

Original article

Reported symptoms to peanut between 4 and 8 years among children sensitized to peanut and birch pollen – results from the BAMSE birth cohort

Background: Specific IgE tests are sometimes difficult to interpret due to structural similarities between certain food and pollen allergens. This may be the reason why concomitant sensitization to peanut and birch pollen is frequently seen. The aim of this study was to investigate reported symptoms to peanut- and birch pollen in relation to sensitization.

Methods: The data originate from 1928 children in the BAMSE birth cohort. Background factors and clinical parameters were obtained and the levels of IgE antibodies to peanut and birch pollen measured at 4 and 8 years.

Results: IgE antibodies to peanut were found in 5.5% and 7.4% of the children at 4 and 8 years, respectively. The IgE antibody levels to peanut were higher in children sensitized to peanut but not birch than in children sensitized to peanut and birch among both 4- and 8-year-olds ($P = 0.093$ and $P = 0.003$, respectively). Eight-year-olds sensitized to peanut but not birch, more often reported symptoms to peanut than children sensitized to both peanut and birch pollen (76% vs 46%, $P = 0.002$). The probability of reported symptoms to peanut increased significantly with increasing IgE levels to peanut, especially in 8-year-olds not sensitized to birch.

Conclusions: Children sensitized to both peanut and birch pollen are less likely to report symptoms to peanut than children sensitized to peanut but not to birch pollen at 8 years. This is likely due to cross reactions between birch pollen and peanut and can explain the high sensitization rate to peanut in areas where birch trees are common.

A. Asarnoj^{1,2}, E. Östblom^{3,4,5},
S. Ahlstedt^{1,4}, G. Hedlin^{2,4}, G. Lilja^{3,5},
M. van Hage⁶, M. Wickman^{1,3,4}

¹National Institute of Environmental Medicine, Karolinska Institutet; ²Department of Paediatrics, Astrid Lindgren's Children's Hospital, Karolinska University Hospital; ³Department of Paediatrics, Sachs' Children's Hospital; ⁴Centre for Allergy Research, Karolinska Institutet; ⁵Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet; ⁶Clinical Immunology and Allergy Unit, Department of Medicine, Karolinska Institutet and University Hospital, Stockholm, Sweden

Key words: BAMSE; birch; IgE; peanut; sensitization; symptoms.

A. Asarnoj
National Institute of Environmental Medicine
Karolinska Institutet
S-171 77 Stockholm
Sweden

Accepted for publication 28 May 2009

Peanut allergy is potentially life threatening and has previously been reported to affect 0.2–1.5% of all children (1–5). Symptoms range from mild oral allergy syndrome (OAS) to anaphylactic reactions and even death (6–8). Skin prick testing and measurement of allergen-specific IgE antibodies to peanut is widely used when diagnosing peanut allergy. Positive allergy test results prompt selective avoidance of foods suspected to be a potential problem (9–12). However, elimination of food from the diet may have a negative impact on quality of life (13, 14). Moreover, avoidance may be unnecessary since sensitization to peanut, even with high IgE levels, may occur without clinical symptoms from peanut (15).

Serological cross-reactivity between pollens and several plant-derived foods has been reported; such cross-reactions might influence the specificity of IgE tests (16, 17). Thus, it has been found that over 90% of school children who are sensitized to peanut have a concomitant sensitization to grass pollen, and a correlation between peanut and grass pollen sensitization has been suggested (18). In Northern Europe, where birch trees are common, birch pollen is the major cross-reacting allergen (19–21). Furthermore, the peanut allergen Ara h 8 is known to cross-react with the major birch pollen allergen Bet v 1 (22). We have recently reported that early sensitization to birch pollen in childhood may serve as a 'promotor' in the process of further sensitization to airborne allergens (23). We have also described the patterns of food-specific IgE in relation to symptoms, particular to peanut, in 4-year-old children (15).

So far no study has examined the process of sensitization to birch pollen and peanut in relation to peanut

Abbreviations: BAMSE, Children, Allergy and Milieu in Stockholm, an Epidemiological study; CI, confidence interval; IgE, immunoglobulin E; OAS, oral allergy syndrome; OR, odds ratio.

allergy and age. The aim of this study was therefore to investigate reported symptoms of peanut allergy in relation to the levels of IgE antibodies to peanut and birch pollen in a cohort of children who were evaluated at both 4 and 8 years of age.

Methods

Study subjects

A total of 4089 children born 1994–1996 in Stockholm, Sweden was included at birth in a population-based birth cohort (BAMSE). Study design, enrolment, criteria for inclusion and procedures for data collection have been described elsewhere (24). Briefly, data on background factors were obtained shortly after birth (at 2 months). At 1, 2, 4 and 8 years of age the parents answered detailed questionnaires on symptoms of allergic diseases and key exposures. At 4 and 8 years of age all children with completed questionnaires at the respective follow-ups were invited to a clinical testing. Definitions of symptoms (asthma, rhinitis and eczema) used in the BAMSE cohort have been described elsewhere (25). Blood was drawn from 2614 and 2480 of the children at 4 and 8 years of age, respectively. Data concerning symptoms to peanut and IgE antibody levels to birch and peanut at both 4 and 8 years of age were available for 1928 children, constituting the basis for the analysis presented in this study. Permission for the study was obtained from the Ethics Committee of Karolinska Institutet. The parents of all participating children gave their informed consent.

Definition of symptoms

Questionnaire data, obtained *prior to blood-sampling*, at 4 and 8 years of age were used. A symptom was defined as a positive answer to any of the following questions in the 4- or 8-year questionnaires:

Symptoms to peanut at 4 years. 'After 2 years of age, has your child at any occasion experienced any problems from eating peanuts such as vomiting, diarrhoea, eczema, urticaria/itching rash, swollen lips/eyes, itchy, blocked or runny nose or asthma?'

Symptoms to peanut at 8 years. 'Is your child allergic to peanuts'. If yes, symptom options were 'nose/eye symptoms', 'mouth-itching', 'breathing difficulties', 'vomiting/diarrhoea', 'eczema', 'urticaria' or 'excluded because of early symptoms'. Peanut had to be indicated on at least one of these symptoms.

Symptoms to birch at 4 years. 'Has your child at any occasion after 2 years of age experienced problems with wheeze, cough, itching skin rash, sneezing, runny or blocked nose or red itchy eyes when the trees are leafing (month of May)?'

Symptoms to birch at 8 years. 'Has your child experienced wheeze or disturbing cough, itching eczema or sneezing, runny or blocked nose or red itchy eyes related to birch pollen?'

Determination of sensitization

The blood samples were analysed with Phadiatop® [a mix of common inhalant allergens: birch, timothy, mugwort, cat, dog, horse, mould (*Cladosporium herbarum*) and house dust mite (*Dermatophagoides pteronyssinus*)] and fx5® (a mix of common food

allergens: cow's milk, egg white, soy bean, peanut, cod fish and wheat) (ImmunoCAP™, Phadia AB, Uppsala, Sweden). Sera that were scored positive for Phadiatop® or fx5®, defined as an IgE antibody level of ≥ 0.35 kU_A/l was further analysed for allergen-specific IgE antibodies to the single airborne and food allergens listed above. Levels between 0.35 and 100 kU_A/l were registered, and an IgE antibody concentration ≥ 100 kU_A/l was given the value of 100 kU_A/l in the statistical evaluation.

Statistical analysis

Prevalence rates are expressed in percent of total number of observations available. Ninety-five percent confidence intervals (95% CI) were calculated and intervals that did not overlap were considered as statistically different. Chi-square test was used for dichotomous variables, for example, comparisons of prevalence between groups. Allergen-specific IgE levels were log normally distributed and subject to a logarithmic transformation before analysis. Student's *t*-test was used for analysis of the continuous IgE-variables. Mean IgE levels are presented as geometric mean. The relationship between symptoms to peanut and IgE antibody levels was estimated using a logistic regression model. The odds ratios (ORs) were estimated using regression models and 95% CI were generated. Fitted predicted probability curves according to the levels of the specific IgE to peanut were plotted using the results from the logistic regression. All tests were according to Wald. Logistic regression was also used to investigate peanut symptoms in relation to sensitization to birch and timothy. Several models for identifying confounders were run. Among others, variables of heredity, sex and exposure to tobacco smoke were tested but since they did not confound the results by 10% or more, they were not included in the analyses. *P* values ≤ 0.05 were considered statistically significant. All analyses were performed with the software STATA® version 9.

Results

The children participating in this study ($n = 1928$) did not differ from the original study base of 4089 children in any major background factors of importance at 2 months of age (data not shown). Furthermore, no significant differences were seen in the prevalence of asthma, rhinitis, eczema or geometric mean IgE levels (Phadiatop® and fx5®), between children in this study and children of the original cohort at the age of 4 and 8 (data not shown).

At 4 years, 106 (5.5%) of the children were sensitized to peanut and 181 (9.4%) were sensitized to birch. At 8 years the corresponding figures were 142 (7.4%) and 293 (15.2%) (Fig. 1). From 4 and 8 years the proportion of children sensitized to peanut, but not birch (subgroup 1), remained essentially unchanged, 2.2% and 1.9% at the two respective ages, whereas the proportion of children sensitized to both peanut and birch pollen (subgroup 2) seemed to increase over the same period (3.3% and 5.4%, respectively, $P = 0.002$) (Fig. 1).

At 4 years 2.9% ($n = 56$) of the 1928 children reported symptoms to peanut and at 8 years the corresponding proportion was 5.7% ($n = 109$). The prevalence of sensitization to peanut in combination with reported

Symptoms to peanut among 4- and 8-year-old children sensitized to peanut and birch pollen

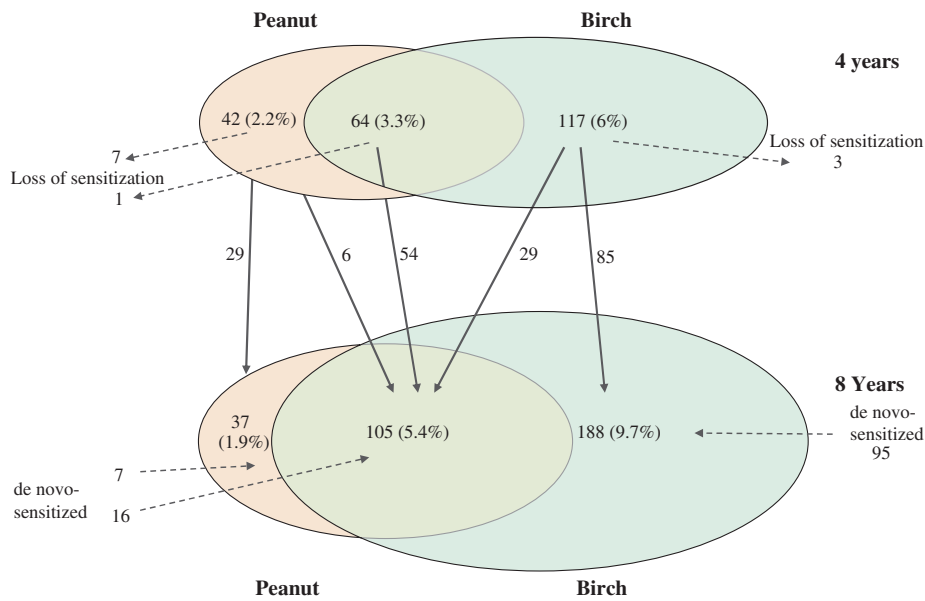


Figure 1. Changes in sensitization to peanut and birch among the same 1928 children residing in Stockholm, tested at both 4 and 8 years of age.

symptoms to peanut was 1.8% ($n = 34$) at 4 years and 3.9% ($n = 76$) at 8 years of age.

At 4 years of age the proportion of children reporting symptoms from peanut did not differ among peanut sensitized children with or without concomitant sensitization to birch pollen (subgroup 2 vs subgroup 1); 34% vs 29% ($P = 0.53$) (Table 1). However, at 8 years of age 76% of the children who were sensitized to peanut but not to birch pollen (subgroup 1) reported symptoms to peanut, whereas among children sensitized both to peanut and birch pollen (subgroup 2) only 46% reported such symptoms, $P = 0.002$. All types of peanut-related symptoms at 8 years of age (see definition of symptoms),

except eczema, were reported more frequently among children in subgroup 1 than in subgroup 2 (data not shown). Significant differences were seen for breathing difficulties; 27% vs 10%, $P = 0.008$ and urticaria; 16% vs 6%, $P = 0.048$.

Interestingly, children *de novo*-sensitized to peanut between 4 and 8 years ($n = 52$) were mostly asymptomatic (85%) to peanut and concomitantly sensitized to birch pollen (87%).

At 4 years of age, although the difference was not statistically significant, the mean IgE antibody level to peanut was higher among children sensitized to peanut and not birch pollen (subgroup 1) than among children

Table 1. Reported symptoms to birch and peanut in relation to sensitization to birch and peanut at 4 and 8 years of age, $n = 1920$ and 1917 , respectively

	No symptoms from birch or peanut		Symptoms from birch not peanut		Symptoms from peanut not birch		Symptoms from birch and peanut	
Sensitization at 4 years	n (1711)	%	n (153)	%	n (37)	%	n (19)	%
Not peanut/not birch, $n = 1699$	1583	93	96	5.6	16	0.9	4	0.2
Birch not peanut, $n = 116^*$	80	69	34	29	0	0	2	1.7
Peanut not birch, $n = 41^\dagger$	26	63	3	7.3	11	27	1	2.4
Birch and peanut, $n = 64^{\ddagger*}$	22	34	20	31	10	16	12	19
Sensitization at 8 years	n (1664)	%	n (144)	%	n (59)	%	n (50)	%
Not peanut/not birch, $n = 1588$	1532	96	40	2.5	16	1.0	0	0
Birch not peanut, $n = 187^\ddagger$	108	62	62	33	5	2.7	12	6.4
Peanut not birch, $n = 37^\S$	7	19	2	5.4	24	65	4	11
Birch and peanut, $n = 105^{\ddagger\S}$	17	16	40	38	14	13	34	32

Data on symptoms induced by birch pollen were missing in 8 and 11 of the questionnaires at 4 and 8 years, respectively.

* $P = 0.012$ symptoms from birch among birch-sensitized children with or without concomitant sensitization to peanut at 4 years.

$^\dagger P = 0.531$ symptoms from peanut among peanut-sensitized children with or without concomitant sensitization to birch at 4 years.

$^\ddagger P < 0.0001$ symptoms from birch among birch-sensitized children with or without concomitant sensitization to peanut at 8 years.

$^\S P = 0.002$ symptoms from peanut among peanut-sensitized children with or without concomitant sensitization to birch at 8 years.

sensitized to both peanut and birch pollen (subgroup 2), being 8.2 kU_A/l (95% CI 4.5–14.9) and 4.5 kU_A/l (2.9–6.9), respectively, $P = 0.093$ (Table 2). However, at 8 years this difference in IgE antibody concentrations was significant: 12.0 kU_A/l (6.1–23.9) and 4.3 kU_A/l (3.1–6.0), respectively, $P = 0.003$.

Children who *remained sensitized* ($n = 90$) to peanut between 4 and 8 years had statistically higher mean levels of IgE antibodies to peanut at 4 years of age than children who *lost their sensitization* ($n = 16$) to peanut; 7.5 kU_A/l (95% CI 5.2–11.0) and 1.2 kU_A/l (0.7–1.8), respectively. The same children who *remained sensitized* ($n = 90$) to peanut between 4 and 8 years had also statistically higher mean levels of IgE antibodies to peanut at 8 years of age than children with *de novo sensitization* ($n = 52$) to peanut; 10.3 kU_A/l (6.9–15.3) and 2.0 kU_A/l (1.4–2.7), respectively.

Further analysis among the peanut-sensitized children regarding the association between IgE-antibody levels to peanut and the probability of reporting symptoms to peanut at 4 and 8 years of age is presented in Fig. 2A and B (children sensitized to peanut but not to birch pollen = subgroup 1, children sensitized to both birch pollen and peanut = subgroup 2). At 4 years the increase in IgE antibody levels to peanut was associated with a rather modest increase in probability of symptoms in both subgroups [subgroup 1; OR 1.51 (95% CI 1.01–2.25), subgroup 2; OR 1.49 (1.08–2.05)]. At 8 years of age the corresponding probability curves were different: there was a statistically significant increase in the risk of symptoms with increasing peanut-IgE-level, especially in subgroup 1 (OR 2.57; 1.36–4.88). However, the probability curves for peanut symptoms in subgroup 1 and 2 at 8 years did not differ significantly from each other.

Among children *with symptoms* to peanut and sensitized both to peanut and birch pollen the IgE antibody levels to *peanut* did not differ significantly from IgE

antibody levels to birch pollen at 4 and 8 years, $P = 0.70$ and $P = 0.16$, respectively. However, in those who were sensitized to both birch and peanut, but *did not report symptoms to peanut*, the IgE levels to *birch* were significantly higher both at 4 and 8 years ($P = 0.002$ and $P < 0.001$, respectively).

The influence of timothy sensitization on peanut symptoms was also examined among peanut-sensitized children. At 4 years the OR of having symptoms to peanut, if the children in addition to peanut were sensitized to birch or timothy, was not significantly increased or decreased (data not shown). At 8 years, timothy sensitization was not associated with a significant reduction of reported symptoms to peanut (OR 0.7; 95% CI 0.3–1.5). However, the reduction of peanut symptoms was significant among those sensitized to birch (OR 0.3; 0.1–0.8).

When the children were 4 years of age, 13 of them had not yet been exposed to peanuts. Exclusion of these 13 children from the analysis did not change the results.

Discussion

The most important finding in this study is that school-aged children who are sensitized to both peanut and birch pollen not only report symptoms to peanuts significantly less often than children sensitized to peanut but not birch pollen, but also report milder symptoms. Our findings can probably be explained by cross-reactivity between birch pollen and peanut allergens (22, 26, 27). When the same children were at preschool age, no similar pattern of peanut symptoms and sensitization to peanut and birch allergen could be demonstrated. One explanation for the change in reported peanut symptoms with age could be that sensitization to peanut precedes symptoms, as has been shown earlier. An alternative explanation is that at

Table 2. Geometric mean levels of peanut-specific IgE at 4 and 8 years among children sensitized to peanut and birch allergen, $n = 1928$

	Total			Symptoms from peanut			No symptoms from peanut		
	<i>n</i>	IgE (kU _A /l)	95% CI	<i>n</i>	IgE (kU _A /l)	95% CI	<i>n</i>	IgE (kU _A /l)	95% CI
Sensitization at 4 years									
Peanut	106	5.7	4.0–8.1	34	12.7‡	7.2–22.4	72	3.9	2.6–5.9
Peanut not birch	42	8.2*	4.5–14.9	12	21.7‡	8.3–56.7	30	5.6	2.7–11.5
Peanut and birch	64	4.5	2.9–6.9	22	9.5	4.6–19.8	42	3.0	1.8–5.0
Sensitization at 8 years									
Peanut	142	5.6	4.1–7.6	76	14.0**	9.2–21.3	66	2.0	1.5–2.6
Peanut not birch	37	12.0§	6.1–23.9	28	24.3¶	12.8–46.2	9	1.3	0.4–4.7
Peanut and birch	105	4.3	3.1–6.0	48	10.1	5.9–17.5	57	2.1	1.6–2.8

Four years: * $P = 0.093$ for difference in peanut-specific IgE between children sensitized to peanut not birch and children sensitized to peanut and birch. † $P = 0.16$ for difference in peanut-specific IgE between peanut-symptomatic children sensitized to peanut not birch and peanut-symptomatic children sensitized to peanut and birch. ‡ $P = 0.0014$ for difference in peanut-specific IgE between children with and without symptoms from peanut.

Eight years: § $P = 0.0032$ for difference in peanut-specific IgE between children sensitized to peanut not birch and children sensitized to peanut and birch.

¶ $P = 0.045$ for difference in peanut-specific IgE between peanut-symptomatic children sensitized to peanut not birch and peanut-symptomatic children sensitized to peanut and birch.

** $P < 0.0001$ for difference in peanut-specific IgE between children with and without symptoms from peanut.

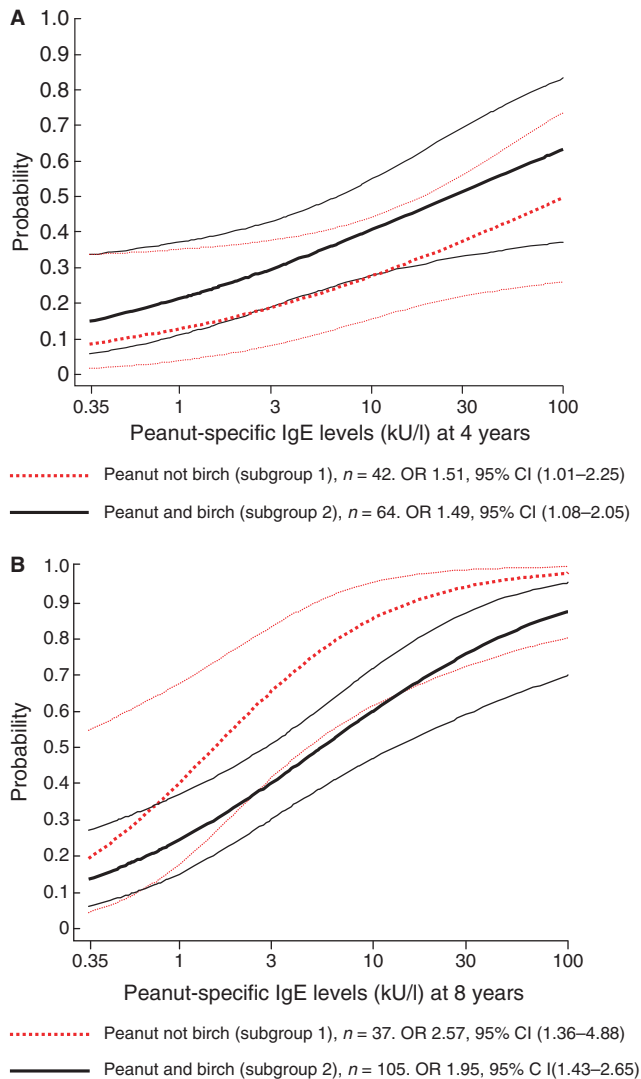


Figure 2. (A) Probability of symptoms to peanut in relation to levels of peanut-specific IgE antibodies among 4-year-old children with or without concomitant sensitization to birch pollen. (B) Probability of symptoms to peanut in relation to levels of peanut-specific IgE antibodies among 8-year-old children with or without concomitant sensitization to birch pollen.

4 years, the children have had only limited exposure to peanut (28). The difference is not explained by the fact that some of the children had not yet tasted peanut at all at that age.

The proportion of children sensitized to peanut remained stable from age 4 to age 8, or even showed a slight decrease. In contrast, the number of children sensitized both to peanut and birch increased by more than 60% during this period. This is in line with our previous results showing that birch pollen is the dominant allergen in our region and that sensitization to birch pollen seems to facilitate the further sensitization process (23). Most of the children with *de novo* sensitization to

peanut at 8 years of age reported no symptoms to peanut, although they were sensitized to both peanut and birch pollen, suggesting that peanut-sensitized children who also show symptoms to peanut are likely to be sensitized early in life. Our results suggest that in children with concomitant birch sensitization, peanut sensitization is rather weakly associated to current peanut allergy, in particular if the levels of IgE to birch are higher than those of IgE to peanut.

Our results are in agreement with a recent study on sensitization and symptoms to hazelnut in relation to birch sensitization, where Flinterman and colleagues reported a pattern similar to that seen in our study (29, 30). The prevalence of reported peanut allergy in our study, 2.9% at 4 years and 5.7% at 8 years of age, is higher than in other studies (3–5). However, when it was required that peanut sensitized children also reported symptoms to peanut, the proportions were 1.8% at age 4 and 3.9% at age 8, respectively. This is still rather high in comparison with other reports but is likely to be partly explained by mild symptoms mainly from the oral cavity among birch-pollen- and peanut-sensitized children. Furthermore, some children may have been diagnosed as 'peanut allergic', based only on a positive allergy test to peanut, in particular if high IgE levels are present, without taking cross-reactivity to birch into consideration (22). Such an interpretation may have a negative impact on many children and their families by inducing fear of severe reactions. This will result in over-reporting of peanut allergy and avoidance of peanut in foods (14).

Elevated peanut-specific IgE levels have been shown to increase the probability of symptoms from peanut (9–11). In our study, this association was significantly stronger at 8 than at 4 years of age, and was most prominent in the subgroup of 8-year-old children who were sensitized to peanut but not birch. The prospective study by Sampson (10) has as its study base children referred to a paediatric department, with a wide range in age, and only 2% were challenged orally in that study. Reported symptoms have been shown to overestimate current food allergy (31). However, when our data of nonchallenged children with symptoms to peanut in relation to increased IgE to peanuts are compared with similar data of children sensitized to peanuts who have been partially challenged, as mentioned above, it seems evident that there are similarities although differences exist (Fig. 3) (10, 15). At 4 years of age, the children in our study may have high levels of peanut-specific IgE, but this does not seem to be strongly related to symptoms to peanut. At the age of 8 years in our population-based study, and in particular among children who are not sensitized to birch, the probability of symptoms to peanut increases with increasing levels of peanut-specific IgE in the same way as presented by Sampson (10). Taken together, the shape of the probability curves in relation to levels of peanut-specific IgE antibodies indicates that our study is unlikely to have overestimated the occurrence of *actual* symptoms

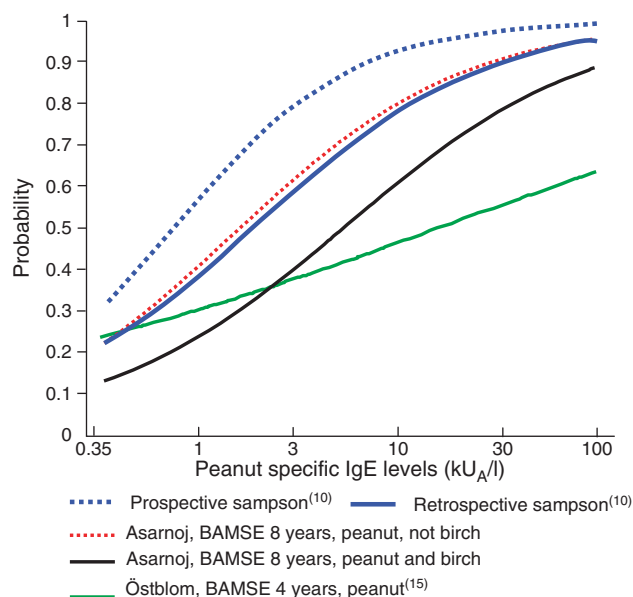


Figure 3. Comparison of the probability of symptoms to peanut in relation to levels of peanut-specific IgE antibodies, as reported in different studies.

among peanut-sensitized children by taking *reported* symptoms at face value. The differences in the shape of the probability curves in our study *vs* the Sampson study are likely to be explained by the population-based design of our study, with two homogenous age groups, *vs* the highly selected group of individuals referred for paediatric care, with a wide age range, in the study by Sampson (10). Many of the peanut-sensitized children in our cohort tolerated peanut even though they were sensitized. These children would never have been tested for peanut sensitization unless they participated in the study. As a consequence, the peanut-specific IgE-levels corresponding to a 95% probability of reporting peanut-related symptoms will be higher in a population based study where children have not been challenged. However, it must be borne in mind that reported symptoms of peanut allergy in our study are not necessarily indicative of true peanut

allergy, as food challenges were not (and for practical/ethical reasons could not) be performed to confirm the true rate of peanut allergy in this population.

The strength of this study is the large number of children tested for presence of IgE to common allergens at both 4 and 8 years of age. To our knowledge there is no other population-based study comprising more than 1900 children, who have been examined for sensitization at two time points. Furthermore, the population-based design and the availability of background data from before onset of disease make our results transferable to the general population.

The components in the peanut allergen which are known to cross-react with birch are the Bet v 1 homologue, Ara h 8, and the Bet v 2-related profilin, Ara h 5 (22, 26, 27, 32). Further analyses of IgE antibodies to these cross-reactive allergens among children in our cohort are underway and will be reported elsewhere.

In summary, our findings suggest that in regions with many birch trees and a high prevalence of sensitization to birch pollen, there is a major risk of misclassifying peanut-sensitized individuals as allergic to peanut, due to the serological cross-reactivity to birch pollen. If IgE levels to birch pollen are higher than those to peanut, the patient's peanut allergy may be mild or even nonexistent.

Sources of funding

This work was supported by the Swedish Asthma and Allergy Foundation, the Swedish Heart and Lung Foundation, the Vardal Foundation for Health Care Sciences and Allergy Research and Stockholm County Council, Stockholm, Sweden. The study was also supported by Phadia AB who provided reagents for the allergen-specific IgE analyses.

Acknowledgment

We thank all the participating families, and all the staff working within the BAMSE project.

References

1. Grundy J, Matthews S, Bateman B, Dean T, Arshad SH. Rising prevalence of allergy to peanut in children: Data from 2 sequential cohorts. *J Allergy Clin Immunol* 2002;**110**:784–789.
2. Osterballe M, Hansen TK, Mortz CG, Host A, Bindslev-Jensen C. The prevalence of food hypersensitivity in an unselected population of children and adults. *Pediatr Allergy Immunol* 2005;**16**:567–573.
3. Sicherer SH, Munoz-Furlong A, Burks AW, Sampson HA. Prevalence of peanut and tree nut allergy in the US determined by a random digit dial telephone survey. *J Allergy Clin Immunol* 1999;**103**:559–562.
4. Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. *J Allergy Clin Immunol* 2003;**112**:1203–1207.
5. Emmett SE, Angus FJ, Fry JS, Lee PN. Perceived prevalence of peanut allergy in Great Britain and its association with other atopic conditions and with peanut allergy in other household members. *Allergy* 1999;**54**:380–385.
6. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 2001;**107**:191–193.
7. Roberts G. Anaphylaxis to foods. *Pediatr Allergy Immunol* 2007;**18**:543–548.

8. Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA, Burks W, Wood RA. The natural history of peanut allergy. *J Allergy Clin Immunol* 2001;**107**:367–374.
9. Maloney JM, Rudengren M, Ahlstedt S, Bock SA, Sampson HA. The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy. *J Allergy Clin Immunol* 2008;**122**:145–151.
10. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;**107**:891–896.
11. 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.
12. Wainstein BK, Yee A, Jelley D, Ziegler M, Ziegler JB. Combining skin prick, immediate skin application and specific-IgE testing in the diagnosis of peanut allergy in children. *Pediatr Allergy Immunol* 2007;**18**:231–239.
13. Bollinger ME, Dahlquist LM, Mudd K, Sonntag C, Dillinger L, McKenna K. The impact of food allergy on the daily activities of children and their families. *Ann Allergy Asthma Immunol* 2006;**96**:415–421.
14. Ostblom E, Egmar AC, Gardulf A, Lilja G, Wickman M. The impact of food hypersensitivity reported in 9-year-old children by their parents on health-related quality of life. *Allergy* 2008;**63**:211–218.
15. Ostblom E, Lilja G, Ahlstedt S, van Hage M, Wickman M. Patterns of quantitative food-specific IgE-antibodies and reported food hypersensitivity in 4-year-old children. *Allergy* 2008;**63**:418–424.
16. Caballero T, Martin-Esteban M. Association between pollen hypersensitivity and edible vegetable allergy: a review. *J Investig Allergol Clin Immunol* 1998;**8**:6–16.
17. Eriksson NE, Formgren H, Svenonius E. Food hypersensitivity in patients with pollen allergy. *Allergy* 1982;**37**:437–443.
18. Mortz CG, Andersen KE, Bindslev-Jensen C. The prevalence of peanut sensitization and the association to pollen sensitization in a cohort of unselected adolescents—The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS). *Pediatr Allergy Immunol* 2005;**16**:501–6.
19. Bohle B. The impact of pollen-related food allergens on pollen allergy. *Allergy* 2007;**62**:3–10.
20. Ebner C, Hirschwehr R, Bauer L, Breiteneder H, Valenta R, Ebner H et al. Identification of allergens in fruits and vegetables: IgE cross-reactivities with the important birch pollen allergens Bet v 1 and Bet v 2 (birch profilin). *J Allergy Clin Immunol* 1995;**95**:962–969.
21. Osterballe M, Hansen TK, Mortz CG, Bindslev-Jensen C. The clinical relevance of sensitization to pollen-related fruits and vegetables in unselected pollen-sensitized adults. *Allergy* 2005;**60**:218–225.
22. Mittag D, Akkerdaas J, Ballmer-Weber BK, Vogel L, Wensing M, Becker WM et al. Ara h 8, a Bet v 1-homologous allergen from peanut, is a major allergen in patients with combined birch pollen and peanut allergy. *J Allergy Clin Immunol* 2004;**114**:1410–1417.
23. Asaranoj A, Ostblom E, Kull I, Lilja G, Pershagen G, Hedlin G et al. Sensitization to inhalant allergens between 4 and 8 years of age is a dynamic process: results from the BAMSE birth cohort. *Clin Exp Allergy* 2008.
24. Wickman M, Kull I, Pershagen G, Nordvall SL. The BAMSE project: presentation of a prospective longitudinal birth cohort study. *Pediatr Allergy Immunol* 2002;**13**:11–13.
25. 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.
26. Kleber-Janke T, Cramer R, Appenzeller U, Schlaak M, Becker WM. Selective cloning of peanut allergens, including profilin and 2S albumins, by phage display technology. *Int Arch Allergy Immunol* 1999;**119**:265–274.
27. Wensing M, Akkerdaas JH, van Leeuwen WA, Stapel SO, Bruijnzeel-Koomen CA, Aalberse RC et al. IgE to Bet v 1 and profilin: cross-reactivity patterns and clinical relevance. *J Allergy Clin Immunol* 2002;**110**:435–442.
28. van Odijk J, Bengtsson U, Borres MP, Hulthen L, Ahlstedt S. Specific immunoglobulin E antibodies to peanut over time in relation to peanut intake, symptoms and age. *Pediatr Allergy Immunol* 2004;**15**:442–448.
29. Flinterman AE, Akkerdaas JH, den Hartog Jager CF, Rigby NM, Fernandez-Rivas M, Hoekstra MO et al. Lipid transfer protein-linked hazelnut allergy in children from a non-Mediterranean birch-endemic area. *J Allergy Clin Immunol* 2008;**121**:423–428.e2.
30. Flinterman AE, Akkerdaas JH, Knulst AC, van Ree R, Pasmans SG. Hazelnut allergy: from pollen-associated mild allergy to severe anaphylactic reactions. *Curr Opin Allergy Clin Immunol* 2008;**8**:261–265.
31. Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. *Pediatrics* 1987;**79**:683–688.
32. Vieths S, Scheurer S, Ballmer-Weber B. Current understanding of cross-reactivity of food allergens and pollen. *Ann NY Acad Sci* 2002;**964**:47–68.