

ORIGINAL PAPER

Phenotypes of food hypersensitivity and development of allergic diseases during the first 8 years of life

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Summary

Background Longitudinal data from population-based studies on the development and persistence of food hypersensitivity (FHS) during childhood are almost absent.

Methods A population-based birth cohort was established, and information on various exposures and symptoms of allergic disease were obtained from questionnaires when the children were 2 months, 1, 2, 4 and 8 years of age. Complete data were available on 3104 children. Children with reported FHS and doctor's diagnosis of food allergy (RDFA) were identified and allocated into transient, intermittent, late-onset and persistent phenotypes. Food allergen-specific IgE-antibodies (abs) to a mix of six common food allergens (fx5[®]) were analysed at 4 and 8 years of age in 1857 children.

Results The overall prevalence of reported FHS in combination with RDFA should be 3.1% at 1 year to 7.6% at 8 years of age. However, reactions to milk, egg, fish and wheat decreased, whereas an increase was seen for peanuts and tree nuts. Reported reactions to egg, peanuts or tree nuts early in life, as well as IgE-abs to food allergens at the age of 4, increased the risk of FHS at 8 years of age. Furthermore, FHS at young ages increased the risk for asthma, eczema and allergic rhinitis at 8 years of age, even when adjustments were made for children with these symptoms during the first 2 years of life.

Conclusion The increasing prevalence of FHS up to the age of 8 years probably reflects an increasing prevalence of allergy to birch pollen and pollen-related reactions to foods. Reactions to egg, peanuts and tree nuts early in life increase the risk of FHS at 8 years. Furthermore, reported FHS at young ages, even though transient, seems to increase the risk for other allergic diseases at 8 years of age.

Keywords BAMSE, children, food allergy, food hypersensitivity, sensitization

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Introduction

Perceived food hypersensitivity (FHS) in young children is common and constitutes an important issue for parents and paediatric health care [1–4]. The uncertainty about the timing and outcome of allergic reactions to food has

severe implications for many families [5]. Even though fatal or near-fatal reactions are rare, children with food allergy or FHS may be socially disintegrated and may have a reduced health-related quality of life, partly because of the stress and anxiety of the parents [1–7].

Sensitization to milk, peanuts, egg, tree nuts, wheat and soy in young children is dominating and has been suggested to explain 90% or more of clinical IgE-mediated reactions to food. However, there are differences in various studies depending on lifestyle and geographical variation [1, 2, 4]. Children with FHS present a wide spectrum of clinical manifestations from mild reactions such as eczema

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or diarrhoea to more severe reactions such as symptoms from the lower respiratory tract and anaphylaxis. For milder symptoms of FHS the underlying role of food allergy might be underestimated, even though a discrepancy between perceived FHS and reproducible symptoms is well known [1, 2, 4, 8]. Many children with FHS/allergy develop tolerance by school age, in particular to milk [2, 4]. However, sensitization to hen's egg has been shown to be a predictor of further development of other allergic disease [2, 9]. There are population-based studies where allergy to cow's milk has been evaluated [10–12]. However, there are only a few population-based studies describing FHS or food allergy in children at various ages [1, 3, 4, 13–16], and only one study has presented longitudinal data on reactions to food in children from 12 to 24 months of age [13].

In two recently published papers of the population-based birth cohort (BAMSE), we have shown that reactions to egg and peanut are associated with the presence of IgE-antibodies (IgE-abs) to egg and peanut at the 4-year follow-up [17]. We could also show that with increasing levels of IgE-abs towards common foods, in particular for milk, eggs and fish, there was an increased odds ratio (OR) for reported symptoms elicited by the same food. This association was not seen for soybean [18]. The aim of this study was to investigate different phenotypes of reported FHS among children during the first 8 years of life in the same birth cohort, in relation to parental report of RDFA, parental report of specific foods inducing specific symptoms, allergic sensitization to common foods and development of asthma, allergic rhinitis (AR) and eczema.

Material and methods

Study design

A population-based birth cohort (BAMSE) of more than 4000 children was established between 1994 and 1996 in Stockholm, Sweden. Detailed data on exposures and parental allergy, as well as information on parental education and employment, were obtained through a parental questionnaire when the children were 2 months old (median age) [19, 20]. Questions focusing on symptoms related to allergic disease, including questions on reactions to foods, were sent out when the children were 1, 2, 4 and 8 years of age with response rates of 96%, 94%, 90% and 84%, respectively [21, 22]. These questions, i.e. questions on asthma, eczema and rhinoconjunctivitis, have been used in the International Study of Asthma and Allergies in Childhood, and similar questions have also been used in other ongoing European birth cohorts [23, 24].

Among 3104 children, data were complete on the relevant outcomes in all questionnaires, and blood samples were obtained at both 4 and 8 years of age in 1857 of

these children. All further analyses presented in this paper are based on these two groups.

Ethical approval was obtained from the Ethics Committee of Karolinska Institutet, Stockholm, and informed consent was obtained from the parents.

Classification of outcome between 1 and 8 years of age

Food hypersensitivity (FHS): At 1, 2, 4 and 8 years, the following parentally reported symptoms related to ingestion of a certain food were defined as FHS: wheeze, itchy eyes and/or runny nose, facial oedema, urticaria, eczema or vomiting/diarrhoea.

Reported diagnosis of food allergy (RDFA): Parental report of doctor-diagnosed food allergy.

Children with reported FHS during the study period were classified into the following phenotypes:

Transient FHS: symptoms between 1 and 4 years of age but not thereafter.

Intermittent FHS: symptoms at 1 and/or 2 years, not at 4 years, but again at 8 years.

Late-onset FHS: symptoms at 4 and 8 years or at 8 years only.

Persistent FHS: symptoms at 1 and/or 2 years, and 4 and 8 years of age.

Asthma was defined as at least four episodes of wheezing in the last 12 months or at least one episode in the last 12 months in combination with prescribed inhaled steroids [17, 18].

Eczema was defined as doctor's diagnosis of eczema and/or dry skin in combination with itch for 2 weeks or more and rash with typical localization (face, arms/legs extension surfaces, arms/legs flexures, wrists/ankles or neck) during the last 12 months [21, 25].

AR was defined as doctor's diagnosis of AR or symptoms of sneezing, a runny or blocked nose, or itchy, red and watery eyes after exposure to furred pets or pollen during the last 12 months [19, 21].

Food-specific IgE-abs in plasma were measured against a mix of common food allergens including milk, egg, codfish, peanut, soybean and wheat (fx5[®]) with the ImmunoCAP[™] System (Phadia AB, Uppsala, Sweden). An IgE-ab level of ≥ 0.35 kU_A/L was considered positive.

Statistical methods

Prevalence is given in total numbers and in percent with 95% confidence intervals (95% CI). Differences in proportions between groups were tested with a χ^2 test. Background factors that may influence the development of FHS and occurrence of allergen-specific IgE-abs to food were tested in order to detect differences among children who dropped out between 2 months and 8 years of age and children remaining in the study. Such factors were sex, parental allergy, exclusive breastfeeding,

socio-economic status and early exposure to tobacco smoke. Levels of IgE-ab to specific food allergens are expressed as geometric mean and 95% CI. A *t*-test was used for comparison of IgE-ab levels among the different groups. A *P*-value < 0.05 was considered to be significant.

OR estimates and corresponding 95% CI were obtained using logistic regression. Potential confounders were identified and adjustments were finally made for parental allergy, because this was the only factor affecting the risk estimates with 10% or more. In the analysis of the OR for FHS at 8 years of age in relation to FHS caused by individual food allergens at 2 years of age, adjustments were made for all other food allergens under study. In the risk analysis of asthma, AR and eczema at 8 years of age for children with different phenotypes of FHS in relation to children who never reported FHS, all children with food-related asthma, AR and eczema at 1 or 2 years of age were excluded from the analysis. All analyses were performed using STATA 9.2 (Stata, College Station, TX, USA).

Results

Children who dropped out before 8 years of age compared with the children of the study base (*n* = 4089) did not differ in any exposure factors such as maternal smoking, breast-feeding or socio-economic class. Up to the age of 4 years, there was no difference in allergic outcome between those who dropped out and those who did not. However, children who dropped out between 4 and 8 years more often had doctor-diagnosed asthma (16%) and eczema (32%) at 4 years of age as compared with 10% and 22% in the children remaining in the study at 8 years (*P* = 0.001 and *P* < 0.001, respectively). Children with available blood samples were similar in all background factors as well as in occurrence of asthma and eczema during the first 4 years of age as compared with children from whom no blood was obtained.

Data on the prevalence of FHS and RDFA over time in relation to sensitization to food ($\text{fx5}^{\text{®}} \geq 0.35 \text{ kU}_A/\text{L}$) are shown in Table 1. There was a statistically significant increase in the prevalence of FHS between 1 and 8 years of age. Furthermore, the proportion of children sensitized to food increased among both children with RDFA and children without such a diagnosis. However, between 1 and 8 years of age, reported reactions to milk and egg decreased (Fig. 1). In contrast, there was an increase of reported reactions to peanuts and tree nuts over time.

Transient, intermittent, late-onset and persistent FHS were found in 13%, 1.6%, 7.7% and 3.7%, respectively; i.e. 26% reported FHS at some point during the 8 years of follow-up. Among children with persistent FHS, a significantly larger proportion (83%) had an RDFA as compared with the other FHS phenotypes (transient FHS 23%, intermittent FHS 61% and late-onset FHS 37%, *P* < 0.01

Table 1. Prevalence of food hypersensitivity (FHS) in relation to sensitization to food ($\text{fx5}^{\text{®}} \geq 0.35 \text{ kU}_A/\text{L}$) and reported diagnosis of food allergy (RDFA) at different ages

	1 year		2 years		4 years		8 years	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI
FHS	9.8	8.7–10.8	9.5	8.4–10.5	10.9	9.5–12.4	13.8	12.5–15.4
Sensitized to food	NA	NA	NA	NA	4.1	3.2–5.1	7.2	6.0–8.4
Not sensitized to food	NA	NA	NA	NA	6.8	5.6–7.9	6.6	5.4–7.7
FHS and RDFA	3.1	2.5–3.7	4.4	3.7–5.1	4.9	3.9–5.9	7.6	6.4–8.9
Sensitization to food	NA	NA	NA	NA	3.2	2.4–4.0	5.3	4.3–6.3
Not sensitized to food	NA	NA	NA	NA	1.7	1.1–2.3	2.4	1.7–3.1
FHS without RDFA	6.7	5.8–7.6	5.1	4.3–5.9	6.0	4.9–7.1	6.1	5.0–7.2
Sensitization to food	NA	NA	NA	NA	1.0	0.5–1.4	1.9	1.3–2.6
Not sensitized to food	NA	NA	NA	NA	5.1	4.1–6.1	4.3	3.6–5.5

95% CI, 95% confidence intervals; FHS, food hypersensitivity; RDFA, reported diagnosis of food allergy; NA, not applicable.

for all). The association with various symptoms of FHS and RDFA are presented in Table 2. Children with persistent FHS significantly more often reported occurrence of wheeze, itchy eyes/runny nose, urticaria and eczema as symptoms caused by foods as compared with children with transient FHS (*P* < 0.001 for all). Irrespective of the phenotype of FHS, almost all children with wheeze or itchy eyes/runny nose had an RDFA, with the exception of children with transient FHS.

Sixteen percent of all children in the cohort were sensitized to food at 4 years, and 20% were sensitized at 8 years. Among children with FHS, 38% were sensitized to food at 4 years and 52% at 8 years. The corresponding figures for children without FHS were 13% at four years and 14% at eight years. Children with persistent FHS exhibited significantly higher IgE-ab levels to food at both 4 and 8 years of age (*P* < 0.001 for both) as compared with the other phenotypes combined (data not shown). The pattern of sensitization was very similar in children who never had FHS and children with transient FHS. More detailed information on sensitization is presented in Table 3. A positive $\text{fx5}^{\text{®}}$ at 4 years of age increased the risk of persistent FHS in comparison with children with intermittent or late-onset FHS ($\text{OR}_{\text{adj}} = 2.2$; 95% CI 1.3–3.9).

The mean number of foods reported to cause symptoms showed a significant increase at 1, 2, 4 and 8 years of age: 1.4 (1.3–1.5), 1.6 (1.5–1.7), 2.1 (1.9–2.2) and 2.3 (2.1–2.5), respectively, and 27% (22–32%), 38% (34–45%), 51% (45–56%) and 51% (46–56%) were reported to react to at

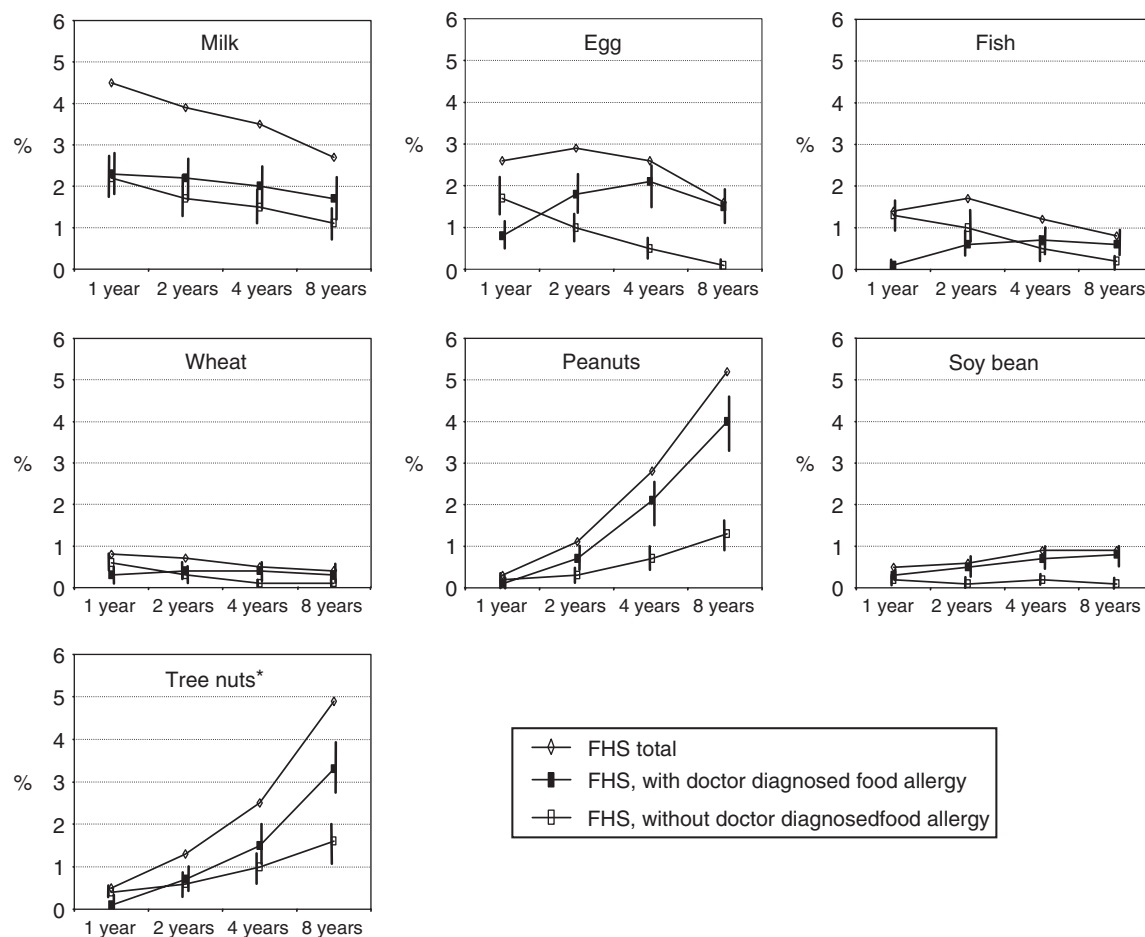


Fig. 1. Prevalence of reported food hypersensitivity (FHS) and 95% confidence intervals to specific foods divided by reported diagnosis of food allergy at a certain age in a birth cohort of 3104 children.

Table 2. Symptoms caused by food in children between 1 and 8 years of age with different phenotypes of food hypersensitivity in relation to reported diagnosis of food allergy (RDFA), $n = 3104$

Symptoms caused by food	Transient ($n = 399$)		Intermittent ($n = 51$)		Late onset ($n = 239$)		Persistent ($n = 115$)	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Wheeze	1.0		20		12		24	
RDFA	0.5	-0.2 to 1.2	18	6.8-28	9.2	5.5-13	23	15-30
Itchy eyes and/or runny nose	7.0		20		18		46	
RDFA	3.3	1.5-5.0	18	6.8-28	9.6	5.9-13	43	33-52
Urticaria	31		43		15		65	
RDFA	11	7.8-14	25	13-38	7.5	4.2-11	59	50-68
Eczema	40		55		13		72	
RDFA	11	7.9-14	37	24-51	6.3	3.2-9.4	62	53-71
Vomiting/diarrhoea	57		55		20		59	
RDFA	13	9.7-16	32	18-45	11	6.9-15	50	40-59
OAS*	-		49		49		46	
RDFA	-		24	11-36	13	8.7-17	41	32-50

*Data only available from the 8-years-of-age questionnaire.
95% CI, 95% confidence intervals; RDFA, reported diagnosis of food allergy; OAS, oral allergy symptoms.

least two foods at the corresponding ages. The foods reported to cause symptoms at 8 years of age were almost identical among children with late-onset FHS, intermittent FHS or persistent FHS. Peanuts and tree nuts together with birch pollen-associated foods were dominating as symptom-eliciting food items. The only difference was seen for persistent FHS, where one-third of the children were reported to have symptoms related to egg. Among children with late-onset FHS only 4% reported egg-related symptoms, and the corresponding figure for intermittent FHS was 10%. Reactions during the first 2 years of life to egg, peanuts and tree nuts significantly increased the risk for FHS at 8 years [$OR_{adj} = 3.6$ (95% CI 1.9-6.7), $OR_{adj} = 4.3$ (95% CI 1.5-12) and $OR_{adj} = 5.3$ (95% CI 1.9-15), respectively]. This was in contrast to fish, wheat and soy, where no significant increase of the OR was seen (data not shown).

Having a certain allergic disease at a certain age is dependent on the presence of the same disease earlier in life. Thus, in order to avoid errors of dependency in the analyses, we excluded children with food-related asthma, eczema or rhinitis at 2 years of age or earlier in life in the analysis of risk for asthma, eczema or rhinitis at 8 years if

Table 3. Proportion and levels (geometric mean) of IgE antibodies to food (fx5[®] 0.35 kUA/L) at 4 and 8 years in relation to phenotypes of food hypersensitivity (FHS) between 1 and 8 years of age in 1857 children of a birth cohort

	Never FHS (n = 1359)		Transient* (n = 246)		Intermittent [†] (n = 33)		Late onset [‡] (n = 144)		Persistent [§] (n = 76)	
	%	kU _A /L	%	kU _A /L	%	kU _A /L	%	kU _A /L	%	kU _A /L
Not sensitized at 4 or 8 years	85	NA	81	NA	36	NA	57	NA	30	NA
Sensitized at 4 years only	4	0.6	3	0.5	6	0.9	6	0.6	0	0
Sensitized at 8 years only	7	0.7	11	0.7	9	1.1	9	0.8	9	1.2
Sensitized at both 4 and 8 years	4	1.0 (at 4) 1.0 (at 8)	5	1.2 (at 4) 1.6 (at 8)	48	9.4 (at 4) 6.4 (at 8)	28	4.5 (at 4) 5.0 (at 8)	61	11 (at 4) 12 (at 8)

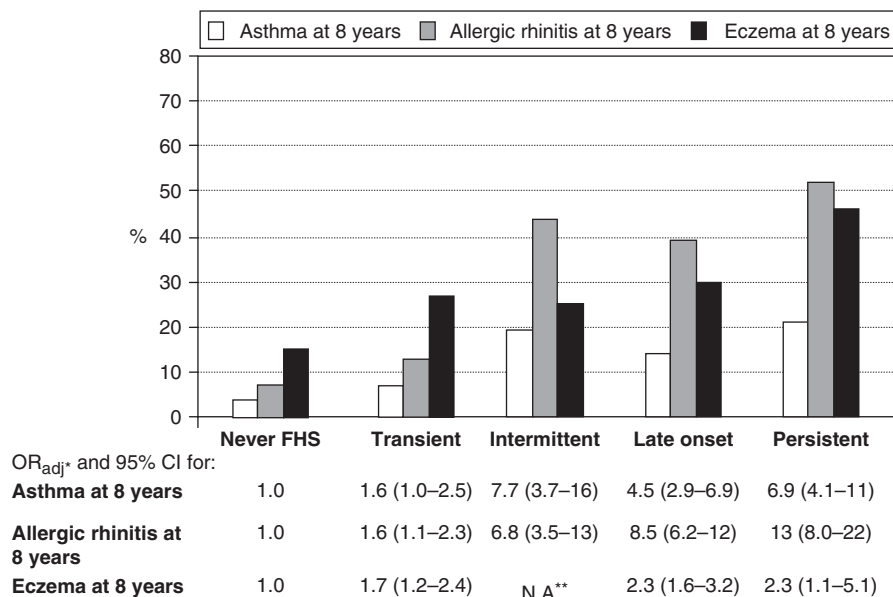
*Transient FHS: symptoms between 1 and 4 years of age but not thereafter.

[†]Intermittent FHS: symptoms at 1–2 years, not at 4 years, but at 8 years again.

[‡]Late onset FHS: from 4 years continuously or from 8 years.

[§]Persistent FHS: symptoms at 1–2 years, 4 and 8 years of age.

FHS, food hypersensitivity; NA, not applicable.

**Fig. 2.** Phenotypes of food hypersensitivity (FHS) and allergic disease [odds ratio (OR) and 95% confidence intervals (95% CSI)] at 8 years of age in 3104 children. *Adjustments were made for parental allergy and for asthma/rhinitis/eczema up to 2 years of age; children with food-related asthma/rhinitis/eczema up to 2 years of age are excluded. **There were too few children in this category to perform the analysis.

age. Still, transient, late-onset or persistent FHS significantly increased the OR for asthma, AR and eczema at the age of 8 years, which was most evident for persistent FHS even after adjustment for non-food-related asthma, eczema or rhinitis at 2 years of age or earlier. (Fig. 2).

Discussion

We have prospectively investigated the prevalence of different phenotypes of parentally reported FHS among more than 3000 children from birth to 8 years of age. Our intention was not to confirm FHS/allergy by challenge, but to elucidate the relationship between early FHS and

RDFA and to investigate if early FHS is a risk factor for the development of other allergic disease later in childhood. To our knowledge, there is no other report providing longitudinal data of FHS during the first 8 years of life. Levels of food-specific IgE-ab in relation to symptoms to foods have been published elsewhere [18].

Reported phenotypes of FHS during the first 8 years of life affected 26% of the children. However, when FHS was combined with positive fx5[®] or RDFA, the occurrence of FHS almost decreased by half. The prevalence of FHS at different time points ranged from 9.8% of 1-year-olds to 13% of 8-year-olds. For children with RDFA in combination with current symptoms of FHS, there was a

significant increase in prevalence over time, which was closely related to an increase in the number of children with reported reactions to peanuts and tree nuts. The observed increase in the proportion of children with FHS with increasing age is likely to reflect an increasing prevalence of sensitization to birch and grass pollen and pollen-related reactions to food, mainly tree nuts and certain fruits [26]. It is noteworthy that few children sensitized to soy or wheat reported reactions to these food items, which strengthens the assumption of cross-reactivity between different foods as well as between pollen and foods [18].

Our data on the prevalence of FHS are in line with the results of a prospective birth cohort from Oslo, where the cumulative incidence of FHS between 1 and 2 years of age was 35%. However, only one-third of the children still reacted after another 6 months [9]. Furthermore, our data on children with RDFA at 1 year of age are also in accordance with the results of a study among infants from the Isle of Wight. In that study, the cumulative incidence of parentally reported FHS was 26% during the first year of life, but a definite food allergy could only be verified with food challenges in < 5.5% of the children [27]. In another study from the Isle of Wight, among children 11–15 years of age, sensitization to food and the prevalence of FHS were rather similar to the 8-year-olds in our study [28]. Under the assumption that the prevalence rates are similar in the different populations, this indicates that our definitions of different phenotypes of FHS are valid compared with other studies.

Because we had longitudinal data on FHS during the first 8 years of life, we were able to assess different phenotypes depending on age of onset and duration of symptoms. In previous studies on asthma in children, allocation has been performed in relation to transient, persistent and late onset of the disease. This allocation has been used to assess risk factors and clinical predictors of remission or persistency of disease [22, 29]. In our study and depending on symptoms, 85–96% of the children with persistent FHS had RDFA, which is to be compared with 50% or less for the children with transient FHS. The rather low proportion of food allergy diagnosed by a doctor in the group of transient FHS is likely because of a rather short period of symptoms as well as a possibility of less severe symptoms. With the allocation into different phenotypes, we were also able to show that children with persistent FHS were sensitized to food significantly more often at both 4 and 8 years of age and exhibited higher IgE-ab levels to the selected food allergens, as compared with children with intermittent or late onset of FHS. Furthermore, it was shown that reported reactions at 2 years of age towards egg, peanuts and tree nuts were associated with FHS at 8 years, which was not seen for other food items. Early sensitization to egg has previously been shown to be associated with later allergic disease [9].

Furthermore, in children allergic to peanuts or tree nuts, development of tolerance to these food items does occur but is not as common as development of tolerance to milk and egg [30, 31]. This could, at least partly, explain the relationship between the report of early symptoms to peanuts or tree nuts and allergic disease later in life.

There are few studies on co-morbidity and FHS. However, in a paper by Sandin *et al.* [32], FHS was more common in wheezing than in non-wheezing children. In a recent French study among 9–11-year old children, food allergy was highly associated with asthma and AR [33]. Moreover, in two prospective Danish studies, an association between cow's milk allergy and later development of asthma or AR was seen [10, 11]. We have shown that FHS in 8-year-olds is highly associated with asthma, AR and eczema at the same age, which implies the importance of overall atopy, and may as well implicate the concept of a systemic disease. We also found that transient, intermittent and persistent FHS, all with an onset before 4 years of age, significantly increased the OR for asthma, AR and eczema at 8 years of age (with the exception of intermittent FHS and eczema). Our data on early FHS as a risk factor for other allergic disease later in childhood remained statistically significant even after exclusion of children with food-related asthma or eczema before 2 years of age if FHS was simultaneously present.

The strength of our study is the high participation rate during the 8 years of follow-up with complete questionnaire data of 3104 children (75%) of the original cohort. Furthermore, we also have access to data on allergen-specific IgE-abs to a mix of the six most common food allergens together with questionnaire data in 60%, even though the non-responders might influence the results of our study and raise the question whether it is adequate to generalize our findings or not. There was no difference in exposure between children remaining in the study compared with the children in the study base. However, more children with asthma and eczema at the age of 4 years dropped out between 4 and 8 years, which may result in an underestimation of our prevalence ratios of phenotypes of FHS at the age of 8 years. The investigated group of children who were IgE tested did not differ in any respect from those without blood samples. Taken together, all this strengthens the assumption that it is adequate to generalize our findings.

We are aware that it would have been optimal to have food-specific IgE-abs at 1 and 2 years of age. Because the majority of the participating children at this age group would have been negative, we did not perform such testing for ethical reasons and because we wanted to reduce the risk of drop-out at follow-up. Oral challenges are the gold standard for verification of food allergy, and it would have been a further strength in this study if such challenges had been performed. However, it would only have been possible to perform oral challenges among the

8-year-olds. We would have needed to include food allergen-sensitized children but without a report of symptoms. This would have caused an ethical dilemma as well in this group of young and mostly healthy children. For future follow-ups and when the participants are in their teenage years, the situation is different.

RDFA increased from 3% to 8% from 1 to 8 years of age. All phenotypes of FHS showed co-morbidity with asthma, AR and eczema at the age of 8 years. Furthermore, early FHS increased the risk for onset of asthma, AR, as well as eczema at 8 years of age. Children with persistent FHS could be characterized by RDFA, high levels of food allergen-specific IgE, early report of reactions to egg, peanuts and tree nuts, more concomitant with other allergic diseases as compared with children with transient, intermittent and late-onset FHS.

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