

Development of specific immunoglobulin E in coughing toddlers: A medical records review of symptoms in general practice

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The aim of this study was to study whether young children, originally immunoglobulin E (IgE) negative and who became sensitized to specific inhalation allergens, presented more frequently to their general practitioner (GP) with other allergy- and asthma-related symptoms than children who remained IgE negative. It was also investigated whether asthma was diagnosed more often in children who developed IgE to inhalant allergens. Coughing children, 1–5 years of age, visiting the participating GPs, were tested for IgE antibodies to mites, dogs, and cats by using radioallergosorbent testing (RAST). All IgE-negative (RAST <0.2 IU/ml) children were re-tested after 2 years. The medical records of 162 children were reviewed on asthma- and allergy-related symptoms and on prescribed medication. After 30 months, 27 of the 162 children (17%) had become IgE positive for one or more allergens. Most children (93%) had visited their GP for treatment of respiratory symptoms during this period. However, the children who had become IgE positive had visited their GP more often than the children who remained IgE negative. Differences in visits were seen for: shortness of breath (52% IgE-positive vs. 19% IgE-negative children, respectively), wheeze (37% vs. 17%), allergic rhinitis (33% vs. 16%), and pneumonia (22% vs. 8%), but not for coughing (89% vs. 88%). The IgE-positive children were more frequently diagnosed by their GP as having asthma (48%) than were the IgE-negative children (23%). In a multivariate analysis, indicators of becoming IgE positive were: a visit for shortness of breath (odds ratio [OR]=6.9; 95% confidence interval [CI]=2.1–23.1) and two or more visits for wheeze (OR=6.0; 95% CI=1.9–19.2), adjusted for breast-feeding, age, and asthma or allergy in the family. The positive predictive value (PPV) of being IgE positive with a diagnosis of asthma was 90% (whereas the negative predictive value was 48.0%) for a child attending their GP for treatment of wheeze. For recurrent coughing (six or more visits) and shortness of breath, the PPVs were 73% and 71%, respectively. The development of sensitization to common inhalant allergens is associated with specific allergy and asthma-related symptoms in young children. IgE-positive children were more frequently diagnosed as having asthma by their GP. This implies that in general practice it is possible to detect children at high risk for developing allergic asthma early in life by their respiratory symptoms and by subsequent testing for specific IgE to inhalant allergens.

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Coughing is common during early childhood and is a frequent complaint for which general practitioners (GPs) are consulted. For GPs it is difficult to identify those young children with persistent

cough who are at a higher risk for asthma. Most children with cough as the only symptom will not develop asthma (1). Identification of high-risk children, especially with allergic asthma, is

important as early treatment may improve their prognosis (2).

According to international guidelines (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. The equipment for assessing lung function that might help distinguish between groups of wheezing infants and for establishing a diagnosis of asthma are neither easily nor routinely used (5). The presence of a family history of atopy is an additional predictor for the presence or development of asthma in these young children (6,7). Also, testing for allergy-mediated immunoglobulin E (IgE) antibodies can help the physician to make a diagnosis of allergic asthma in young children. The detection of IgE to inhalant allergens will guide the physician in his/her advice on allergen-avoidance measures (8).

However, it is not effective for the GP to test all young children who present with respiratory symptoms for specific IgE. The majority of these children (75–80%) will test negatively to inhalant allergens (9–11). We were therefore interested in whether young children, who become IgE positive for house dust mite, cat and/or dog dander, contact their GP more often and with other symptoms than young children who will remain IgE negative. Furthermore, are these children who become IgE positive more frequently diagnosed as having allergic asthma than the IgE-negative children? In other words, can a GP identify the young children in whom IgE testing is a useful additional tool, in order to distinguish those who are at higher risk for developing allergic asthma.

Subjects and methods

Selection of the study population

Between February 1995 and January 1997, 136 GPs from the northwestern and central regions of the Netherlands (both urban and rural areas) recruited children for a study on the development of inhalation allergy in toddlers. Those children, 1–5 years of age, who had had a cough for longer than 5 days and were not known to have had allergic reactions or to be IgE positive, were included. Informed consent was obtained from the children's parents.

On entrance to the study, the parents completed a questionnaire with 11 questions on coughing, asthma and allergy in the family, breast-feeding, and contact with pets. Three drops of blood spotted onto filter paper were drawn from the children for the determination of total IgE and

specific IgE for house dust mite, cat, and dog. Children scoring IgE positive, i.e. >0.2 radio-allergosorbent test (RAST) units per millilitre (RU/ml) on one or more of the allergens were excluded for further participation in the study. After a 2-year follow-up, the children who were originally IgE negative ($n=530$) were invited to attend their GP for donation of a second blood sample. Again, blood was spotted onto filter paper and tested for total IgE and specific IgE for house dust mite, cat, and dog.

The medical records of the participating children were reviewed by a researcher (J.H.) who was unaware of the outcome of the second RAST. For logistic reasons, review of the medical records was carried out on a sample ($n=25$) of the participating practices. The records of the children who were re-tested before June 1998 and who had the same GP as 2 years previously, were reviewed. The parents gave their written permission for the review of their children's medical records at the GP's office. The study was approved by the Medical Ethics Committee of the Academic Medical Center, University of Amsterdam.

Case record form/medical records

For reviewing the medical records, we designed a case-record form with asthma- and allergy-related items. The case-record form was constructed by comparing questionnaires (12,13) on allergies and asthma. To this, relevant items of the *Asthma in Children* guidelines of the Dutch College of GPs (3) were added as well as items of the *Dutch National Pharmacotherapeutical and Diagnostic Formulary*. All data from the children's medical records (including correspondence with specialists) on occurrence of asthma- and allergy-related symptoms and complaints of the children during the 2-year follow-up, were collected. The feasibility of the case-record form was tested by reviewing the medical records of children with respiratory problems from a non-participating general practice.

In the case-record form, the number of contacts with the GP was counted with respect to respiratory complaints, eczema, rhinitis or conjunctivitis. The respiratory complaints included bronchitis, doctor-diagnosed pneumonia, and doctor-diagnosed asthma. The number of contacts for asthma-related symptoms were registered in which coughing, shortness of breath, tightness of the chest, wheezing, phlegm, and sputum were mentioned as reasons for consultation.

Finally, the number of prescriptions during the 2-year follow-up was registered. Only drugs that

Table 1. Characteristics of the 162 children in the study population

	IgE positive	IgE negative	Total
Total n	27 (16.7)	135 (83.3)	162 (100)
Gender			
Male	11 (40.7)	69 (51.1)	80 (49.4)
Female	16 (59.3)	66 (48.9)	82 (50.6)
Mean age at time of first RAST*	32.2 (± 13.1)	31.3 (± 13.7)	31.4 (± 13.6)
Mean age at time of medical record review*	62.6 (± 14.6)	60.7 (± 14.6)	61.0 (± 14.5)
Age at time of medical record review			
3 years	4 (14.8)	30 (22.2)	34 (21.0)
4 years	9 (33.3)	34 (25.2)	43 (26.5)
5 years	8 (29.6)	36 (26.7)	44 (27.2)
6 years	3 (11.1)	27 (20.0)	30 (18.5)
7 years	3 (11.1)	8 (5.9)	11 (6.8)
Positive family history of asthma and/or allergy	17 (63.0)	66 (48.9)	83 (51.2)
Breastfed	22 (81.5)	89 (65.9)	111 (68.5)
Parents smoking at home	9 (33.3)	58 (43.0)	67 (41.4)
Eczema as a baby	8 (29.6)	27 (20.0)	35 (21.6)
Specific IgE			
House dust mite	16 (59.3)	0 (0)	16 (9.9)
Cat	9 (33.3)	0 (0)	9 (5.6)
Dog	8 (29.6)	0 (0)	8 (4.9)
Total IgE (95% CI) of the first blood sample (IU/ml)	23.0 (13.4–40.0)	12.3 (9.5–15.8)	13.6 (10.8–17.2)
Total IgE (95% CI) of the second blood sample (IU/ml)	52.4 (25.6–107.5)	23.1 (18.1–29.6)	26.3 (20.7–33.4)

IgE, immunoglobulin E; RAST, radioallergosorbent test.

*In months.

Data are expressed as numbers (percentages), means ($\pm$ SD), or geometric means (95% CI).

could be prescribed according to the *Dutch National Pharmacotherapeutical Formulary* for respiratory symptoms, eczema, rhinitis, and conjunctivitis, were taken into account. The respiratory medication included drugs for coughing and asthma (corticosteroids, β_2 -sympathomimetics, parasympatholytics/anti-cholinergic bronchodilators, anti-histaminics, sodium-cromoglycate) and antibiotics (prescribed for respiratory symptoms).

Laboratory methods

A convenient method for obtaining blood from young children was applied: essentially three drops of blood, obtained by fingerprick, were spotted onto filter paper (Schleicher & Schuell 2294, K120258; Schleicher & Schuell, Dassel, Germany). Blood samples were eluted from the filter paper using 1 ml of phosphate-buffered saline (PBS)/0.05% (v/v) Tween-20. Assays for measuring total IgE and specific IgE were adjusted for application of small amounts of plasma. Total serum IgE was measured as previously described (14). Specific IgE to house dust mite, and to cat and dog dander, was determined by an adjusted RAST procedure (15). Total IgE results were expressed in international units per millilitre (IU/ml), RAST results were expressed in RU/ml; one RU represents ≈ 2.4 ng of specific IgE. All tests were corrected for actual

amounts of plasma used in the tests, using serum albumin (42 g/l in human blood) as a reference protein.

Values lower than 0.2 RU/ml were considered negative. Allergy was defined as being IgE positive (>0.2 RU/ml) for one or more allergens.

Data analysis

The results of the second RAST were dichotomized as IgE negative or IgE positive. The number of patients in the separate classes of specific allergens was insufficient to allow a more detailed analysis to be undertaken. For each child the number of contacts with the GP during the follow-up period (according to the records) for allergy- and asthma-related symptoms was counted. The number of contacts for coughing was divided into three categories (none to two, three to five, and more than five contacts). For contacts with respect to eczema, shortness of breath, and wheezing, the categories were: no contacts, one contact, and two or more contacts.

The children had different follow-up periods (19–40 months), implying that children with a longer follow-up period had more chance to contact the GP. Therefore, for each child the number of contacts in 30 months was calculated (65.5% of the children consulted their GP within 30 months after the first blood sample). No

Table 2. Symptoms and prescribed medication of the children (%) who visited their general practitioner (GP) (according to the medical records) (n=162)

	IgE positive n (%)	IgE negative n (%)	Total n (%)
All respiratory complaints	26 (96.3)	125 (92.6)	151 (93.2)
Coughing complaints	24 (88.9)	119 (88.1)	143 (88.3)
Bronchitis	6 (22.2)	25 (18.5)	31 (19.1)
Shortness of breath*	14 (51.9)	25 (18.5)	39 (24.1)
Wheeze*	10 (37.0)	23 (17.0)	33 (20.4)
Pneumonia*	6 (22.2)	11 (8.1)	17 (10.5)
Phlegm	5 (18.5)	20 (14.8)	25 (15.4)
Rhinitis/conjunctivitis*	9 (33.3)	22 (16.3)	31 (19.1)
All prescriptions for respiratory complaints	24 (88.9)	107 (79.3)	131 (80.9)
Prescriptions for coughing complaints	9 (33.3)	56 (41.5)	65 (40.1)
Asthma medication	18 (66.7)	68 (50.4)	86 (53.1)
Inhalation corticosteroids*	13 (48.1)	31 (23.0)	44 (27.2)
β2-sympathomimetics*	14 (51.9)	42 (31.1)	56 (34.6)
Anti-cholinergic bronchodilators	3 (11.1)	14 (10.4)	17 (10.5)
Anti-histaminics	4 (14.8)	12 (8.9)	16 (9.9)
Sodium-cromoglycate*	6 (22.2)	12 (8.9)	18 (11.1)

*p-value <0.05.

IgE, immunoglobulin E.

children were excluded from the analyses. As a result of this re-calculation, only in a limited number of children (n=8) did a change in category of the number of contacts occur.

Logistic regression analysis was used to identify independent predictors (odds ratios [OR] with 95% confidence intervals [CIs]) for becoming IgE positive after adjusting for age at the time of the second blood sample, gender, family history of asthma/allergy, and breast-feeding. A second logistic regression analysis was used to assess whether being IgE positive (in the second blood sample) was an independent predictor of being diagnosed as having asthma, adjusted for confounding variables. In this last model, children with a presumptive diagnosis of asthma and children with a confirmed doctor's diagnosis of asthma were considered as one group, i.e. as having a doctor's diagnosis of asthma.

In all analyses, a p-value of <0.05 was regarded as statistically significant. Likelihood ratio statistics were used as a criterion for selection in the logistic regression model. Statistical analyses were performed using SPSS 7.5.3 for Windows.

Results

General characteristics

The parents of 166 of the 202 (82.2%) eligible children, who were re-tested before June 1998, returned their written permission form for reviewing the medical records of their children at the GP's office. Four out of these 166 parents did not give their consent. Therefore, data on both the second allergy test and on asthma- and allergy-

related symptoms from the medical records of 162 children were available for further analyses.

Of these 162 children, 135 remained IgE negative and 27 had become IgE positive (59% for house dust mite) (Table 1). The mean age at the time of the first RAST was 31.4 months; at the time of the review of the medical records the mean age was 61 months, with the majority (53.7%) being either 4 or 5 years of age. The children who became IgE positive more frequently had a positive family history of asthma and/or allergy in the first remove or degree (parents have asthma and/or allergy) (p=0.182). Of the IgE-negative children, 89 (65.9%) were breast-fed compared with 22 (81.5%) of the IgE-positive children (p=0.112). The geometric mean total IgE of the first blood sample was lower for the children who remained IgE negative (12.3 IU/ml) than for the children who had become IgE positive (23.0 IU/ml) for inhalant allergens (p=0.092). There was also a difference in mean total IgE between the IgE-negative and IgE-positive group in the second blood sample (23.1 IU/ml and 52.4 IU/ml, respectively, p=0.013).

Association between respiratory symptoms and development of specific IgE

All but 11 of the 162 children (93.2%) had visited the GP at least once for respiratory symptoms between the first and second blood sample (Table 2). Shortness of breath was a reason to contact the GP for 51.9% of the IgE-positive children and 18.5% of the IgE-negative children (p < 0.001). Moreover, a significantly greater number of IgE-positive children had visited their GP for treatment of wheeze (37.0% vs.

Table 3. Immunoglobulin E (IgE) (allergy) in relation to number of visits for treatment of a certain complaint

Complaint	IgE positive†	IgE positive‡	IgE positive§
Eczema			
0 visits	1	1	
1 visit	1.2 (0.4–3.8)	1.5 (0.4–5.2)	
≥2 visits	1.1 (0.4–3.4)	1.2 (0.3–3.4)	
Rhinitis/conjunctivitis	2.6 (1.0–6.5)*	3.5 (1.3–9.8)*	
Bronchitis	1.3 (0.5–3.4)	1.3 (0.5–3.8)	
Coughing complaints			
0–2 visits	1	1	
3–5 visits	1.2 (0.4–3.5)	1.1 (0.4–3.5)	
≥6 visits	1.8 (0.7–4.8)	1.8 (0.6–4.9)	
Shortness of breath			
0 visits	1	1	1
1 visit	5.4 (1.8–16.3)*	6.9 (2.1–23.1)*	6.7 (1.9–22.8)*
≥2 visits	4.2 (1.5–12.4)*	4.5 (1.4–14.7)*	2.1 (0.5–8.4)
Wheeze			
0 visits	1	1	1
1 visit	1.1 (0.2–5.3)	1.1 (0.2–5.9)	1.2 (0.2–6.9)
≥2 visits	4.8 (1.7–13.6)*	6.0 (1.9–19.2)*	4.9 (1.2–20.0)*
Pneumonia	3.2 (1.1–9.7)*	3.9 (1.2–12.8)*	
Phlegm	1.3 (0.4–3.9)	1.3 (0.4–4.1)	

*Significant at $p < 0.05$.

†Univariate analyses.

‡'Univariate' analyses adjusted for family history of allergy, breast-feeding and age at the time of the second blood sample.

§Stepwise multivariate analysis adjusted for family history of asthma/allergy, breast-feeding and age at the time of the second blood sample.

17.0%, $p = 0.018$) and pneumonia (22.2% vs. 8.1%, $p = 0.029$), than IgE-negative children. The IgE-positive children visited the GP twice as often as the IgE-negative children for treatment of allergic rhinitis or conjunctivitis (33.3% vs. 16.3%, respectively, $p = 0.040$).

The IgE-positive children were prescribed asthma-related medication more frequently than the IgE-negative children; inhalation corticosteroids, β_2 -sympathomimetics, and sodium-cromoglycate were prescribed twice as often.

In a univariate analysis (Table 3), symptoms with respect to rhinitis/conjunctivitis (OR=2.6; 95% CI=1.0–6.5), shortness of breath (OR=5.4; 95% CI=1.8–16.3 for one contact and OR=4.2; 95% CI=1.5–12.4 for two or more contacts), wheeze for two or more contacts (OR=4.8; 95% CI=1.7–13.6), and pneumonia (OR=3.2; 95% CI=1.1–9.7), were associated with becoming IgE positive. When this analysis was performed adjusted for the confounding variables of family history of allergy, age, and breast-feeding, the ORs of rhinitis/conjunctivitis, shortness of breath, two or more contacts for wheezing, and pneumonia, were associated with becoming IgE positive (Table 3).

A stepwise logistic regression analysis was performed with all symptoms in the model and adjustment for family history, age, and breast-feeding. One contact for shortness of breath (OR=6.7; 95% CI=1.9–22.8) and two or more contacts for wheezing (OR=4.9; 95% CI=1.2–

20.0), were important indicators for becoming IgE positive.

Association between (allergic) asthma, symptoms, and presence of specific IgE

The GPs diagnosed 44 of the 162 young children as having presumptive or confirmed asthma (13 IgE-positive and 31 IgE-negative children). There were no significant differences with respect to airway symptoms in children in either group. We examined whether children with (doctor-diagnosed) asthma were different with respect to airway symptoms and, more specifically, were more frequently IgE positive for inhalants than children without asthma, using logistic regression analyses (Table 4). Young children diagnosed with asthma had visited their GP more often for respiratory symptoms than the children without asthma. Becoming IgE positive for inhalants was an independent indicator (OR=3.4; 95% CI=1.4–8.3) for being diagnosed as having asthma by the GP, adjusted for a family history of asthma, breast-feeding, and age.

The positive predictive value (PPV) of allergy testing on a diagnosis of asthma, when a child attended their GP with asthma-related respiratory symptoms, was analyzed. When children present with wheeze and the GP decides to test for specific IgE to cat, dog and/or house dust mite, 90% (PPV; nine of 10) of the children who turn out to be IgE positive have (been diagnosed as having) asthma compared to 48% (11/23) of the children presenting

Table 4. Doctor's diagnosis of asthma in relation to immunoglobulin E (IgE) and number of visits for treatment of a certain complaint

Complaint	Asthma†	Asthma‡
Eczema		
0 visits	1	1
1 visit	0.5 (0.1–1.6)	0.4 (0.1–1.4)
≥2 visits	2.2 (0.9–5.1)	2.5 (1.0–6.3)
Rhinitis/conjunctivitis	1.6 (0.7–3.7)	1.8 (0.7–4.3)
Bronchitis	2.8 (1.2–6.2)*	2.6 (1.1–6.1)*
Coughing complaints		
0–2 visits	1	1
3–5 visits	2.1 (0.8–5.5)	2.1 (0.8–5.7)
≥6 visits	5.9 (2.4–14.6)	6.2 (2.4–15.9)*
Shortness of breath		
0 visits	1	1
1 visit	3.5 (1.2–9.8)*	3.1 (1.0–9.0)*
≥2 visits	7.1 (2.6–19.0)*	8.5 (2.9–24.8)*
Wheeze		
0 visits	1	1
1 visit	3.3 (1.0–10.3)*	3.3 (0.9–56.9)
≥2 visits	12.3 (4.0–37.3)*	16.9 (5.0–56.9)*
Pneumonia	6.2 (2.1–18.1)*	6.0 (2.0–18.3)*
Phlegm	1.6 (0.7–4.0)	1.7 (0.7–4.5)
IgE positive	3.1 (1.3–7.3)*	3.4 (1.4–8.3)*

*Significant at $p < 0.05$.

†Univariate analyses.

‡'Univariate' analyses adjusted for family history of asthma, breast-feeding and age at the time of the second blood sample.

Results are presented as odds ratios (with 95% CI), $n=162$ (44 children with a diagnosis of asthma and 118 without a diagnosis of asthma).

with wheeze who turn out to be IgE negative. Of the children presenting with recurrent coughing (six or more visits), the children who tested IgE positive had been diagnosed with asthma in 73% (eight of 11) in contrast to 24% (28/119) of the IgE-negative children. For the children presenting with shortness of breath and being either IgE positive or negative, the respective percentages were 71% (10/14) and 44% (11/25), respectively.

Discussion

In this study we have, by means of a review of medical records, analyzed the association between the development of specific IgE, and allergy- and asthma-related symptoms, in young children (1–5 years of age), originally IgE negative, who visited their GP for treatment of coughing. Almost 17% of the children who were originally IgE negative became sensitized to inhalants during the 2-year follow-up. The review showed that the children who had become IgE positive to common inhalant allergens (house dust mite, cat, and/or dog) during follow-up, had visited their GP more frequently and with more specific respiratory symptoms (shortness of breath, wheezing, allergic rhinitis or conjunctivitis, and pneumonia) than the children who remained IgE negative. Subsequently, we found that sensitization to mite or dander allergens resulted in a three-fold higher risk of receiving a doctor's diagnosis of (allergic) asthma.

Our results indicate that in children younger than 6 yr of age who visit their GP for treatment of coughing (six or more visits), shortness of breath, wheezing (two or more visits), and pneumonia, testing for specific IgE to inhalant allergens is worthwhile and, in the case of a positive test, has a strong predictive value for being diagnosed with (allergic) asthma. There was no difference whether the children visited the GP for shortness of breath once or more frequently. For wheezing, however, the development of specific IgE was only statistically significant in children who presented with wheeze more than once, suggesting that specifically those persistent respiratory symptoms may be associated with an increased risk of sensitization.

It is important to reach a definitive diagnosis of asthma as early as possible, in order to start adequate prevention and treatment (8). A reduction in exposure to allergens is associated with fewer symptoms and improved lung function in sensitized individuals (16,17). (Early) allergic sensitization to common inhalant allergens, particularly to dust mite and pet dander, has been associated with asthma and bronchial responsiveness in several previous studies (18–20). These studies strongly suggest that atopy is an important determinant of the outcome of childhood asthma into early adult life (18) and the majority of children who become sensitized during the first 3 years of life develop asthma-like symptoms later in life (19,20). Furthermore, previous studies have

shown that children with more severe asthma at an older age, have developed symptoms of allergy earlier in life, viz. in the first 3 years of life (9,21,22). It is therefore important to detect early in life the children who will become sensitized. As it is not feasible in general practice to test all young children with coughing or wheezing for allergen-specific IgE, the children for whom testing could be useful, should preferably be distinguished in another way. According to our results, this is possible, as these children present with a more distinctive disease pattern than children who will remain IgE negative.

Children who had suffered from pneumonia, according to their medical records, had a higher risk of developing inhalation allergy than the children who had not had pneumonia. This was even more apparent in children diagnosed with asthma. Previous studies (23,24) have shown a relatively high rate of asthma (6–8%) in children under 2 years of age who were admitted to hospital with pneumonia. Recently it was found that the cumulative prevalence of asthma after childhood pneumonia was high and that childhood pneumonia might in fact be an un-recognized presentation of asthma (25). In our study, most of the children were 2–4 yr of age when they had pneumonia. At this age, pneumonia can be confused with other airway infections, but it may also be un-recognized asthma. As in the study of Clark et al. (25) we cannot confirm whether pneumonia was a predisposing factor for asthma. However, considering the young age of the children, pneumonia probably occurred before development of the inhalation allergy.

In our study, the number of allergy- and asthma-like symptoms presented by children with coughing (mild respiratory symptoms) was higher than the number found in GP's populations in the Netherlands (26) and is comparable to other studies (27). This suggests that the children in our study who already presented with coughing, even if they were IgE negative at the time, are at a higher risk of developing allergy than are asymptomatic children.

We found an increase in the number of breast-feeding mothers in the IgE-positive group (Table 1). This might be explained by the fact that it is advised to breast-feed the child when a positive family history of allergy exists. Nevertheless, no significant differences were found in the percentages of breast-fed children with a positive family history compared to breast-fed children with a negative family history. Furthermore, there was no interaction between breast-feeding and a family history of allergy and becoming IgE

positive, neither was it a matter of confounding. Therefore, the increased numbers of breast-feeding mothers cannot be explained from the increased numbers with a family history of allergy. The same was true for smoking and positive family history of allergy.

Of the 44 children with a diagnosis of asthma, 31 were IgE negative for inhalants. If these IgE-negative children do not become IgE positive, they might have non-allergic asthma or they might not have asthma at all, as suggested by others (19,28). These children presented with coughing and wheezing, as did the IgE-positive children with a diagnosis of asthma, but they did not have atopic symptoms or allergen-specific IgE. Recent studies suggest that these non-allergic children with early wheezing do not show the characteristics of 'classic' asthma. Specifically, these children do not seem to be more atopic than children who do not wheeze (29). This early wheezing seems to be associated with a good prognosis (28). In our study, the IgE-negative children with a diagnosis of asthma might have had lower respiratory tract illnesses, such as respiratory syncytial virus (RSV) bronchiolitis, during infancy. It is possible that these children have smaller airways and therefore present with similar symptoms, but that by the time they are 10–13 years of age, they might have overcome their asthma (19,20,30).

For describing the airway symptoms of these young children, we used the method of medical records' review. A limitation of this kind of review is that the information in the medical records is dependent on the precision and completeness of registration by the physician. Moreover, it is not always clear which criteria the GP used in making a diagnosis of asthma, as in young children the diagnosis is predominantly a clinical diagnosis. However, the respiratory symptoms we studied are an essential part of the routine registration in general practice in children presenting with respiratory diseases. Therefore, record review was a valid approach for this study.

We do not know when exactly the children became IgE positive during the 2-year follow-up. We know that they were IgE negative at the start and became IgE positive somewhere during the follow-up, and were labeled with (doctor-diagnosed) asthma. This being a relatively short time-period, one might assume that the symptoms were present during follow-up. One can argue about the need to know when exactly these children became IgE positive. For all but six children it was not known whether they were IgE positive, because the GP did not test the children for specific IgE. But the fact is that the children had symptoms during follow-up and if the child is tested and turns out to

be IgE positive, it does not matter whether this positivity was present 3 months earlier.

In our study we investigated the presence of allergy after 2 years of follow-up, in children originally IgE negative between 1 and 4 years of age. As a consequence, a (substantial) number of the children (20%) were younger than 4 years of age. As reported in other studies (8,9), and also found in our study, few children will become sensitized to aeroallergens during the first 3 years of life. This means that the younger children in our study had less chance of becoming IgE positive. Hence, if all the IgE-negative 3-year-olds had had their RAST at 5 or 6 yr of age, a number of them would also have been found to be IgE positive. This could mean that the effects we identified are even stronger.

In summary, we investigated whether children becoming IgE positive can be recognized in general practice on the basis of their clinical symptoms, and whether IgE testing could contribute to a diagnosis of asthma besides clinical symptoms. In this study, we found that the development of sensitization to common inhalant allergens is associated with specific allergy- and asthma-related symptoms, even if the child is younger than 5 years of age. Furthermore, children who became IgE positive for cat, dog, and/or house dust mite, had a three times greater chance of being diagnosed as asthmatic than children who were still IgE negative. This implies that in general practice it is possible to identify young children (<5 years of age) at high risk for allergic asthma early in life by their respiratory symptoms and by subsequent testing for specific IgE to inhalant allergens. Therefore, according to our results, in these young children with respiratory symptoms, IgE testing can contribute to making a decision of whether the child has asthma, besides clinical symptoms. Careful follow-up of such children is necessary to facilitate their early treatment. When asthma is not allergic asthma, allergen-avoidance measures are not always needed.

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