier (scaled)**	**AUC***
P0 (used for main model)	✓			✓			1226	345	(28.1)	0.23	0.78
P1			✓	✓			769	285	(37.1)	0.21	0.77
P2		✓		✓			697	272	(39.0)	0.22	0.77
P3	✓				✓		1239	331	(26.7)	0.25	0.80
P4	✓					✓	1053	71	(6.7)	-0.51†	0.87

Baseline and outcome criteria refer to the past 12 months, if not otherwise stated

*Area under receiver operating characteristic curve

† The negative scaled Brier score is due to the large difference in the prevalence of the outcome in P0 and P4. A simple recalibration without changing the score would lead to a scaled Brier score of 0.24

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Table E4. Sensitivity analysis II: Testing performance of *newly developed asthma prediction models* based on alternative study populations

	Baseline criteria 1-3 year-olds			**Outcome definition** 5 yrs later								
Study population	Health care visit and any wheeze or chronic cough	Health care visit and any wheeze	Any wheeze	Any wheeze and asthma medication	Any wheeze and ever doctor-diagnosed asthma	>4 episodes of wheeze and inhaled corticosteroids	**No. of binary predictors in the model**	**N** Total	**n** Outcome	**(%)**	**Brier (scaled)**	**AUC***
P0 (used for main model)	✓			✓			22	1226	345	(28.1)	0.23	0.78
P1			✓	✓			25	769	285	(37.1)	0.22	0.77
P2		✓		✓			23	697	272	(39.0)	0.23	0.78
P3	✓				✓		26	1239	331	(26.7)	0.26	0.81
P4	✓					✓	20	1053	71	(6.7)	0.28	0.89

Baseline and outcome criteria refer to the past 12 months, if not otherwise stated

*Area under receiver operating characteristic curve

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TABLE E5. Selected predictors in sensitivity analysis II and corresponding ORs

		Main model*	New models (alternative populations)			
		Odds Ratio (OR)	P1† OR	P2‡ OR	P3§ OR	P4‖ OR
Demographic and perinatal data						
Male		1.48	1.43	1.49	1.68	1.00
Age (years)	≥2	1.19	1.53	1.51	1.28	1.00
	3	1.00	1.00	1.01	1.06	0.95
Gestational age <37 weeks		1.11	1.13	1.00	1.16	1.00
Birth weight <2500 g		1.17	1.18	1.28	1.34	1.00
South Asian ethnicity (versus white)		1.00	1.00	1.00	1.00	0.53
Wheeze-related symptoms¶						
Current wheeze		1.18	1.00	1.00	1.59	1.46
Wheeze without colds		1.40	1.55	1.45	1.42	2.11
Frequency of attacks	≥1	1.00	1.00	1.00	1.05	1.00
	>3	1.65	1.53	1.60	1.37	1.16
	>12	1.00	1.00	1.00	1.00	2.10
Activity disturbance	any	1.28	1.30	1.25	1.28	1.49
	moderate or a lot	1.16	1.31	1.17	1.14	1.00
	a lot	1.63	1.94	1.87	1.81	2.18
Shortness of breath	sometimes or always	1.98	1.90	1.91	1.84	2.06
	always	1.56	1.40	1.41	2.10	2.70
Sleep disturbance	≥1/week	1.00	1.00	1.00	1.10	1.00
	>1/week	1.00	1.00	1.00	1.00	1.20
Exercise-related wheeze/cough**		1.26	1.09	1.15	1.40	1.27
Aeroallergen-related wheeze/cough		1.22	1.05	1.04	1.33	1.00
Food-related wheeze/cough		1.00	1.03	1.02	0.97	1.00
Other symptoms¶						
Cough without colds		1.09	1.10	1.07	1.16	1.37
Cough at night		1.00	1.12	1.13	1.06	1.00
Frequency of colds	>3	1.00	1.00	1.00	1.00	1.06
	>6	1.00	0.97	1.00	1.00	1.00
Duration of colds (weeks)	≥1	0.97	0.89	0.90	0.80	1.00
	>2	1.00	1.00	1.00	1.00	1.00
Ear infection(s)	≥1	1.00	1.13	1.00	1.00	1.00
	>1	1.00	1.00	1.00	1.00	1.00
Nasal symptoms		1.17	1.14	1.13	1.18	1.14
Snoring		1.00	1.00	1.00	1.00	1.00
Eczema (ever)		1.52	1.42	1.50	1.39	1.62
Parental history						
Wheeze or bronchitis	mother or father	1.23	1.14	1.06	1.45	1.07
	mother or both	1.00	1.00	1.00	1.00	1.00
	both parents	1.26	1.57	1.36	1.39	2.02
Hay fever	mother or father	1.03	1.00	1.00	1.00	1.09
	mother or both	1.00	1.05	1.01	1.00	1.00

both parents	1.12	1.28	1.37	1.41	1.34

Baseline and outcome criteria refer to the past 12 months, if not otherwise stated

* Inclusion criteria: 1-3 year-olds with health care visit plus either wheeze or cough without colds or cough at night;
Outcome: Wheeze plus asthma medication at age 6-8 yrs

† Inclusion criterion: 1-3 year-olds with wheeze; Outcome: same as in main model

‡ Inclusion criteria: 1-3 year-olds with health care visit plus wheeze; Outcome: same as in main model

§ Inclusion criteria: same as in main model; Outcome: Current wheeze plus doctor's diagnosis of asthma (ever) at age 6-8 yrs

" Inclusion criteria: same as in main model; Outcome: >4 episodes of wheeze and using inhaled corticosteroids

¶ During the last 12 months

**Wheeze or cough with running, playing, laughing or crying

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Table E6. Predictive performance of simplified versions of the main asthma prediction model

Simplification approach		No. of binary predictors in the model	Brier score (scaled)		AUC*	
Main model	no simplification	22	before val‖ 0.23	after val¶ 0.20	before val‖ 0.78	after val¶ 0.76
Rounded model†	factor 10	20	0.23	0.19	0.78	0.75
	factor 5	19	0.23	0.21	0.78	0.77
	factor 3††	13	0.22	0.16	0.78	0.74
Reduced model	first five predictors only‡	5	0.14	0.13	0.75	0.64
	first three predictors only§	3	0.12	0.11	0.73	0.60
Frequent wheeze only**		3	0.13	0.12	0.70	0.57

* Area under receiver operating characteristics curve

†: Using simplified regression coefficients of the model (regression coefficients of main model multiplied by 10, by 5 or by 3, respectively, and rounded to the next integer)

‡ Shortness of breath due to wheeze, frequent wheeze episodes (>3), wheeze without colds, activity disturbance due to wheeze; exercise-related wheeze/cough

§ Shortness of breath due to wheeze, frequent wheeze episodes (>3), wheeze without colds

" Before internal validation: assessment using same sample as used to develop the model

¶ After internal validation: assessment using leave-one-out crossvalidation

** A 4-level variable coded as 3 binary dummy variables; analysis using logistic regression without penalization

†† Preferred model

Table E7. Performance measures of the prediction tool for different cutoff-values (calculated in sample used to develop the tool without crossvalidation)

Score-cutoff	Sensitivity	Specificity	PPV	NPV	LR+	LR-
0	>0.99	<0.01	0.28	NA	1.00	*
1	>0.99	0.02	0.29	0.95	1.02	0.12
2	0.96	0.14	0.30	0.89	1.11	0.30
3	0.91	0.37	0.36	0.92	1.45	0.23
4	0.79	0.57	0.42	0.87	1.84	0.37
5	0.72	0.71	0.49	0.86	2.47	0.40
6	0.62	0.80	0.55	0.84	3.18	0.47
7	0.52	0.88	0.62	0.82	4.19	0.55
8	0.42	0.92	0.68	0.80	5.53	0.63
9	0.33	0.96	0.77	0.79	8.32	0.70
10	0.22	0.98	0.79	0.76	9.36	0.80
11	0.13	0.99	0.80	0.74	10.45	0.88
12	0.06	>0.99	0.83	0.73	12.77	0.95
13	0.02	>0.99	0.89	0.72	20.43	0.98
14	0.01	>0.99	>0.99	0.72	*	0.99
15	<0.01	>0.99	NA	0.72	*	>0.99

PPV, positive predictive value; *NPV*, negative predictive value; *LR+*, likelihood ratio positive; *LR-*, likelihood ratio negative

Sensitivity, Specificity, PPV, NPV: restricted to values between 0 and 1

* Great uncertainty of estimate due to sensitivity and specificity close to 0 or 1

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