

Sensitization Predicts Asthma Development Among Wheezing Toddlers in Secondary Healthcare

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Summary. Introduction: Some wheezing toddlers develop asthma later in childhood. Sensitization is known to predict asthma in birth cohorts. However, its predictive value in secondary healthcare is uncertain. Aim: This study examines the predictive value of sensitization to inhalant allergens among wheezing toddlers in secondary healthcare for the development of asthma at school age (≥ 6 years). Methods: Preschool children (1–3 years) who presented with wheezing in secondary healthcare were screened on asthma at school age with the International Study of Asthma and Allergies in Childhood questionnaire. The positive and negative predictive value (PPV and NPV) of specific IgE to inhalant allergens (cut-off concentration 0.35 kU/L) and several non-invasive variables from a child's history (such as hospitalization, eczema, and parental atopy) were calculated. The additional predictive value of sensitization when combined with non-invasive predictors was examined in multivariate analysis and by ROC curves. Results: Of 116 included children, 63% developed asthma at school age. Sensitization to inhalant allergens was a strong asthma predictor. The odds ratio (OR), PPV and NPV were 7.4%, 86%, and 55%, respectively. Eczema (OR 3.4) and hospital admission (OR 2.6) were significant non-invasive determinants. Adding sensitization to these non-invasive predictors in multivariate analysis resulted in a significantly better asthma prediction. The area under the ROC curve increased from 0.70 with only non-invasive predictors to 0.79 after adding sensitization. Conclusion: Sensitization to inhalant allergens is a strong predictor of school age asthma in secondary healthcare and has added predictive value when combined with non-invasive determinants. *Pediatr Pulmonol.* 2017; 9999:XX–XX. © 2017 Wiley Periodicals, Inc.

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INTRODUCTION

Approximately one third of all children experience at least one episode of wheezing in the first 3 years of life.^{1,2} About 40% of preschool wheezers in the general population develop asthma later in childhood.^{1,3,4} Pediatricians care for a selected subset of wheezing toddlers, who have relatively severe symptoms and who might be at greater risk of developing asthma. Data from birth cohort studies can therefore not be extrapolated to clinical care.

It is important to identify toddlers most at risk for developing asthma, because early treatment may reduce respiratory symptoms.^{5,6} Furthermore, asthma risk prediction enables healthcare workers to inform parents accordingly and to decide which children should receive follow-up care. Many asthma predictors that have previously been identified (such as age, parental atopy, or eczema) are determinants from a child's history.^{7–9} Invasive tests are also used to predict asthma in wheezing toddlers, such as measurement of specific IgE to inhalant allergens. Because of its invasive nature, specific IgE testing should only be performed if it offers sufficient

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predictive value compared to non-invasive clinical predictors from a child's history.

The predictive value of sensitization to inhalant allergens has mainly been studied in birth cohorts, with odds ratios (OR) varying between 1.8 and 7.4.^{1,4,10,11} As discussed above, this information is not directly applicable to toddlers in secondary healthcare. Little is known about the predictive value in this specific group of wheezing children.^{12,13} This raises the question whether it is justified to measure specific IgE in secondary healthcare and how to interpret test results in daily practice.

The aim of this study is to examine the predictive value of sensitization to inhalant allergens in wheezing toddlers (1–3 years old) in a secondary care setting for the development of asthma at school age (≥ 6 years).

MATERIALS AND METHODS

Study Population

All children who visited the St. Antonius Hospital between January 1, 2007 and December 31, 2011 with wheezing at the age of 1, 2, or 3 years (12–48 months) were retrospectively identified. This was done by screening the medical records of all children with a diagnosis code (in the hospital financial registry) of “asthma/bronchial hyperactivity” or “atopic syndrome of the airways” for wheezing in this time period. The hospital's population consists of patients who are referred to secondary care by their primary care physician for further evaluation of wheezing symptoms or acutely during an exacerbation. Patients who had been admitted to the pediatric ward or who visited the outpatient (emergency) clinic were included. At time of the follow-up questionnaire (April 1, 2014–November 30, 2014) children had to be at least 6 years old. Exclusion criteria were chromosomal abnormalities, major developmental disorders, psychomotor impairment, neuromuscular diseases, other pulmonary disorders (such as bronchopulmonary dysplasia, cystic fibrosis, or anatomical abnormalities), epilepsy and wheezing caused by foreign body aspiration. Additionally, children not currently living in the Netherlands were excluded for logistic reasons. Informed consent was obtained from both parents. The study was judged to be exempt from ethical review by the hospital's ethics committee.

Data Collection

The Dutch version of the “International Study of Asthma and Allergies in Childhood” (ISAAC) core questionnaire was used to collect data about wheezing symptoms at school age.¹⁴ Questions about medical history, possible predictors of asthma and current use of asthma medication were added. Information about specific IgE measurement at the age of 1–3 years and hospitalization for respiratory problems was obtained

from the patients' medical records. Determinants to be analyzed in logistic regression analysis were chosen beforehand, based on previous literature.^{13,15–23}

Specific IgE to house dust mite, cat, dog, a mix of pollens and a mix of moulds was measured by fluoroenzyme-immunometric assay (Immulite, Siemens, Den Haag, the Netherlands). A cut-off concentration of 0.35 kU/L was applied. IgE concentrations below 0.35 were reported as negative. In case specific IgE measurement was performed more than once during the preschool period the first measurement at the age of 1–3 years was used in the analysis.

Definitions

Asthma at school age was defined as the use of corticosteroid inhalant medication in the past 12 months or a positive answer to one or both of the following questions: “Has your child had wheezing in the chest in the last 12 months?” or “In the last 12 months, has your child's chest sounded wheezy during or after exercise?”

Parental atopy was considered to be present when one or both of the parents reported a positive history on asthma, eczema, or hay fever.

Cow's milk allergy was considered to be present if parents reported a positive double-blind placebo-controlled provocation test in their child's history.

Parental smoking was defined as maternal smoking during pregnancy or parental smoking during the first year of life.

Age was dichotomized into children aged 1 or 2 versus 3 years at time of specific IgE measurement, because we wanted to distinguish between children with relatively early and children with late onset of symptoms (and referral to secondary healthcare). This approach was chosen because in some previous studies children with late onset of wheezing were more likely to develop asthma at school age.^{16,18,24}

Data Analysis

SPSS 22.0 for Windows was used for statistical analysis. Differences between groups were compared with Fisher's exact tests for categorical variables and student's *t*-tests for continuous variables. *P*-values smaller than 0.05 were considered statistically significant. In case of missing data, the subjects were excluded from the analysis. The positive predictive value (PPV), negative predictive value (NPV), odds ratio (OR), and likelihood ratio (LR) of sensitization and other candidate predictors were only calculated in the subgroup of children with specific IgE measurement at the age of 1–3 years. The 95% confidence intervals (CI) of the PPV and NPV were calculated with a calculator that corrects for small sample sizes. Odds ratios and the corresponding 95% CI were calculated by logistic regression analysis.

Candidate predictors with a P -value ≤ 0.1 in univariate logistic regression were included in multivariate analysis. In case a covariate showed no statistically significant prediction in multivariate analysis, it was removed from the model. Hereby, the best combination of non-invasive predictors was identified (model 1). Next, sensitization was added (model 2). The additional predictive value of sensitization when combined with non-invasive predictors was determined by comparing the areas under the receiver operating characteristic (ROC) curves of both models. ROC curves were constructed with the predicted probability of asthma for each child, which was calculated according to the formula: $\text{probability} = 1/(1 + e^{-[\text{constant} + \text{RC1} \times \text{Variable1} + \text{RC2} \times \text{Variable2} + \text{RC3} \times \text{Variable3}]})$. The difference between the ROC curves was tested for statistical significance with DeLong's test. Additionally, a likelihood ratio test was performed to examine the improvement of model 2 compared to model 1.

RESULTS

Study Population

Using the financial registry codes 579 children were identified, of which 359 experienced wheezing at the age of 1, 2, or 3 years. Nine children were excluded. Of the remaining 350 children 166 responded (Fig. 1). There were no significant differences between the study population and the children whose parents did not respond regarding gender, age, hospital admission for respiratory symptoms, and the rate of positive specific IgE to inhalant allergens. Parental atopy was slightly less prevalent in the study population. Specific IgE was tested in 116 out of the 166 included children (69.9%) compared to 100 out of the 184 children who did not participate (54.3%).

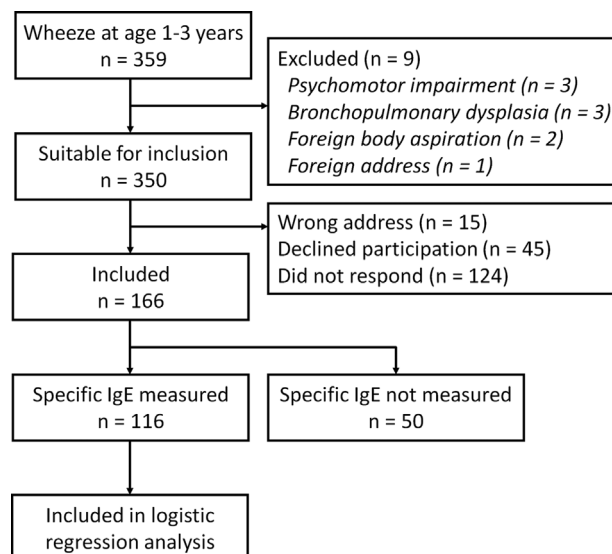


Fig. 1. Flowchart.

The majority of the study population were boys (69.3%). The mean age at follow-up was 7.8 years (Table 1). The 116 children with specific IgE measurement differed significantly from the children without specific IgE measurement regarding current asthma, cow's milk allergy, low birth weight, and parental smoking. There were no significant differences regarding gender, age, ethnicity, parental atopy, hospital admissions, prematurity, breastfeeding, eczema, and day care attendance.

The prevalence of asthma was 54.8% in the whole study population and 62.9% in the subgroup with specific IgE measurement. Of the 73 children with asthma, 36 had both wheezed and used corticosteroid inhalant medication in the past year, 22 had only wheezed, and 15 had only used medication. Forty-two children were 1 year old at time of IgE measurement, 40 were 2 years old, and 34 were 3 years old. Specific IgE was positive in 50 toddlers (43.1%), of which 15 were sensitized to a single allergen (or a single allergen mix) and 34 to multiple allergens (or multiple allergen mixes). In one child it was not possible to measure IgE to the different allergens separately, due to a small blood sample.

Univariate Logistic Regression Analysis

Only the 116 children with specific IgE measurement were included in logistic regression analysis. There were no missing data. Sensitization to inhalant allergens was a relatively strong predictor of asthma. Sensitization to house dust mite was the most common. Sensitization to cat, dog, pollens, or moulds was highly predictive of asthma development: 38 children (32.8%) were sensitized to at least one of these allergens and 35 of them developed asthma (92.1%). However, the negative predictive values were low.

Eczema in the first year of life, hospital admission for respiratory problems in the first 3 years of life and cow's milk allergy (proven by a double-blind placebo-controlled provocation test) were significant predictors from a child's history. Parental atopy and parental smoking did not predict asthma in this cohort (Table 2).

Sensitization to multiple allergens resulted in a higher chance of developing asthma compared to sensitization to a single allergen, with PPVs of 91.2% (CI 76.1–97.6%) and 80.0% (CI 53.9–93.5%), respectively. However, this difference was not statistically significant (P -value 0.353).

Younger children (specific IgE measurement at 12–36 months of age) and older children (specific IgE measurement at 36–48 months of age) had similar PPV (85% and 88%), NPV (55% and 50%), and OR (6.8 and 7.0) for sensitization. The LR+ was better in the young group (4.1 vs. 2.2), but the LR- was worse (0.6 vs. 0.3).

TABLE 1—Characteristics of the Study Population

Characteristics	All (n = 166)	Included in further analysis (n = 116)	Excluded from further analysis (n = 50)	P-value
Demographics				
Gender, male	115 (69.3)	75 (64.7)	40 (80.0)	0.066
Age at follow-up (years)	7.7 ± 1.3 Range 6–11	7.8 ± 1.3 Range 6–11	7.4 ± 1.2 Range 6–10	0.069
Ethnicity, Caucasian ¹	130 (78.8)	86 (74.8)	44 (88.0)	0.064
Outcome (past 12 months)				
Current asthma	91 (54.8)	73 (62.9)	18 (36.0)	0.002
Corticosteroid inhalant medication	63 (38.0)	51 (44.0)	12 (24.0)	0.016
Wheezing (any)	71 (42.8)	58 (50.0)	13 (26.0)	0.006
Wheezing during exercise ¹	32 (19.5)	25 (21.9)	7 (14.0)	0.289
Preschool age				
Parental atopy	103 (62.0)	77 (66.4)	26 (52.0)	0.085
Hospital admission for respiratory problems at age 0–3 years	106 (63.9)	80 (69.0)	26 (52.0)	0.052
Proven cow's milk allergy	12 (7.2)	12 (10.3)	0	0.019
First year of life				
Gestational age <37 weeks	21 (12.7)	11 (9.5)	10 (20.0)	0.076
Birth weight <2,500 g	20 (12.0)	9 (7.8)	11 (22.0)	0.017
Maternal smoking during pregnancy	15 (9.0)	9 (7.8)	6 (12.0)	0.388
Parental smoking during first year of life	33 (19.9)	18 (15.5)	15 (30.0)	0.037
Breast feeding during first 4 months of life	102 (61.4)	69 (59.5)	33 (66.0)	0.489
Eczema in the first year of life ¹	55 (33.3)	40 (34.5)	15 (30.6)	0.719
Day care attendance in first year of life	66 (39.8)	43 (37.1)	23 (46.0)	0.303

Data expressed as number (percentage) or mean ± standard deviation. Patients with specific IgE measurement were included in logistic regression analysis, patients without specific IgE measurement were excluded.

¹Missing observations on ethnicity (n = 1), wheezing during exercise (n = 2), and eczema (n = 1).

Multivariate Logistic Regression Analysis

Eczema in the first year of life combined with hospital admission in the first 3 years of life resulted in the best prediction of asthma at school age based on non-invasive determinants. The odds ratios of these determinants in a combined model were 4.6 (CI 1.7–12.3) and 3.7 (1.5–9.0), respectively (model 1). Cow's milk allergy could not be included in multivariate analysis, because all children with cow's milk allergy developed asthma and the OR would therefore be infinity. Combined with eczema and hospital admission, sensitization remained a strong predictor of asthma (model 2), with respective odds ratios of 2.7 (CI 0.9–7.8), 4.2 (CI 1.5–11.4), and 6.8 (2.4–18.9) in multivariate analysis. The area under the ROC curve was 0.70 (CI 0.60–0.79) for model 1 and 0.79 (CI 0.71–0.88) for model 2 (Fig. 2). This difference was statistically significant (*P*-value 0.024). Also, the likelihood ratio test showed a significantly improved prediction (*P*-value <0.001).

DISCUSSION

Interpretation of Main Findings

A majority of wheezing toddlers in secondary health-care developed asthma at school age. The prevalence of asthma in this cohort (including the children without specific IgE measurement) was 55%, which is higher than

previously reported in birth cohort studies and in primary care setting.^{1,3,4,16,25}

Sensitization to inhalant allergens was a relatively strong predictor of asthma at school age, with a PPV of 86% (CI 73–93%) and a NPV of 55% (CI 43–66%). As the pre-test probability (prevalence) was 63%, a positive test substantially increased the chance of asthma development. However, specific IgE testing was not sufficient to exclude asthma, because 45% of the toddlers with a negative test still developed asthma at school age.

An important objective of asthma risk prediction is to inform caretakers about the expected disease course. IgE measurement offered a relevant distinction between high and moderate risk patients (86% vs. 45% risk of asthma development), which is important to communicate to parents. Also, specific IgE testing may be helpful in therapeutic decisions, although the total clinical presentation (including severity and frequency of wheezing attacks) should obviously be considered.

Likelihood ratios and odds ratios showed that for most individual predictors the shift in asthma probability was limited. However, sensitization to cat, dog, pollens, or moulds was highly predictive of asthma. Children who are sensitized to these allergens should be followed-up by their pediatrician or general practitioner and their parents should be carefully instructed to monitor future asthma symptoms. It is important to note that negative predictive

TABLE 2—Frequency and Predictive Values of Early Life Determinants on Asthma at Preschool Age

Determinant	Frequency total (%) n = 116	Frequency asthma (%) n = 73	Frequency no asthma (%) n = 43	Odds ratio (CI)	P-value	PPV [%] (CI)	NPV [%] (CI)	LR+ (CI)	LR- (CI)
Sensitization (any) ¹	50 (43.1)	43 (58.9)	7 (16.3)	7.4 (2.9–18.8)	<0.001	86.0 (73.4–93.3)	54.5 (42.6–66.0)	3.6 (1.8–7.3)	0.49 (0.37–0.65)
House dust mite ²	37 (31.9)	31 (42.5)	6 (14.3)	4.4 (1.7–11.8)	0.003	83.8 (68.4–92.6)	46.2 (35.5–57.1)	3.0 (1.4–6.5)	0.67 (0.55–0.82)
Cat	27 (23.3)	26 (35.6)	1 (2.4)	22.7 (2.9–174.6)	0.003	96.3 (79.9–100)	46.6 (36.5–56.9)	14.0 (2.1–106.3)	0.66 (0.56–0.78)
Dog	23 (19.8)	22 (30.1)	1 (2.4)	17.7 (2.3–136.8)	0.006	95.7 (77.0–100)	44.6 (34.8–54.7)	12.7 (1.8–90.6)	0.72 (0.61–0.83)
Pollens ³	24 (20.7)	23 (31.5)	1 (2.4)	18.9 (2.4–145.7)	0.005	95.8 (77.8–100)	45.1 (35.3–55.3)	13.2 (1.9–94.5)	0.70 (0.60–0.82)
Moulds ⁴	8 (6.9)	8 (11.0)	0	∞	0.026	100 (62.2–100)	39.3 (30.5–48.7)	∞	0.89 (0.82–0.97)
Eczema in the first year of life	40 (34.5)	32 (43.8)	8 (18.6)	3.4 (1.4–8.4)	0.007	80.0 (64.9–89.7)	46.1 (35.3–57.2)	2.4 (1.2–4.6)	0.69 (0.56–0.85)
Hospital admission for respiratory problems at age 0–3 years	80 (69.0)	56 (76.7)	24 (55.8)	2.6 (1.2–5.9)	0.020	70.0 (59.2–78.9)	52.8 (37.0–68.0)	1.4 (1.0–1.8)	0.52 (0.33–0.85)
Parental atopy	77 (66.4)	51 (69.9)	26 (60.5)	1.5 (0.7–3.3)	0.302	66.2 (55.1–75.8)	43.6 (29.3–59.0)	1.2 (0.87–1.5)	0.76 (0.50–1.2)
Age three years at IgE measurement	34 (29.3)	26 (35.6)	8 (18.6)	2.4 (1.0–6.0)	0.056	76.5 (59.7–87.7)	42.7 (32.6–53.5)	1.9 (0.95–3.8)	0.79 (0.66–0.95)
Gender, male	75 (64.7)	51 (69.9)	24 (55.8)	1.8 (0.8–4.0)	0.128	68.0 (56.7–77.5)	46.3 (32.1–61.2)	1.3 (0.92–1.7)	0.68 (0.45–1.0)
Proven cow's milk allergy	12 (10.3)	12 (16.4)	0 (0)	∞	0.003	100 (71.3–100)	41.3 (32.4–51.0)	∞	0.83 (0.75–0.92)
Parental smoking	21 (18.1)	14 (19.2)	7 (16.3)	1.2 (0.5–3.3)	0.696	66.7 (45.2–82.8)	37.9 (28.8–48.0)	1.2 (0.52–2.7)	0.97 (0.86–1.1)

Frequency: number and percentage of patients in whom the determinant was present; CI: 95% confidence interval; P-value: P-value of Odds ratio; PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio.

¹In one non-asthmatic patient with positive specific IgE it was not possible to measure IgE to the different allergens separately, due to a small blood sample.

²Dermatophagoides pteronyssinus.

³Anthoxanthum odoratum, Lolium perenne, Phleum pratense, Secale cereale, Holcus lanatus, Alnus incana, Betula pendula, Corylus avellana, Quercus alba, Salix caprea, Artemisia vulgaris, Plantago lanceolata, Chenopodium album, Solidago virgaurea, Urtica dioica.

⁴Penicillium chrysogenum, Cladosporium herbarum, Aspergillus fumigatus, Candida albicans, Alternaria alternata.

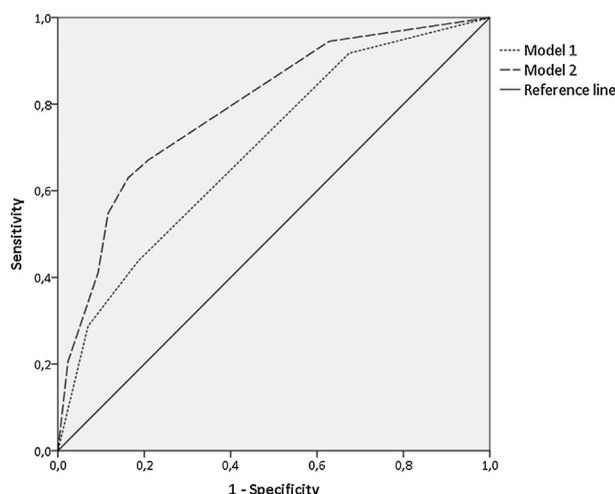


Fig. 2. ROC curves of both multivariate models. The area under the curve of model 1 (containing “eczema in the first year of life” and “hospital admission due to respiratory problems during preschool age”) is 0.70 (CI 0.60–0.79). After adding sensitization to these predictors (model 2), the area under the curve increases to 0.79 (CI 0.71–0.88). This difference is statistically significant (P -value 0.024).

values were low and that the small groups resulted in broad confidence intervals.

Eczema in the first year of life combined with hospital admission for respiratory problems in the first 3 years of life was the best combination of non-invasive predictors. Adding sensitization to these clinical determinants resulted in a clinically relevant and statistically significant increase in discriminative ability.

Parental atopy did not predict asthma in this population (OR 1.5 [CI 0.7–3.3]), unlike in several birth cohort studies.^{4,11,21,22,26} However, consistent to our findings, a family history of atopy did not predict asthma in several other studies in secondary care setting.^{12,13,27}

We did not aim to develop an asthma prediction tool, because of the retrospective nature and limited sample size of our study. Previously published prediction tools were developed in birth cohorts and some showed rather good asthma prediction with only non-invasive determinants.^{21–23,28} However, these prediction models have not been validated for use in secondary healthcare. One cannot assume that asthma predictors in these tools are of equal importance in secondary healthcare, because the asthma prevalence is much higher than in birth cohorts and because wheezing toddlers in secondary healthcare are a selected subgroup.

Previous Literature on Sensitization in Secondary Healthcare

To our knowledge, only two previous studies reported data by which it is possible to calculate the PPV and NPV of sensitization to inhalant allergens for the prediction of

asthma (≥ 6 years) in wheezing toddlers in secondary healthcare. Kotaniemi-Syrjänen et al.¹³ reported an asthma prevalence, PPV and NPV of 40%, 79% (CI 52–93%), and 68% (CI 56–78%), respectively. The OR was 9.8 (1.9–49.7). The second study, by Vial Dupuy et al.,¹² categorized the children as having no, intermittent or persistent asthma. The prevalence of “persistent asthma” was 33% and the PPV of sensitization to inhalant allergens was 75% (CI 40–93%).

The present study found a higher PPV and lower NPV. This is partly explained by the higher prevalence of school age asthma in our cohort (63%). This might be caused by the Dutch healthcare system, in which wheezing toddlers are generally treated by a general practitioner and only children with severe symptoms are referred to a pediatrician. Another Dutch study reported a similar high prevalence of school age asthma (67%) in children with a history of wheezing in secondary healthcare.²⁹

Other factors might also explain the higher PPV in our study. Firstly, toddlers aged 12–48 months were included, while Kotaniemi-Syrjänen et al.¹³ and Vial Dupuy et al.¹² studied children aged 1–24 months old. Secondly, different definitions of asthma were used. Thirdly, Vial Dupuy et al.¹² used “persistent asthma” as the outcome measure, while we analyzed all asthma (including children who would have been classified as having “intermittent asthma” in the study of Vial Dupuy et al.¹²).

Several other studies examined the predictive value of sensitization to inhalant allergens in secondary healthcare in populations with different characteristics. Wever-Hess et al.¹⁷ examined preschool children with asthma-like symptoms (not limited to wheezing). Of the children aged 2–4 years at inclusion, 77% developed asthma and the PPV of sensitization of inhalant allergens was 98% (CI 92–100%). Delacourt et al.³⁰ studied children after hospitalization with wheezing at the age of 1–25 months. Sensitization to inhalant allergens predicted the persistence of wheezing for at least 1 year. Sahiner et al.³¹ studied wheezing preschoolers at an outpatient clinic that functions both as a primary and a tertiary care centre. Skin prick test results did not predict wheeze recovery rates among these children.

In the present study, 43% of the tested children were sensitized to inhalant allergens. In other hospital-based studies 16–35% of wheezing preschoolers were sensitized to inhalant allergens.^{12,13,32,33} The relatively high sensitization rate in our cohort is probably caused by selection, since not all children were tested.

Strengths and Limitations

One of the major strengths of this study is that only children who wheezed at the ages of 1–3 years were included. In younger children wheezing is more often caused by other conditions, especially bronchiolitis.^{34–36}

Besides, sensitization to inhalant allergens is uncommon in the first year of life.^{17,37}

Secondly, the predictive value of sensitization was compared to non-invasive clinical determinants. This is important because specific IgE measurement is an invasive and costly test. Physicians should therefore refrain from IgE testing if determinants from a child's history offer sufficient predictive value.

An important limitation of the present study is the risk of selection bias. This is partly caused by the low response rate. Most baseline parameters did not differ significantly between the study population and the children whose parents did not respond. However, the rate of specific IgE testing was higher among the included children (70%) than among the excluded patients (54%). The poor response rate might be due to the long time period between the initial presentation and the present study (up to several years) and the need for written informed consent of both parents.

Secondly, selection was introduced because specific IgE was not measured in all children. The decision whether or not to measure specific IgE was made by individual pediatricians. There are no strict criteria for IgE measurement in our institution. It is likely that the severity of symptoms and allergic complaints contributed to these decisions and therefore IgE was more often measured in children with a higher asthma risk. By clearly describing the differences between the two groups (Table 1) insight was provided into the factors that might have biased the results. The asthma prevalence was higher among the children with specific IgE measurement (63%) compared to the whole cohort (55%). This resulted in a small overestimation of the PPV and underestimation of the NPV. However, the pronounced difference between pre-test (63%) and post-test probability (86%) remains a useful indicator of the predictive value of sensitization. Therefore, we believe that despite the selection bias our findings are important for the pediatric clinician. It is important to realize that in daily practice specific IgE testing is not performed in all wheezing toddlers. Accordingly, the results of our selected study population might be well applicable to the selected group of wheezing toddlers in whom specific IgE is currently tested in clinical practice. Prospective longitudinal follow-up of wheezing toddlers in secondary healthcare is needed to provide more reliable and more detailed information about asthma prediction among wheezing toddlers in secondary healthcare.

Parents do not always correctly report the presence of wheezing³⁸ and in clinical practice the diagnosis of asthma requires assessment via complete history taking and physical examination.³⁹ Therefore, an asthma definition derived from questionnaires is always an estimate. For the present study both wheezing symptoms and the use of inhalant medication were used as an

asthma proxy, because there are children with asthma who don't use medication and because asthma patients can have good symptom control on medication and therefore might not have wheezed within the past year. The fact that we did not use a more stringent asthma definition, like doctor diagnosed asthma, may have led to some overestimation of the asthma prevalence in our study.

CONCLUSION

A majority of wheezing toddlers in secondary healthcare in the Netherlands develop asthma at school age. In this specific group, sensitization to inhalant allergens at the age of 1–3 years is probably a strong predictor of asthma. The predictive value of sensitization remains high when combined with non-invasive clinical determinants from a child's history. Prospective longitudinal research is needed to further evaluate the prognosis and predictors of asthma in secondary healthcare.

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