The role of IgG and IgE in the development of allergy and asthma
Eijsink, P.E.D.

Citation for published version (APA):
Eijsink, P. E. D. (2004). The role of IgG and IgE in the development of allergy and asthma

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Accuracy of specific IgE in the prediction of asthma:
Development of a scoring formula for general practice

P.E.D. Eysink, G. ter Riet, R.C. Aalberse,
W.M.C. van Aalderen, C.M. Roos,
J.S. van der Zee, P.J.E. Bindels

British Journal of General Practice (Accepted for publication)
Abstract

**Aim** To assess the predictive accuracy of specific IgE to cat, dog and/or house dust mite in young children for the subsequent development of asthma at the age of 6.

**Design** Prospective follow-up study.

**Setting** 72 general practices.

**Methods** 654 children, aged 1-4, visiting their GPs for persistent coughing (≥5 days), were tested for IgE antibodies by RAST. Parents completed a questionnaire on potential risk indicators. The IgE positive (12.7%) and a random sample of the IgE negative (<0.5 U/ml) children were followed up to the age of 6 when the asthma status was established.

**Main outcome measures** Asthma at the age of 6 (combination of both symptoms and/or use of asthma medication, and impaired lung function).

**Results** Addition of RAST results to a prediction model based on age, wheeze, and family history of pollen-allergy, increased the area under the ROC curve from 0.76 to 0.87. Furthermore, RAST improved patient discrimination as indicated by a change in the range of asthma probabilities from 6 to 75% before the IgE test, to 1 to 95% after the IgE test.

**Conclusion** Sensitization to inhalant-allergens in 1-4 year olds, as shown by RAST, is a useful diagnostic indicator for the presence of asthma at the age of 6, even after a clinical history has been obtained. Preferably, this model should be validated in a new population before it can be applied in practice.

Introduction

In general practice, coughing is the main complaint in about 13% of all consultations for 0-4 year olds [1]. For GPs it is difficult to identify the subgroup of children for whom the risk to develop asthma is high enough to
justify (a more aggressive) treatment. After all, the majority of the children with isolated cough will not develop asthma [2].
According to international consensus [3,4], asthma in children younger than 6 years of age is predominantly a clinical diagnosis, based on the presence of recurrent coughing and wheezing. In those children, the equipment for assessing lung function is neither easily nor routinely used [5]. In the majority of the children over two with asthma, allergies play an important role [6,7]. Therefore, in these young children GPs might decrease their diagnostic uncertainty by establishing whether an allergy is present, in addition to information from clinical history. If an allergy is present, this may have consequences for clinical management [3,8].
Therefore, we assessed the extent to which the determination of specific IgE to cat, dog, and house dust mite-in addition to the easier obtainable information from the clinical history—may help GPs to predict asthma.

Patients and Methods

Selection of the study population
Between February 1995 and February 1997, 72 general practitioners in the northwestern part of the Netherlands, included one to four year old children in a study on the development of inhalation allergy and asthma in preschool children. Children with complaints of coughing for at least the previous five days and their parents visiting their GP were invited to participate and informed consent was obtained from the parents.
At baseline, data on age, gender and geographical region were collected. Furthermore, the parents completed a structured questionnaire with 11 questions on duration of coughing, presence of atopy in the family, breast-feeding, infantile eczema, smoking by parents and contact with pets. A blood sample was obtained from the children and total IgE and specific IgE for cat, dog and house dust mite were determined. The IgE positive children
were matched to IgE negative children in each of the 16 strata defined by age (4 categories of one year), gender and region (urban vs. rural). In case an IgE negative control could not be traced \( n = 12 \), was not willing to participate \( n = 15 \) or was lost to follow-up \( n = 16 \), a new matched control was selected among the IgE negatives from the original cohort.

At the age of six, the parents of the IgE positive and a selection of the IgE negative children were contacted again. Their written consent was asked for reviewing the child's medical record at the GP's office and a lung function measurement at the clinic, to determine the child's asthma status. At that time, parents completed two questionnaires on their child's asthma and allergic symptoms [9,10].

The study was approved by the Medical Ethics Committee of the Academic Medical Center, University of Amsterdam.

**Laboratory methods**

Total IgE and allergen-specific IgE were determined as described earlier [11]. In brief: blood, obtained by finger prick, was adsorbed on filter paper and eluted. Total IgE was expressed in international units per millilitre (IU/ml), RAST results were expressed in RAST units per millilitre (U/ml, one RAST unit representing approximately 2.4 ng of specific IgE [12]). All test results were corrected for actual amounts of plasma used in the tests, using serum albumin as a reference protein.

**Medical records' review**

The GP or research assistant completed a case record form, which consisted of items on the child's asthma and allergy related symptoms, and medication used during follow-up. These data were used to establish the definitive asthma diagnosis in combination with the results from the lung function tests.
Lung function measurements and histamine challenge

Children were required to withhold all bronchodilators 48 hours before the test. In case of shortness of breath the child was allowed to use salbutamol up to 8 hours before the test. The FEV₁ was measured until three reproducible recordings were obtained, the two best (within 5% or 100 ml of each other) were used for analysis. Measurements were performed with a Pulmoassist 2 spirometer (Jaeger, Wurzburg, Germany). Values for the FEV₁ are those of Zapletal et al [13]. FEV₁ values were obtained on the day the histamine challenge test was performed.

Bronchial histamine challenge tests were performed with a gauged DeVilbiss 646 nebulizer (DeVilbiss, Somerset, MA, USA) with an output of 0.13 ml/min according to the modified method of Cockcroft et al. [14]. A 0.9% phosphate-buffered saline solution and doubling histamine concentrations from 0.03 to 16 mg/ml, were inhaled for two minutes during tidal breathing with the child's nose clipped. FEV₁ was measured 30 and 90 seconds after each inhalation until FEV₁ had fallen by at least 20% from the initial value. The provocation concentration of histamine that induced a 20% fall in FEV₁ (PC₂₀) was calculated from a log-dose response curve.

Data-analysis

Independent variables

The results of the RAST were dichotomized as IgE negative or IgE positive. IgE positivity to cat, dog and/or house dust mite was defined as >0.5 kU/l. The information collected at baseline was used to derive predictor variables for the presence of asthma at the age of six. The questionnaire did not include questions on wheezing. Therefore, we reconstructed the wheezing status at baseline of each child using the medical records.

Dependent variables

Asthma was defined as a combination of both symptoms and/or use of asthma medication, and impaired lung function. Symptoms were defined as:
Figure 7.1 Flow chart of the study design

- Inclusion (index visit), n = 752
  - 1st blood sample
  - Inclusion questionnaire

- Eligible, n = 654

- Lost to follow-up, n = 23
  - IgE-positive, n = 83
  - IgE-negative, n = 571

- House visit, n = 156
  - Questionnaires, blood sample, medical record’s review

- Airway symptoms, asthma medication use, n = 112
  - No symptoms, no asthma medication, n = 44

- No lung function, n = 34*
  - Lung function, n = 78
  - Provocation test, n = 72

- Airway symptoms and/or use of asthma medication in previous 12 months and positive lung function

- Asthma status missing, n = 27

- Asthma, n = 34**

- No asthma, n = 95**

*no lung function test, reasons:
  - Unable to perform LF, n = 5
  - Not motivated, no time, n = 10
  - No symptoms anymore, n = 7
  - Unknown, n = 12

** Because of missing data for wheezing, the data of 33 children with asthma and 90 children without asthma were used in the final analyses.
current complaints or complaints during the previous 12 months of wheezing and/or shortness of breath and/or recurrent coughing. In addition, use of asthma medication was defined as use of $\beta_2$-agonists or inhaled corticosteroids currently or during the previous 12 months. *Impaired lung function* was defined as a positive histamine test. A positive histamine test was defined as $PC_{20} < 8 \text{ mg/ml}$.

All children who had not experienced any symptoms during the previous years and had not used asthma medication were not invited for lung function measurement and were designated as non-asthmatics.

**Multivariable model**

Combinations of demographic characteristics and clinical variables were selected using a forward stepwise logistic regression analysis with asthma as the dependent variable. Likelihood ratio statistics were used as a criterion for selection in the model. Variables with a $P$-value for entry $< 0.05$ and a $P$-value for removal $< 0.10$ were selected in the model. The regression coefficients from the best model were used to derive the probabilities of asthma for each child. Two models were constructed: the first model was based on demographic characteristics and clinical history at baseline. In the second model the RAST results were added. All variables were coded as indicator variables using 0-1 coding.

For each child a score was calculated by multiplying the values of the regression coefficients by zero (in case the child's test result belonged to the reference category) or by one (in any other case). Furthermore, in each model the probabilities of developing asthma were calculated for each child using the formula $probability = \frac{1}{1 + e^{-(\text{score} + \text{constant})}}$, where the constant is the intercept from the regression model. The scores associated with each covariate pattern were plotted against the probabilities of having asthma at the age of six. We accounted for the clustering of an average of 3 children per GP practice using robust variance estimators [15]. The matching proce-
duration was accounted for by a special regression analysis that weights observations by their sampling probability in each of the 16 strata [15].

Finally, we compared the differences between the areas under the curve (AUC) corresponding to the model without and with the RAST-results. The final versions of the two logistic regression models were fitted 10,000 times using bootstrap methodology and the 10,000 corresponding differences between the AUCs were used to construct a more robust confidence interval around this AUC difference.

Data-analysis was performed with SPSS 10.0 for Windows, except for the standard errors of the predicted probabilities and the bootstrapping procedure, which were calculated using STATA 7.0.

**Results**

During the inclusion period, 654 children were eligible, 83 of them (12.7%) were IgE positive for cat, dog and/or house dust mite. 96 test-negatives were selected from the remaining 571 IgE negative children matching the IgE positive children. At the age of six, 23 IgE positive children had been lost to follow-up (Figure 7.1). The children lost to follow-up did not differ significantly at inclusion from the children included in the final analysis. Thus 60 IgE positive and 96 IgE negative children were available for descriptive analysis. 112 children having symptoms and/or using asthma medication were invited for the lung function test. Complete results for lung function were available for 72 out of these 112 children. No children showed airway obstruction as assessed by FEV\(_1\) (FEV\(_1\) <75% FEV\(_1\),pred). Challenge showed 56 children with low PC\(_{20}\) (Table 7.1).

Twenty-seven children did not attend the lung function test or had an insufficient technique, so we had 27 missing values on the dependent variable. In this group of children, both children with and children without symptoms dropped out. No significant differences were found in the distributions of other test results. For six children we could not reconstruct a value for
wheezing from the records or questionnaires. Thus regression analyses were performed on 123 children. The median number of days of coughing before the index visit to the GP was 14 days (IQR = 7-25 days). Table 7.2 shows their general characteristics. Thirty-three (26.8%) children were identified as having asthma: 23 (54.8%) IgE positive and 10 (12.3%) IgE negative children.

**Table 7.1** Clinical characteristics of the children in the study (n = 123)

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>total (n = 123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>use of asthma medication during previous 12 months according</td>
<td>23 (18.7)</td>
</tr>
<tr>
<td>to parents</td>
<td></td>
</tr>
<tr>
<td>respiratory symptoms ever</td>
<td></td>
</tr>
<tr>
<td>wheeze</td>
<td>70 (56.9)</td>
</tr>
<tr>
<td>shortness of breath</td>
<td>26 (21.1)</td>
</tr>
<tr>
<td>respiratory symptoms in previous 12 months</td>
<td></td>
</tr>
<tr>
<td>wheeze</td>
<td>40 (32.5)</td>
</tr>
<tr>
<td>coughing</td>
<td>29 (23.6)</td>
</tr>
<tr>
<td>wheezing at time of inclusion</td>
<td>51 (41.5)</td>
</tr>
</tbody>
</table>

**Lung function characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC as % of predicted²</td>
<td>98.8 (11.3)</td>
</tr>
<tr>
<td>FEV₁ as % of predicted²</td>
<td>107.1 (11.7)</td>
</tr>
<tr>
<td>PC₂₀ (mg/ml)*²</td>
<td>3.0 (3.3)</td>
</tr>
<tr>
<td>PC₂₀ (n, %)*²</td>
<td></td>
</tr>
<tr>
<td>no responsiveness</td>
<td>15 (21.1)</td>
</tr>
<tr>
<td>mild responsiveness</td>
<td>29 (40.8)</td>
</tr>
<tr>
<td>moderate responsiveness</td>
<td>24 (33.8)</td>
</tr>
<tr>
<td>severe responsiveness</td>
<td>3 (4.2)</td>
</tr>
</tbody>
</table>

Data expressed as numbers (percentages), means (± sd) or geometric means (95% CI)

1 27 children did not attend spirometry or were afraid of challenge testing

2 Children with complete data on the lung function tests, n = 72
Table 7.2  Patient characteristics of the children in the study population (n = 123)

<table>
<thead>
<tr>
<th></th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n total</td>
<td>123 (100)</td>
</tr>
<tr>
<td>asthma</td>
<td>33 (26.8)</td>
</tr>
<tr>
<td>gender</td>
<td></td>
</tr>
<tr>
<td>boys</td>
<td>68 (55.3)</td>
</tr>
<tr>
<td>girls</td>
<td>55 (44.7)</td>
</tr>
<tr>
<td>rural region</td>
<td>70 (56.9)</td>
</tr>
<tr>
<td>urban region</td>
<td>53 (43.1)</td>
</tr>
<tr>
<td>mean age at time of 1st RAST in months (± sd)</td>
<td>34.3 (± 11.4)</td>
</tr>
<tr>
<td>age at time of 1st RAST (inclusion) (years)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>24 (19.5)</td>
</tr>
<tr>
<td>2</td>
<td>46 (37.4)</td>
</tr>
<tr>
<td>3</td>
<td>35 (28.5)</td>
</tr>
<tr>
<td>4</td>
<td>18 (14.6)</td>
</tr>
<tr>
<td>specific IgE (1st RAST)</td>
<td>42 (34.1)</td>
</tr>
<tr>
<td>number of positive RAST-scores (1st RAST)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>81 (65.9)</td>
</tr>
<tr>
<td>1</td>
<td>34 (27.6)</td>
</tr>
<tr>
<td>2</td>
<td>5 (4.1)</td>
</tr>
<tr>
<td>3</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>specific IgE in 1st RAST to</td>
<td></td>
</tr>
<tr>
<td>cat</td>
<td>14 (11.4)</td>
</tr>
<tr>
<td>house dust mite</td>
<td>29 (23.6)</td>
</tr>
<tr>
<td>dog</td>
<td>10 (8.1)</td>
</tr>
<tr>
<td>total IgE (95% CI) in IU/ml (1st RAST)</td>
<td>29.7 (0.9-933.6)</td>
</tr>
<tr>
<td>positive family history of asthma</td>
<td>35 (28.5)</td>
</tr>
<tr>
<td>positive family history of allergy for</td>
<td></td>
</tr>
<tr>
<td>house-dust mites</td>
<td>37 (30.1)</td>
</tr>
<tr>
<td>pollen</td>
<td>37 (30.1)</td>
</tr>
<tr>
<td>animals</td>
<td>36 (29.3)</td>
</tr>
</tbody>
</table>

data expressed as numbers (percentages), means (± sd) or geometric means (95% CI)
**Probability of developing asthma at the age of 6**

The prediction model included age at inclusion, wheezing, and family history of pollen-allergy (Table 7.3). Adjustment for the matching procedure yielded similar results as the unadjusted analysis (data not shown). Therefore, the latter was used.

### Table 7.3

Results from logistic regression analyses (odds ratios (with 95% CI) and regression coefficients) for two models with demographic variables, variables with respect to clinical history and specific IgE. All variables included in the model were present (= 1) or absent (= 0) at inclusion. Dependent variable is asthma (n = 123), children without asthma used as references.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>Coefficient</th>
<th>Odds Ratio (95% CI)</th>
<th>Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-4 years of age at inclusion</td>
<td>2.0 (1.0-4.0)</td>
<td>0.7</td>
<td>1.7 (0.8-3.7)</td>
<td>0.5</td>
</tr>
<tr>
<td>Positive family history of allergy for pollen</td>
<td>3.3 (1.4-7.5)</td>
<td>1.2</td>
<td>2.4 (0.9-6.1)</td>
<td>0.9</td>
</tr>
<tr>
<td>Wheeze at inclusion</td>
<td>7.2 (2.6-20.1)</td>
<td>2.0</td>
<td>17.9 (5.0-63.5)</td>
<td>2.9</td>
</tr>
<tr>
<td>Specific IgE (&gt;0.5 IU/ml)</td>
<td>18.7 (5.4-64.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. model with demographic variables and clinical history (n = 123), intercept of the model: -2.7
2. as 1 but model includes specific IgE, intercept of the model: -4.3

Model 1: Score = 0.7*(3-4 years of age) + 1.2*familial allergy for pollen + 2.0*wheeze

Model 2: Score = 0.5*(3-4 years of age) + 0.9*familial allergy for pollen + 2.9*wheeze + 2.9*specific IgE

For both scores the corresponding probabilities of developing asthma can be calculated from

\[ Pr = \frac{1}{1 + e^{\text{score} + \text{intercept}}} \]

For example: The score of a three year old girl, presenting with coughing complaints and having a positive family history of pollen-allergy and who tests negative on all ‘tests’ that make up the clinical history, would be 1.9, which is associated with an asthma probability of 29.6%. After a negative IgE test result her score will be 1.4 and the probability of developing asthma for this girl decreases to 4.9%. After a positive IgE test result her score will be 4.3 and her probability increases to 49.2%. This can also be seen in figures 7.2a and 7.2b.

Minor differences occur in computer derived probabilities and scoring derived probabilities due to rounding of the coefficients in the scoring formula.
The summed scores ranged from 0 to 3.9 for the model without specific IgE (model 1) and from 0 to 7.2 for the model containing specific IgE (model 2), with corresponding predictive values ranging from 6.1% to 75.2% for model 1 (Figure 7.2a) and from 1.3% to 94.5% for model 2 (Figure 7.2b). After the IgE test, the number of children in the extremes of the distribution increased at the expense of the middle range, indicating increased discrimination. The area under the curve (AUC) for the model containing items obtained by history increases from 0.76 (95 CI = 0.68-0.85) to 0.87 (95% CI = 0.80-0.94) when specific IgE is added (Figure 7.3). Bootstrap methodology yielded confidence intervals from 0.65 to 0.84 for model 1 and 0.78 to 0.92 for model 2; the 95% confidence interval for the AUC difference was from 0.04 to 0.22.

**Figure 7.2a** Relation of scores (derived from 3-4 year olds, wheezing, familial allergy for pollen) to probability of developing asthma. Straight line represents a three year old girl with a positive family history of pollen allergy (before IgE test)
For each covariate pattern the probability of developing asthma can be calculated before and after a RAST-result. For example, a three year old child that wheezes and has a negative family history of pollen-allergy had a probability of developing asthma of 48.1%. After a negative or a positive RAST, his/her probability changed to 28.3% and 88.1%, respectively. Consider a GP who is willing to start treatment if the probability of developing asthma is greater than 50%. Since the covariate patterns without wheeze all yield probabilities less than 50%, the GP will refrain from treatment. Not even a positive RAST will change this and can therefore be omitted in these cases. By contrast, for the covariate patterns with wheeze and a negative family history of pollen-allergy, the RAST may very well change the treatment decision.

Figure 7.2b Relation of scores (derived from 3-4 year olds, wheezing, familial allergy for pollen and specific IgE) to probability of presence of asthma. Lines represent girl with a positive family history of pollen allergy after a negative (1) and after a positive (2) IgE test.
Table 7.4  Estimated probability of developing asthma at age 6

<table>
<thead>
<tr>
<th>characteristics</th>
<th>model 1 (without IgE test)</th>
<th>model 2 (with IgE test)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-4 yrs&lt;sup&gt;1&lt;/sup&gt;</td>
<td>pollen&lt;sup&gt;2&lt;/sup&gt;</td>
<td>wheeze&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>no</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>yes</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>

Estimated probabilities with 95% confidence interval between brackets

<sup>1</sup> age at inclusion
<sup>2</sup> family history of allergy for pollen
<sup>3</sup> wheezing at inclusion
<sup>4</sup> number of children with this covariate pattern
Figure 7.3 ROC for the models with asthma as the dependent variable. The first model (1) contains age and variables obtained by clinical history, and the second (2) contains age, clinical history and specific IgE.

Data not bootstrapped:
1. model with age and clinical history (wheeze and family history for pollen-allergy)
   \[ AUC = 0.76 \quad 95\% \text{ CI} = 0.68-0.85 \]
2. model with age, clinical history and specific IgE
   \[ AUC = 0.87 \quad 95\% \text{ CI} = 0.80-0.94 \]
AUC model 1 vs. AUC model 2:
AUC difference = 0.11, \( \chi^2 = 5.61, P = 0.0179 \)

Data bootstrapped:
1. model with age and clinical history (wheeze and family history for pollen-allergy)
   \[ AUC = 0.76 \quad 95\% \text{ CI} = 0.65-0.84 \]
2. model with age, clinical history and specific IgE
   \[ AUC = 0.87 \quad 95\% \text{ CI} = 0.78-0.92 \]
AUC difference = 0.11, 95\% CI = 0.04-0.22
Discussion

In this study, we have investigated the diagnostic accuracy of IgE tests (RAST) to cat, dog and house dust mite for the prediction of asthma at the age of 6 in under-fives presenting with complaints of persistent coughing in primary care. After considering patient characteristics and clinical history, IgE testing improved the predictive accuracy, as indicated by an increase of the area under the curve by 11%. Furthermore, IgE testing improved patient discrimination as indicated by a change in the range of asthma probabilities from 6 to 75% pre-test to 1 to 95% post-test.

As was found in other studies [7,16], wheezing appears to be an important predictor of asthma. Children who did not wheeze had a less than 50% probability of developing asthma, even after a positive IgE test. For purposes of illustration, we used a 50% probability of asthma as a threshold for a GP to decide whether or not to start treatment. In reality, GPs' treatment thresholds may differ. Unfortunately, our study cannot answer the question where a threshold should be. Ultimately, that question can only be addressed by formal cost-effectiveness or cost-utility analyses. The current study may inform such analyses, which may then clarify the proper role of testing for IgE. Three other studies [17-19] examined specific IgE as a diagnostic tool for asthma and found that it was important in predicting asthma. These results are in line with our study, although the children in these studies had wheezing as a presenting symptom and the studies were hospital-based.

There are some limitations to this study. First, this study being based in general practice, the predictive function we constructed is likely to be valid for children who present at GPs' surgeries, and not necessarily for children in the general population. This is important as most research on asthma and allergy in children is either population-based or hospital-based and results from these studies cannot be applied straightforwardly to the primary care situation.

The second limitation is that some children may have received some form(s) of (intermittent) treatment. These were not included in the model. This
implies that the predictive function we describe may be valid under current treatment practices according to international guidelines. If early treatments do not influence the probability of asthma at 6, the function may have wider applicability. Currently, the impact of treatment is still controversial [5,20,21], although there is evidence that early treatment, e.g. inhaled corticosteroids, might improve lung function on the long run. In that case in general practice, where most children with asthma are diagnosed, identifying those young children with a high enough probability of developing asthma is of clinical relevance [21,22].

Data on wheezing was not collected at baseline. Therefore, we reconstructed this variable from the retrospective review of the medical records and questionnaires completed after inclusion. If some random mis-classification is assumed, wheezing may play an even more discriminative role than reported here. There was no significant difference between reported wheeze in the IgE negative and IgE positive children at inclusion. Thus, children in families with a heightened awareness of atopy were not more likely to have reported wheeze and therefore have them recorded.

Ideally speaking, all children at follow-up should have had the same diagnostic procedures. However, in this study, asthma was defined as the presence of asthma related symptoms or use of asthma medication in the previous 12 months, and a positive test result (a positive histamine test) on the lung function test. This means that children without asthma related symptoms or medication in the previous 12 months will be diagnosed as not having asthma. Therefore, in symptom-free children a lung function test was not performed because it does not have any additional value for the diagnosis of asthma.

In diagnostic cohort studies, in contrast to etiologic studies, the emphasis is not on some exposure of interest whose influence is to be quantified and adjusted for confounding factors. Rather, the contrasts in patients’ test results (where ‘tests’ include clinical history items) are used to predict the likelihood of asthma at a later point in time. This also implies that the analysis is
centred around efficiency, that is, optimal prediction using information that becomes available early in the diagnostic work-up and often virtually for free (clinical history). Next, the diagnostic impact of added information that does not come for free (lab test, imaging) is estimated conditional on the information already available. So, the issue of confounding in etiologic cohorts changes into an issue of redundancy of diagnostic information in studies such as the current one [23]. Ideally, a prediction rule should be derived, and then validated prospectively on a separate population. Although we used bootstrapping techniques, the results are likely to be somewhat less robust when applying them to a separate population [24]. Therefore, the prediction rule should be validated in another primary care population.

In conclusion, assessment of specific IgE to inhalants may be helpful in discriminating children with persistent cough (≥5 days) who will and will not develop asthma at the age of six. In particular, children who wheeze may be usefully categorised into low and high risk groups. A simple scoring formula using wheeze and a family history of pollen-allergy in coughing children younger than 5 years of age may support GPs to selectively order an IgE test.

Acknowledgements

The study was supported by a research grant from the Netherlands Asthma Foundation. We would like to thank the GPs, all children and their parents for participating in the study. We would also like to thank J. de Vrieze for performing the RASTs and the Department of Immunoochemistry of the CLB for measuring albumin in the blood samples, S.J.A. Lone-Latif for performing the lung function tests, and A.G.H. Kessels for writing the bootstrap command.
References


