

Original article

Patterns of quantitative food-specific IgE-antibodies and reported food hypersensitivity in 4-year-old children

Background: Diagnosis of food hypersensitivity (FHS) is difficult and interpretation of food allergy tests is complicated.

Objective: To investigate the probability of reported FHS in relation to levels of food-specific IgE-antibodies (AB) in a population-based setting of 4-year-old children ($n = 2336$).

Methods: Information on FHS was obtained from a questionnaire and specific IgE-AB to milk, egg, fish, peanut, soy and wheat were analysed.

Results: Thirty-one per cent of the children with reported FHS ($n = 284$) were sensitized (≥ 0.35 kU_A/l) to at least one of the tested foods compared with 11% of children without FHS ($n = 2052$). Furthermore, the probability of reported symptoms to milk, egg and fish increased with increasing levels of food-specific IgE-AB to the same food allergens. A similar trend was seen for peanut and wheat, but not for soy. Increasing levels of specific IgE-AB to milk or egg were also associated with an increasing risk of reported symptoms caused by other foods.

Conclusions: Quantitative measurements of IgE-AB to milk, egg and fish are useful to evaluate IgE-associated FHS in preschool children also in a population based sample. Such measurements appear to be of limited value for soy bean and wheat, in particular as a screening method.

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The mechanisms behind food allergy/hypersensitivity are not always evident. Immunoglobulin E (IgE)-mediated reactions against food allergens are common early in life (1–3). However, young children may have IgE antibodies (AB) to food allergens without showing any allergic symptoms (4–6). Besides, non-IgE-mediated reactions to foods are prevalent (1, 7–10). All these factors hamper accurate diagnosis and make it difficult to provide tailored information and advice to children and parents on how to manage the condition (1).

Several studies have reported an association between the levels of IgE-AB to food and clinically verified food allergy. For some foods, certain levels of allergen-

specific IgE have been suggested to be sufficient indication of food allergy, thus eliminating the need for food challenges (11–14). However, these studies were performed on children in hospital settings and mostly in heterogeneous age groups. In population-based studies, quantitative data on levels of IgE-AB in relation to probability of wheeze, asthma, rhinitis and eczema have been presented (4, 15). However, the association between reported food hypersensitivity (FHS) and quantitative levels of food allergen-specific IgE-AB in a population-based cohort of children has not been assessed.

The aim of this study was to elucidate the association between the levels of IgE-AB to common food allergens and reported FHS and whether the information could be a useful tool for evaluation of FHS among 4-year-old children in a large population survey (BAMSE: Children, Allergy and Milieu in Stockholm, an Epidemiological Study).

Abbreviations: AB, antibodies; BAMSE, Children, Allergy and Milieu in Stockholm, an Epidemiological study; CI, confidence intervals; AB, antibodies; FHS, food hypersensitivity; IgE, immunoglobulin E; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value.

Material and methods

Study design

A population-based birth cohort (BAMSE) of 4089 children was established between 1994 and 1996 in Stockholm, Sweden. Information on various background exposures, allergic heredity and other demographic data were obtained through a parental questionnaire when the children were 2-month old (median age) as described elsewhere (16–18). Questionnaires focusing on symptoms related to allergic disease and on key exposures were sent out to the parents when the children were 1, 2 and 4 years of age.

All children for whom questionnaire data were available from the 4 year follow-up ($n = 3742$; 92%) were invited for clinical testing. Two thousand nine hundred and sixty-five children agreed to participate in this testing, and blood samples were obtained from 2614 children. Drop-out analysis on background factors, obtained at the median age of 2 month, was performed among the 340 children who did not answer the 4 year questionnaire. Data on reported doctor's diagnosis ever of 'food allergy', 'asthma' or 'eczema' at 2 years of age were compared between children remaining in the study and children who dropped out after 2 years of age ($n = 101$). In addition, data on prevalence of allergic diseases, such as asthma, eczema and allergic rhinitis according to previously used definitions (18–20) were compared between children from whom blood was taken ($n = 2614$) and children from whom no blood was obtained ($n = 1128$).

All analyses in the present study were performed on children for whom questionnaire data were complete at 2 months (background data) and at 4 years of age (symptoms of FHS), and for whom complete data on IgE-AB to food were available ($n = 2336$). Ethical approval was obtained from the Ethics Committee of Karolinska Institutet, Stockholm, and informed consent was obtained from the parents.

Classification of outcome, parental allergic disease and selected exposures

Food hypersensitivity in a child was defined as reported symptoms such as eczema, vomiting/diarrhoea, urticaria, facial oedema, itchy eyes/runny nose or asthma related to ingestion of a specified food, between ages 2 and 4 years. Fifty-eight children were reported to have unspecific food-related reactions, such as rash around the mouth, and two children were reported to have celiac disease and intolerance to lactose without any other signs of FHS. All those 60 children were excluded from this study.

Allergen-specific IgE-AB in plasma were measured against a mix of common food allergens (fx5®; cow's milk, egg white, cod fish, peanut, soybean and wheat, Immuno-CAP™, Phadia AB, Uppsala, Sweden). An IgE-AB level of ≥ 0.35 kU_A/l was considered positive. Levels of allergen-specific IgE-AB > 100 kU_A/l were set at 100 kU_A/l.

Statistical methods

Prevalence of allergic disease and sensitization is given in total numbers and in per cent. Differences in proportions between groups were tested with chi-square or proportionality test. A P -value < 0.05 was considered as significant. Two by two tables were used to calculate sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for dichotomized food-allergen IgE-AB (cut-off value 0.35 kU_A/l) and FHS. A multiple logistic regression was used to evaluate how increasing levels of food allergen-specific IgE-AB were associated with the risk of FHS

connected with any of the foods tested assessed as odds ratios (OR) and 95% confidence interval (CI). Logarithmic transformation of the levels of IgE-AB was performed. Fitted predicted probability curves with 95% CI were plotted using the results from the multiple logistic regression analysis. Spearman's rank test was used for correlation of sensitization to soy bean and peanut. All analyses were performed using STATA 8.0 (Stata, College Station, TX, USA).

Results

The characteristics of children in the study group were similar to those of the children who dropped out regarding background factors (breastfeeding, early exposure to furred pets or tobacco smoke, parental allergy and socioeconomic status) and doctor's diagnosis of various allergic diseases (data not shown). At the age of 4 years, 284 (12%) children with FHS were identified. These children reported significantly more frequently a doctor's diagnosis of asthma (24% vs 9%), eczema (52% vs 18%), allergic rhinitis (7% vs 1%) and food allergy (44% vs 3%), ($P \leq 0.001$ for all differences) compared with the remaining children in the cohort ($n = 2052$).

The most commonly reported symptom of FHS was eczema (50%) followed by vomiting/diarrhoea (39%), urticaria (30%), facial oedema (26%), itchy eyes/nose (18%) and finally asthma (6%).

Sensitization to food (allergen-specific IgE-AB ≥ 0.35 kU_A/l to at least one of milk, peanut, egg, soy bean, wheat or fish) was found in 305 (13%) children (Table 1). Among children with FHS, 31% were sensitized to the tested foods compared with 11% of children without FHS ($P < 0.001$). The proportions of children sensitized to the tested foods are presented in Table 1. In children sensitized to milk, only 11% were reported to have milk-related symptoms, 29% of children sensitized to egg had reports of egg-related symptoms and 41% of fish-sensitized children reported symptoms caused by fish. The corresponding figures for IgE-sensitization and reported clinical symptoms of FHS to food allergens of plant

Table 1. Prevalence of sensitization* to common food allergens in a cohort of 2336 4-year-old children without and with food hypersensitivity (FHS)

Allergens	Total ($N = 2336$), n (%)	No FHS ($N = 2052$), n (%)	FHS ($N = 284$), n (%)
Any food**	305 (13)	218 (11)	87 (31)
Animal origin			
Cow's milk	197 (8)	151 (7)	46 (16)
Hen's egg	112 (5)	70 (3)	42 (15)
Cod fish	17 (1)	7 (0)	10 (4)
Plant origin			
Peanut	125 (5)	63 (3)	62 (22)
Soy bean	70 (3)	31 (2)	39 (14)
Wheat	88 (4)	54 (3)	34 (12)

*Allergen-specific IgE-antibodies ≥ 0.35 kU_A/l.

**Allergen-specific IgE-antibodies ≥ 0.35 kU_A/l to at least one of the foods tested.

origin, peanut, soy bean and wheat were 38%, 10% and 6%, respectively (data not shown). For sensitization (≥ 0.35 kU_A/l) to any of the tested food items, the sensitivity, specificity, PPV and NPV in relation to FHS were 31%, 89%, 40% and 89% respectively.

The analysis was extended to quantitative food-specific IgE-AB levels. In this first step, we analysed the levels of food-specific IgE-AB, one by one, and the relation to the probability of reported reactions *to the specific food*, Fig. 1. With the exception of wheat [OR_{crude} 3.6 (1.6–8.1) and OR_{adj} 2.9 (1.1–8.1)], the IgE-AB variables were independent as the OR for each allergen, after adjustment for sensitization to all of the other food allergens tested, changed < 10%. In the further analysis, crude ratios were used. A 90% probability for milk-related symptoms was found at an IgE level of 22 kU_A/l to cow's milk. The corresponding IgE-AB level giving a 90% probability of food-related reactions to egg was 13 kU_A/l. It is worth noting that for fish, a high probability was reached already at a much lower IgE-AB level, 4.7 kU_A/l, compared with all other allergens tested. In contrast to cow's milk, hen's egg and fish, a 90% probability of symptoms with increasing IgE-AB levels towards peanut, soy bean and wheat was not reached. Interestingly, at an

IgE-AB level of ≥ 100 kU_A/l to peanut, there was only a 63% probability of report of peanut-related symptoms (Fig. 1). Among 26 children with a peanut-specific IgE-level ≥ 50 kU_A/l, one child was reported not to have yet tasted peanut, 15 were reported to have peanut-related FHS and 10 children did not report any symptoms of FHS. The characteristics of these 10 children are presented in Table 2. At the highest IgE level to soy bean (44 kU_A/l), there was only a 40% probability of reported soy-related symptoms. It is also noteworthy that of 70 soy-sensitized children, 65 were also sensitized to peanut and that quantitative IgE-levels to peanut and soy bean correlated ($r_s = 0.7$, $P \leq 0.001$). For report of symptoms to wheat, an IgE-AB level of 100 kU_A/l to the same food allergen was needed to depict the maximum probability of 89%.

Hence, in the next step, increasing IgE-AB levels and risks of IgE-associated FHS caused by *any* of the foods tested were evaluated to check for food specificity (Fig. 2). The probability curves for increasing levels of IgE-AB to milk, egg, fish and peanut and increased risk of reported reactions to any of the foods included remained almost the same (Fig. 2) as the curves for increasing levels of food-specific IgE-AB and reactions to the same foods

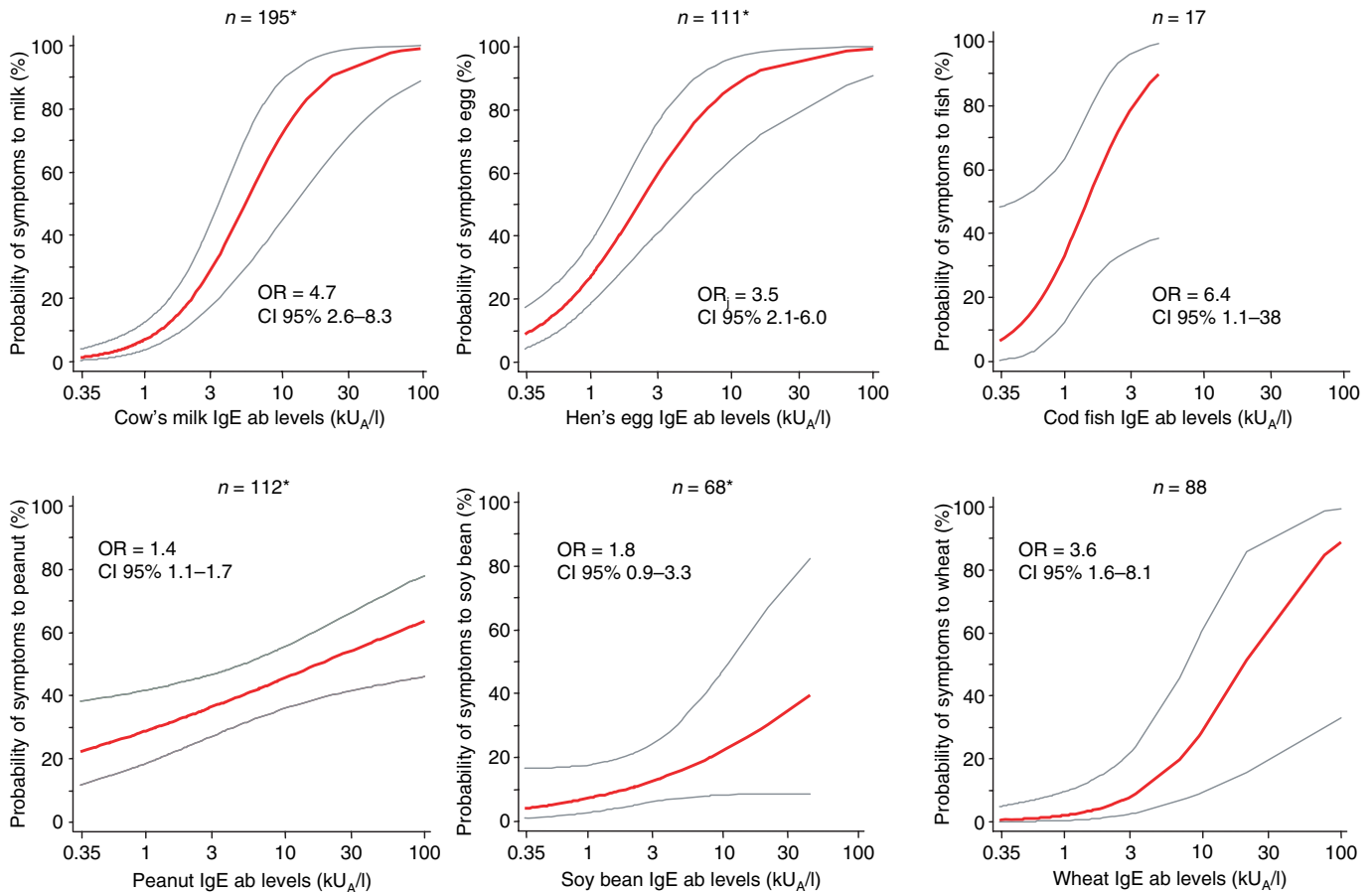


Figure 1. Probability of reported food hypersensitivity to each of the tested foods in relation to increasing levels of food-specific IgE-antibodies expressed as odds ratio (OR) and 95% confidence intervals (CI).

Table 2. Children highly sensitized to peanut but with no report of food hypersensitivity

No.	1	2	3	4	5	6	7	8	9	10
Peanut	68	79	81	85	96	100	100	100	100	100
Cow's milk	<0.35	<0.35	<0.35	<0.35	7.4	<0.35	<0.35	0.5	0.5	3.5
Hen's egg	<0.35	<0.35	<0.35	2.0	100	0.7	0.5	<0.35	<0.35	2.4
Cod fish	<0.35	<0.35	<0.35	<0.35	1.1	0.6	<0.35	1.1	0.9	<0.35
Soy bean	<0.35	<0.35	<0.35	<0.35	9.5	8.8	0.8	1.4	3.4	0.4
Wheat	<0.35	<0.35	<0.35	<0.35	3.2	0.5	<0.35	<0.35	0.7	1.1
Allergic disease other than FHS	Asthma	No allergic symptoms	No allergic symptoms	Eczema rhinitis	Eczema rhinitis	Rhinitis	Eczema	Asthma	Asthma rhinitis	Asthma rhinitis

FHS, food hypersensitivity.

(Fig. 1). However, for increasing IgE levels to soy bean and wheat, the risk of reported symptoms changed considerably, with the curve for soy bean now being similar to the curve for peanut and the curve for wheat becoming more similar to the curves for milk, egg and fish. Increasing levels of IgE-AB to milk, egg and peanut were also used to depict the probability of report of a *certain symptoms* of FHS, such as asthma, itchy eyes/rhinitis, facial oedema, urticaria, eczema and vomiting/

diarrhoea associated with IgE. The number of children who showed these symptoms in response to the other allergens was insufficient for statistical analysis. For increasing levels of IgE-AB to milk and egg, the risk for report of each specific symptom increased significantly, except for vomiting/diarrhoea with increasing levels of IgE-AB to milk (Fig. 3). For increasing levels of IgE-AB to peanuts, there was no increased risk of certain symptoms (OR 1.0–1.1; data and figures not shown).

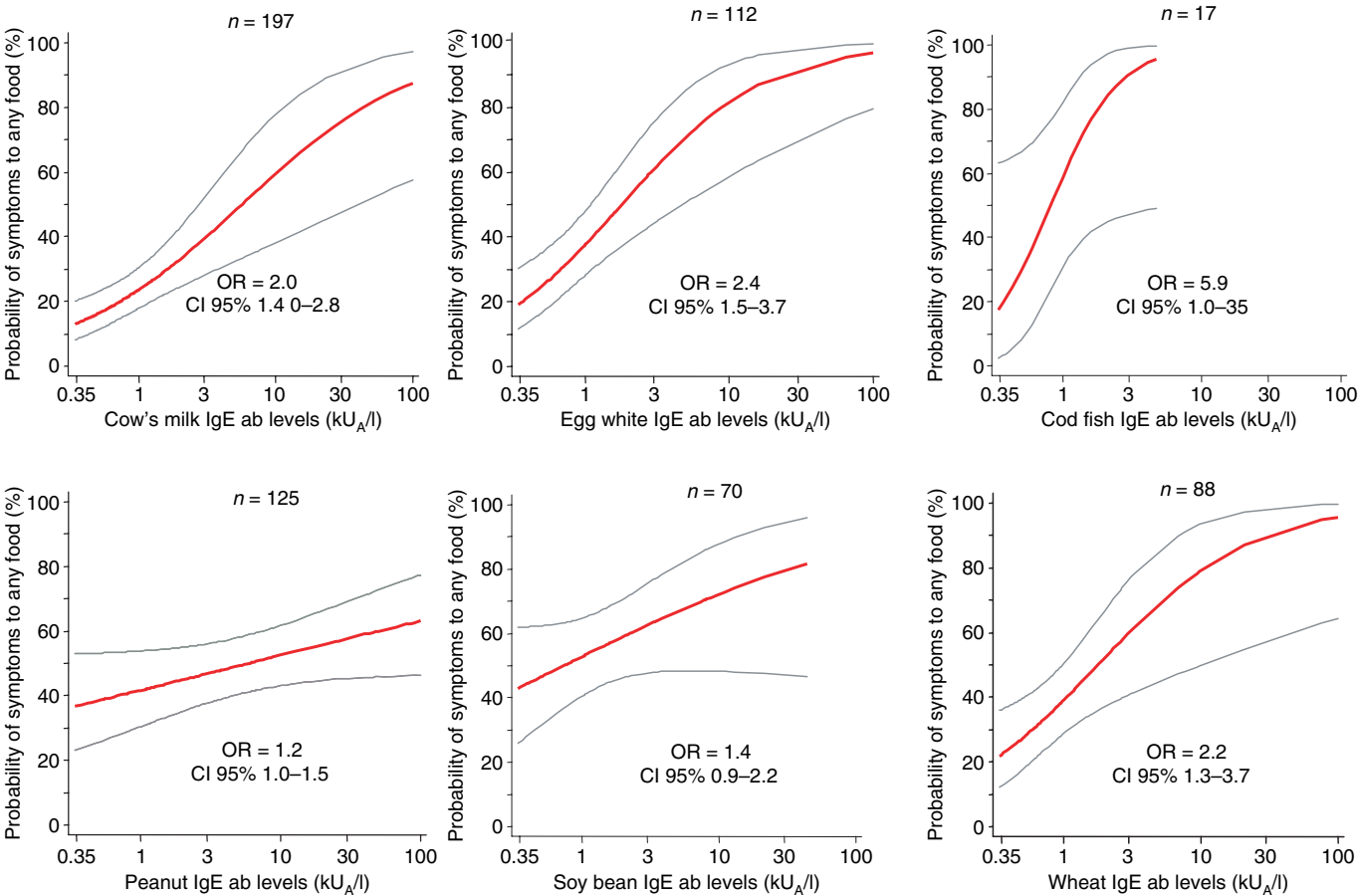


Figure 2. Probability of reported food hypersensitivity to any food in relation to increasing levels of food-specific IgE-antibodies expressed as odds ratio (OR) and 95% confidence intervals (CI).

Reported food hypersensitivity in relation to IgE-levels

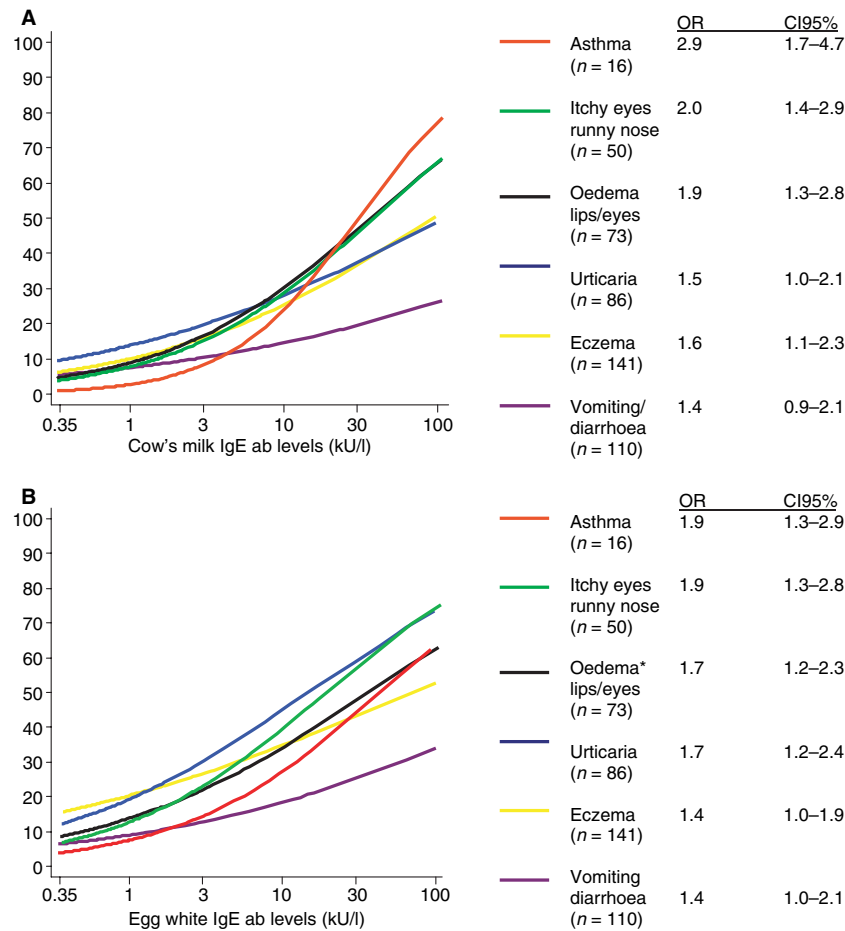


Figure 3. Probability of specific symptoms in relation to increasing: (A) milk-specific IgE-antibodies expressed as odds ratio (OR) and 95% confidence intervals (CI); (B) egg-specific IgE-antibodies expressed as OR and 95% CI.

Discussion

In epidemiological studies, there is often a discrepancy between reported FHS, food allergen-specific IgE-AB and food allergy verified by oral food challenge (1, 6, 7, 21). Here, for the first time, in a large population-based sample of 4-year-old children participating in a birth cohort, quantitative IgE-AB to common foods were used to investigate levels for occurrence of reported symptoms of FHS mediated by these foods.

In this study, the sensitivity and PPV of using sensitization to food with a cut-off level of 0.35 kU_A/l to predict FHS were low. This is in agreement with previous studies (13, 14). However, using quantitative data on food allergen-specific IgE-AB levels gave better agreement between increasing levels of IgE-AB to milk, egg and fish and risk of reported symptoms elicited by these foods. This has been shown by others in children referred to hospital with suspected IgE-mediated FHS and evaluated by oral challenges (12–14), but never in a population-based study. However, the oral challenge is still the gold standard for diagnosing food allergy or FHS, but oral food challenges were not performed as part of this study.

Our results for IgE to cod fish and symptoms to fish need to be interpreted with caution as only 17 of the children were sensitized.

Increasing levels of IgE-AB to milk and egg were demonstrated to increase the risk for report of certain symptoms such as from the respiratory tract, facial oedema and symptoms involving the skin. There were not enough children with IgE-AB to fish to allow this type of analysis. For increasing levels of IgE-AB to peanut, soy bean and wheat, the risk of reported symptoms increased only moderately and the probability curves showed a pattern different from those for milk, egg and fish. Similar observations have been presented by other authors (11–13, 22–25). In some studies, the 95% predicted probabilities of reacting at oral food challenge were given at a certain IgE-AB level (12–14, 22, 25–27). In several of these studies, an association was demonstrated at an IgE-AB level for peanut allergen of 15 kU_A/l; this should be compared with the present study where we found a 63% predicted probability of reactions to peanuts at a peanut IgE-AB level of 100 kU_A/l (12, 22, 26). That the results differ between the studies is likely to be explained by the fact that the children in some of the studies were

referred to the hospital with a suggested IgE-mediated food allergy. In contrast, our study reflects the situation of an unselected and population-based group of children all of the same age, and with asymptomatic but sensitized children. We cannot exclude that some of these children would have reacted in a food challenge. Furthermore, we do not have data on, to what extent children who were not reported to have FHS were exposed to specific foods. However, their parents have clearly stated that their child does not have any FHS whatsoever.

Forty-two per cent of the children sensitized to peanuts reported reactions to peanut. However, there were 10 children with high levels of peanut-specific IgE levels who reported no symptoms at all of FHS. These findings suggest that sensitization, as determined by analysis of IgE-AB to peanut, can be related to symptoms, but such symptoms are not necessarily associated with increasing levels of IgE-AB to peanut at a group level. As we have not performed a food challenge, we cannot assume that none of these children would react upon exposure. As food allergy in general and peanut allergy in particular can induce serious allergic reactions and even cause death, children are often recommended an elimination diet (28). Thus, the discrepancy between reported FHS caused by peanut in our study and sensitization to peanut is problematic and may be a potential health hazard for these children. This warrants further investigation and improvements in the tests used to provide tailored information and advice to children and parents regarding the management of the condition.

Only 7 of the 68 children sensitized to soy bean reported symptoms to soy. For wheat, the corresponding figure was five of 88 children. These results were in-line with those in a study by Sampson and Ho where a 95% probability for reactions towards soy or wheat was not reached (12). It is also noteworthy that the probability curves for reactions to wheat and soy at oral challenges performed on a patient-based material presented in the paper by Celik-Bilgili et al. are almost identical with our population-based data (13). According to our data, sensitization to soy bean seems to be a marker for sensitization to peanut rather than a marker for soy-related symptoms, which may contribute to the explanation of negative challenges in the previously mentioned studies (11–13). We found an increased risk of reactions to any of the foods tested with increasing levels of IgE to wheat, and a complete change of pattern of this probability curve (Fig. 2) compared with the probability curve where wheat-related symptoms and an increase in wheat-specific AB were assessed (Fig. 1). This indicates that sensitization to whole wheat extract could be considered as a marker of sensitization to food in general rather than a marker for wheat-related FHS.

The difference in the predicted probability curves between milk, egg and fish on one hand, and soy bean and wheat on the other, may suggest that children who were reported to have FHS caused by different groups of foods

of animal origin compared to food originating from plants, are likely to be a heterogeneous group. Thus, the presented levels of allergen IgE-AB to these foods in relation to symptoms need to be interpreted differently. This view is congruent with the findings of Flinterman et al. who investigated children sensitized to hazelnut (29). The authors showed that more than 50% of children with suspected hazelnut allergy, all sensitized to hazelnut, were negative at food challenge to hazelnuts. This may further emphasize the need for quantitative measurement of IgE-AB as a tool to evaluate the risk of food-related symptoms rather than the use of mere presence of sensitization to food allergens.

The strength of our study is the high participation rate of 90% of the cohort up to the age of 4 years, and objective measurements of food allergen-specific IgE-levels against the six most common food allergens among 70% of the participating children. The homogeneous age group is a considerable strength of this study as food allergy is a very dynamic process during the first years of life. On the other hand, our data may not be valid for older children, i.e. children of school age. Our reasons for not performing any food challenges were both ethical and practical as the majority of these very young children had not been under hospital care. Thus, the reported FHS and association to increased IgE-AB levels cannot stringently be attributed to an actual food allergy diagnosis, but this was not the purpose of the study. We asked for symptoms during a 2-year period, i.e. between 2 and 4 years of age. It is possible that parents might have underreported symptoms that were present only between 2 and 3 years and not present between 3 and 4 years. However, such bias would lead to an underestimation of our results. Some of these children are likely to be sensitized to foods at 4 years which will dilute our results. The absence of difference between children remaining in the study and drop outs allows us to generalize our data.

In conclusion, reported FHS is common at 4 years of age. Oral provocation remains the gold standard to diagnose food allergy, but quantitative measurement of allergen-specific IgE-AB to allergens in milk, egg, fish and to some degree also to peanut is of value to the clinician to evaluate IgE-associated reactions to foods. Analysis of IgE-AB levels to soy bean and wheat seems to have limited value in particular in screening for allergic children without a history of symptoms to these allergens.

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References

1. Sampson HA. Update on food allergy. *J Allergy Clin Immunol* 2004;**113**:805–819.
2. Rancé F, Kanny G, Dutau G, Moneret-Vautrin D-A. Food hypersensitivity in children: clinical aspects and distribution of allergens. *Pediatr Allergy Immunol* 1999;**10**:33–38.
3. Kulig M, Bergmann R, Klettke U, Wahn V, Tacke U, Wahn U et al. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. *J Allergy Clin Immunol* 1999;**103**:1173–1179.
4. Wickman M, Lilja G, Soderstrom L, Van Hage Hamsten M, Ahlstedt S. Quantitative analysis of IgE antibodies to food and inhalant allergens in 4-year-old children reflects their likelihood of allergic disease. *Allergy* 2005;**60**:650–657.
5. Wickman M, Ahlstedt S, Lilja G, Van Hage Hamsten M. Quantification of IgE antibodies simplifies the classification of allergic disease in 4-year-old children. A report from the prospective birth cohort study – BAMSE. *Pediatr Allergy Immunol* 2003;**14**:441–447.
6. Osterballe M, Hansen T, Mortz C, Host A, Bindlsev-Jensen C. The prevalence of food hypersensitivity in an unselected population of children and adults. *Pediatr Allergy Immunol* 2005;**16**:567–573.
7. Roehr CC, Edenharter G, Reimann S, Ehlers I, Worm M, Zuberbier T et al. Food allergy and non-allergic food hypersensitivity in children and adolescents. *Clin Exp Allergy* 2004;**34**:1534–1541.
8. Sampson HA. Food allergy Part 2: diagnosis and management. *J Allergy Clin Immunol* 1999;**103**:981–999.
9. Niggemann B, Reibel S, Roehr CC, Felger D, Ziegert M, Sommerfeld C et al. Predictors of positive food challenge outcome in non-IgE mediated reactions to food in children with atopic dermatitis. *J Allergy Clin Immunol* 2001;**108**:1053–1055.
10. Kurkulaaratchy R, Matthews S, Arshad S. Defining childhood atopic phenotypes to investigate the association of atopic sensitization with allergic disease. *Allergy* 2005;**60**:1280–1286.
11. Sampson HA. Utility of food-specific IE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;**107**:891–896.
12. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997;**100**:444–451.
13. Celik-Bilig S, Mehl A, Verstege A, Staden U, Nocon M, Beyer K et al. The predictive value of specific immunoglobulin E levels in serum for the outcome of oral food challenges. *Clin Exp Allergy* 2005;**35**:268–273.
14. Garcia-Ara MC, Boyano-Martinez MT, Diaz-Pena JM, Martin-Munoz MF, Martin-Esteban M. Cow's milk specific immunoglobulin E levels as predictors of clinical reactivity in the follow-up of the cow's milk allergy in infants. *Clin Exp Allergy* 2004;**34**:866–870.
15. Simpson A, Soderstrom L, Ahlstedt S, Murray CS, Woodcock A, Custovic A. IgE antibody quantification and the probability of wheeze in preschool children. *J Allergy Clin Immunol* 2005;**116**:744–749.
16. Lannerö E, Kull I, Wickman M, Pershagen G, Nordvall SL. Environmental risk factors for allergy and socioeconomic status in a birth cohort (BAMSE). *Pediatr Allergy Immunol* 2002;**13**:182–187.
17. Wickman M, Kull I, Pershagen G, Nordvall SL. The BAMSE project: presentation of a prospective longitudinal birth cohort study. *Pediatr Allergy Immunol* 2002;**13**(Suppl. 15):11–13.
18. Kull I, Almqvist C, Lilja G, Pershagen G, Wickman M. Breast-feeding reduces the risk of asthma during the first 4 years of life. *J Allergy Clin Immunol* 2004;**114**:755–760.
19. Böhme M, Svensson Å, Kull I, Nordvall L, Wahlgren CF. Clinical features of atopic dermatitis at two years of age: a prospective, population-based case-control study. *Acta Derm Venereol* 2001;**81**:193–197.
20. Kull I, Bergstrom A, Lilja G, Pershagen G, Wickman M. Fish consumption during the first year of life and development of allergic diseases during childhood. *Allergy* 2006;**61**:1009–1015.
21. Venter C, Pereira B, Grundy J, Clayton CB, Arshad SH, Dean T. Prevalence of sensitization reported and objectively assessed food hypersensitivity amongst six-year-old children: a population-based study. *Pediatr Allergy Immunol* 2006;**17**:356–363.
22. Clark A, Ewan P. Interpretation of tests for nut allergy in one thousand patients, in relation to allergy or tolerance. *Clin Exp Allergy* 2003;**33**:1041–1045.
23. Fleischer D, Conover-Walker M, Matsui E, Wooh R. The natural history of tree nut allergy. *J Allergy Clin Immunol* 2005;**116**:1087–1093.
24. Fleischer D, Conover-Walker M, Christie L, Burks W, Wood R. The natural progression of peanut allergy: resolution and the possibility of recurrence. *J Allergy Clin Immunol* 2003;**112**:183–189.
25. García-Ara C, Boyano-Martínez T, Díaz-Pena JM, Martín-Muñoz F, Reche-Frutos M, Martín-Esteban M. Specific IgE-levels in the diagnosis of immediate hypersensitivity to cow's milk protein in the infant. *J Allergy Clin Immunol* 2001;**107**:185–190.
26. Roberts G, Lack G, The Avon Longitudinal Study of Parents and children Study Team. Diagnosing peanut allergy with skin prick and specific IgE testing. *J Allergy Clin Immunol* 2005;**115**:1291–1296.
27. Boyano-Martínez T, García-Ara C, Díaz-Pena JM, Muñoz FM, García Sánchez G, Esteban MM. Validity of specific IgE antibodies in children with egg allergy. *Clin Exp Allergy* 2001;**31**:1464–1469.
28. Foucard T, Malmeden-Yman I. Food-induced anaphylaxis. *Pediatr Allergy Immunol* 2001;**12**:S14.
29. Flinterman A, Hoekstra M, Meijer Y, Van Ree R, Akkerdaas J, Bruijnzeel-Koomen C et al. Clinical reactivity to hazelnut in children: association with sensitization to birch pollen or nuts? *J Allergy Clin Immunol* 2006;**118**:1186–1189.