

## ORIGINAL ARTICLE

# Prospective association between food sensitization and food allergy: results of the LISA birth cohort study

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## Clinical & Experimental Allergy

### Summary

**Background** Food allergy is common, especially in childhood, where 6–8% of children are affected. Identification of early and efficient markers for later development of food allergy is very important.

**Objective** We examined the ability of repeated measurements of food sensitization in early childhood to predict doctor-diagnosed food allergy (DDFA) at the age of 6 years.

**Methods** The analysis was based on data from a prospective birth cohort study. Information was collected by parental questionnaires, and blood samples were obtained at 2 and 6 years of age. Children with repeated determination of sensitization to food allergens at 2 and 6 years of age were categorized into the sensitization phenotypes: no, early onset, late onset and persistent sensitization. The association between sensitization phenotypes and DDFA was prospectively investigated using multiple logistic regression analyses.

**Results** Of 3097 children recruited at birth, a complete follow-up of IgE measurements and questionnaires at 1.5, 2 and 6 years were available for 1082 children. Early food allergen sensitization (fx5) was a strong risk for DDFA at 6 years [odds ratio (OR) = 4.7; 95% confidence intervals (95% CI) 2.0–11.2] and for a new onset of DDFA at 6 years (OR = 4.1; 95% CI 1.5–11.3). Additionally, persistent food allergen sensitization increased the risk of DDFA at 6 years (OR = 6.1; 95% CI 2.7–13.7). Early sensitized children with a history of parental atopy showed the highest risk for DDFA at 6 years.

**Conclusion** Food-sensitized children during the first 2 years of life, especially with a family history of atopy, might be considered as a susceptible subgroup that requires specific attention concerning the development of food allergy-related symptoms.

**Keywords** children, food allergy, food sensitization, specific IgE

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### Introduction

A meta-analysis recently indicated that the prevalence of self-reported food allergy ranges between 3% and 35% in the general population [1]. The reasons for this heterogeneity are, besides geographic differences also, differences in study design and inconsistent methods to define food allergy. As most studies are based only on

the perception of adverse reactions to food, they certainly overestimate the prevalence of food allergy. Nevertheless, food allergy is very common, especially in the paediatric population, where 6–8% of infants suffer from food allergy [2, 3]. This high prevalence of food allergy in childhood and growing public awareness make efficient diagnosing of suspected food allergy very important.

Till today double-blind, placebo-controlled food challenges (DBPCFC) are still the gold standard for the diagnosis of food allergy. But they are time consuming, expensive and imply the risk of anaphylaxis [4]. Therefore, identification of early and efficient markers for later development of food allergy is very important. In recent years, the determination of food-specific IgE antibodies has facilitated the diagnostic analysis of food allergy [4, 5]. While most food allergies are IgE mediated, there is sensitization to food allergens with and without clinical manifestation [2, 6]. Even so, several studies could indicate that the quantification of food-specific IgE antibodies is useful to identify symptomatic allergy to egg, milk, peanut and fish [1, 5, 7, 8]. Considering that allergies are largely progressive diseases during early life with sensitization represented at an early stage and the onset of symptoms shown at a later stage, one may take the time of the first sensitization into account for the prediction of food allergy [2].

Until today, there are only few population-based birth cohorts, which measured specific IgE antibodies at two points of time in early life [9]. Thus, the aim of this study was to examine the ability of food sensitization phenotypes, defined as early onset, late onset and persistent sensitization to food-specific allergens, to assess the risk of doctor-diagnosed food allergy (DDFA) at the age of 6 years.

## Methods

### Study design

Data from the ongoing birth cohort study 'Influences of lifestyle-related factors on the immune system and the development of allergies in childhood' (LISA) were analysed up to the age of 6 years. The study design of this prospective population-based birth cohort study has been described in detail before [10]. In brief, 3097 healthy full-term neonates born between November 1997 and January 1999 were enrolled at selected maternity hospitals in four German cities (Munich, Leipzig, Wesel and Bad Honnef). Self-completion questionnaires were biannually filled in by the parents from birth to 2 years and at 4 and 6 years. Blood samples were obtained at 2 and 6 years. Informed consents were obtained from the parents of all children. Ethical approval for the study was obtained from the local ethics committees.

### Classification of food sensitization and food allergy

Allergen-specific IgE antibodies were measured using a mix of common food allergens (fx5: hen's egg, cow's milk, peanut, soybean, wheat flour and codfish). A positive result in this screening test was followed by measurements of the single allergens (hen's egg, cow's milk and peanut)

at 2 years and for all six allergens, at 6 years of age. IgE specific to soybean, wheat flour and codfish were not measured at the age of 2 years, because these food allergies play only a minor part compared with egg, milk and peanut allergy during early childhood. Standardized methods with the CAP System FEIA (Pharmacia Diagnostics, Freiburg, Germany) were used. Sensitization was defined as an IgE antibody level  $\geq 0.35$  kU/L.

Sensitization to food allergens (fx5) and to three single allergens (hen's egg, cow's milk and peanut) was classified into the following four sensitization phenotypes:

*No sensitization:* no IgE at 2 and 6 years.

*Early onset sensitization:* IgE only at 2 years.

*Late onset sensitization:* IgE only at 6 years.

*Persistent sensitization:* IgE at 2 and 6 years.

Questionnaires included parental statement on DDFA for each year up to the age of 6 years. DDFA at 2 and 6 years was defined as physician's diagnosis of food allergy during the preceding 12 months at the age of 2 and 6 years, respectively. Food allergy is, by definition, an adverse immune response to a food protein. However, we had no information on what kind of diagnostic this physician's diagnosis of food allergy is based on. Thus, the doctors diagnosis has to be considered with caution, as in some cases it might refer to all food-related problems and not only to reactions mediated by the immune system. Additionally, we defined children with new onset of DDFA at the age of 6 years. Consequently, children with a reported physician's diagnosis of food allergy at the age of 2 years were excluded.

### Statistical analysis

Prevalence and incidence of DDFA was calculated for the total study population and differences in relation to gender and parental atopy were tested using the  $\chi^2$ -test. Parental atopy was defined as one or both parents with at least one reported atopic disease. In addition, the prevalence of children with symptoms reported related to the ingestion of certain food and of children with former symptoms but remission after elimination was determined.

The following analysis was restricted to those children with a complete data set of 1.5-, 2- and 6-year questionnaires and serum-specific IgE measurement at 2 and 6 years. The sensitization phenotypes were calculated stratified for gender, study region and parental atopy. We investigated the relationship between DDFA and the sensitization phenotypes to common food allergens, using Fisher's exact test to determine statistically significant differences. Multiple logistic regression analyses were performed for the association between sensitization phenotypes and food allergy. Results were presented as crude

odds ratio (OR) and adjusted odds ratio (aOR) with 95% confidence intervals (95% CI). Adjustment was carried out for the *a priori* defined potential confounding factors of study region, gender, parental education and parental atopic diseases. Additionally, the association between sensitization phenotypes and food allergy was stratified for parental atopy. All statistical analyses were performed with SAS 9.1 (SAS Institute, Cary, NC, USA).

## Results

### Study population

Of 3097 children who were recruited at birth, a complete follow-up of IgE measurements at 2 and 6 years and questionnaires at 1.5, 2 and 6 years were available for 1082 children (Table 1). In this final study population, more boys ( $P=0.02$ ), children with a family history of atopy ( $P<0.01$ ) and with a higher level of parental education ( $P<0.01$ ) could be observed compared with the children with incomplete data. However, there was no difference concerning the presence of positive cord blood IgE ( $\geq 0.35$  kU/L). Concerning the study region, in Munich and Bad Honnef, the responder rate, the level of parental education and the atopy-linked heredity were higher. But no differences between the four geographical areas in relation to gender, DDFA at 2 and 6 years and sensitization phenotypes could be observed.

### Doctor-diagnosed food allergy

The annual incidence of DDFA decreased from an average of 4.7% per year during the first 2 years to an average of

1.2% for the fifth and sixth year of age. The peak prevalence was 6.6% in the second year; after that, it almost remained constant at about 3.9% per year. More than 90% of all children with DDFA-reported symptoms related to the ingestion of certain food and more than 80% performed successful elimination diet concerning this food. No significant differences between boys and girls were found. However, children with a parental heredity for atopy had about twice as many DDFA at 2 years (OR = 0.5; 95% CI 0.3–0.9) compared with those without parental atopy. This difference could not be shown for DDFA at 6 years (OR = 1.0; 95 CI 0.5–1.7).

### Sensitization at 2 and 6 years of age and sensitization phenotypes

Prevalence of sensitization to food allergens (fx5 positive) increased from 9.4% at 2 years to 11.7% at 6 years of age. This was reflected by an increased sensitization to peanuts from 2.1% to 5.2%. In contrast, the prevalence of IgE to hen's egg and cow's milk decreased with age, from 5.7% to 2.7% (hen's egg) and from 5.0% to 4.3% (cow's milk) (Table 2). There were no substantial differences concerning the sensitization to food allergens at 2 years between the study population and the drop outs without any IgE at 6 years of age.

Early onset, late onset and persistent sensitization to food allergens (fx5) were found in 4.6%, 6.9% and 4.8%, respectively. However, the sensitization phenotypes showed differences with respect to the various food allergens. Early onset was more common for hen's egg (4.3%) and cow's milk (3.1%) sensitization compared with peanut sensitization (0.9%). Accordingly, late onset of

Table 1. Characteristics of responders and non-responders

|                               | Responders ( $N=1082$ ) |      | Non-responder ( $N=2015$ ) |      | P-value |
|-------------------------------|-------------------------|------|----------------------------|------|---------|
|                               | <i>n</i>                | %    | <i>n</i>                   | %    |         |
| Gender                        | $N=1082$                |      | $N=2015$                   |      | 0.02    |
| Male                          | 586                     | 54.2 | 1000                       | 49.6 |         |
| Study region                  | $N=1082$                |      | $N=2015$                   |      | <0.01   |
| Munich                        | 541                     | 50.0 | 926                        | 46.0 |         |
| Leipzig                       | 297                     | 27.5 | 679                        | 33.7 |         |
| Wesel                         | 100                     | 9.2  | 248                        | 12.3 |         |
| Bad Honnef                    | 144                     | 13.3 | 162                        | 8.0  |         |
| Other children living at home | $N=1082$                |      | $N=2011$                   |      | 0.11    |
| Yes                           | 528                     | 48.8 | 921                        | 45.8 |         |
| Parental education            | $N=1072$                |      | $N=1988$                   |      | <0.01   |
| High                          | 769                     | 71.7 | 1197                       | 60.2 |         |
| Medium                        | 266                     | 24.8 | 640                        | 32.2 |         |
| Low                           | 37                      | 3.5  | 151                        | 7.6  |         |
| Parental atopic diseases      | $N=1078$                |      | $N=2012$                   |      | <0.01   |
| Yes                           | 604                     | 56.0 | 981                        | 48.8 |         |
| Cord blood IgE                | $N=703$                 |      | $N=1280$                   |      | 0.87    |
| Yes                           | 230                     | 32.7 | 414                        | 32.3 |         |

**Table 2.** Prevalence of sensitization to common food allergens in the study population of 1082 children

| Age     | Allergen |      |           |     |          |     |          |     |          |     |             |     |          |     |
|---------|----------|------|-----------|-----|----------|-----|----------|-----|----------|-----|-------------|-----|----------|-----|
|         | Fx5      |      | Hen's egg |     | Cow'milk |     | Peanut   |     | Soybean  |     | Wheat flour |     | Codfish  |     |
|         | <i>n</i> | %    | <i>n</i>  | %   | <i>n</i> | %   | <i>n</i> | %   | <i>n</i> | %   | <i>n</i>    | %   | <i>n</i> | %   |
| 2 years | 102      | 9.4  | 62        | 5.7 | 54       | 5.0 | 23       | 2.1 | *        |     | *           |     | *        |     |
| 6 years | 127      | 11.7 | 29        | 2.7 | 47       | 4.3 | 56       | 5.2 | 41       | 3.8 | 50          | 4.6 | 7        | 0.7 |

\*No data available.

Sensitization, allergen-specific IgE-antibodies  $\geq 0.35$  kU/L; fv5, mix of common food.**Table 3.** Prevalence of sensitization phenotypes to common food allergens in the study population of 1082 children

| Allergen   | Sensitization phenotypes |      |             |     |            |     |            |     |
|------------|--------------------------|------|-------------|-----|------------|-----|------------|-----|
|            | No sensitization         |      | Early onset |     | Late onset |     | Persistent |     |
|            | <i>n</i>                 | %    | <i>n</i>    | %   | <i>n</i>   | %   | <i>n</i>   | %   |
| Fv5        | 905                      | 83.6 | 50          | 4.6 | 75         | 6.9 | 52         | 4.8 |
| Hen's egg  | 1007                     | 93.1 | 46          | 4.3 | 13         | 1.2 | 16         | 1.5 |
| Cow's milk | 1002                     | 92.6 | 33          | 3.1 | 26         | 2.4 | 21         | 1.9 |
| Peanut     | 1015                     | 93.9 | 10          | 0.9 | 43         | 4.0 | 13         | 1.2 |

No sensitization, no sensitization at 2 and 6 years; Early onset, sensitization only at 2 years; Late onset, sensitization only at 6 years; Persistent, sensitization at 2 and 6 years; Sensitization, allergen-specific IgE-antibodies  $\geq 0.35$  kU/L; fv5, mix of common food.

peanuts sensitization was more frequent (4.0%) than egg (1.2%) and milk (2.4%) sensitization (Table 3).

A description of the study population according to the sensitization phenotypes to fv5 is given in Table 4. Persistent sensitization was twice as common in boys as in girls. This phenotype was also more often seen among children with atopic parents, but this difference was not statistically significant. Furthermore, there were no significant differences between the sensitization phenotypes in relation to the geographical areas.

#### *Association between sensitization phenotypes and food allergy*

In the descriptive analysis, early onset and persistent sensitization to food allergens (fv5) were associated with a higher prevalence of DDFA at the age of 6 years in comparison with late onset sensitization. This was more pronounced for the persistent phenotype, where 18.0% of the children had a DDFA at 6 years compared with 14.2% for the early onset phenotype. However, for children with a DDFA only at the age of 6 years, an early onset sensitization showed the greatest influence. Thus, 10.4% of the children with early fv5 IgE compared with 4.1% for those with late or persistent fv5 IgE showed a DDFA only at 6 years. Similar results were shown for hen's egg, cow's milk and peanut sensitization except for DDFA at 6 years

only. Here, children with persistent egg or milk sensitization indicated the strongest association to a DDFA only at the age of 6 years, but this remained no longer significant (Table 5). An additional analysis, in which sensitization was defined as specific IgE levels of at least 0.70 kU/L, changed the results only slightly. Persistent sensitization to food allergens (fv5) was still associated with a higher prevalence of DDFA at the age of 6 years in comparison with a late onset sensitization. However, children with an early onset sensitization to fv5 did not show an elevated prevalence of DDFA at 6 years. Thus, persistent food allergen sensitization increased the risk of DDFA at 6 years (OR = 14.22; 95% CI 5.6–36.0). However, these results have to be considered with caution, because of the low prevalence of the sensitization phenotypes, which is reflected in the broad confidence intervals.

In the multivariate analysis, an early food allergen sensitization increased the risk of DDFA at 6 years (OR = 4.7; 95% CI 2.0–11.2) and of DDFA, at 6 years only (OR = 4.1; 95% CI 1.5–11.3). Additionally persistent food allergen sensitization showed a strong association with DDFA at 6 years (OR = 6.1; 95% CI 2.7–13.7). After adjustment for study region, gender, parental education and parental atopic diseases, these associations, OR and 95% CI did not change significantly (Table 6). The stratification for parental atopy indicated that early sensitized children with a history of parental atopy are at a high risk for DDFA at 6 years (see Fig. 1). Apart from that, children with atopic heredity had a higher risk for a DDFA at the age of 2 years (OR = 1.8; 95% CI 1.1–3.0), but not at 6 years (OR = 1.0; 95% CI 0.6–1.8).

#### **Discussion**

This study is one of few investigations on the association between repeated determination of sensitization to food-specific allergens and food allergy. We have a follow-up of food-specific IgE measurements at 2 and 6 years of age for more than 1000 children of a population-based birth cohort.

Only a few population-based birth cohorts have measured food-specific IgE at different points of time during early life, but without analysing the ability of multiple

**Table 4.** Characteristics of the study population ( $N = 1082$ ) according to the sensitization phenotypes according to a mix of common food allergens (fx5)

| Sensitization phenotypes | $N$ | No sensitization<br>$N = 905$ (83.6%) |      | Early onset<br>$N = 50$ (4.6%) |     | Late onset<br>$N = 75$ (6.9%) |     | Persistent<br>$N = 52$ (4.8%) |     |
|--------------------------|-----|---------------------------------------|------|--------------------------------|-----|-------------------------------|-----|-------------------------------|-----|
|                          |     | $n$                                   | %    | $n$                            | %   | $n$                           | %   | $n$                           | %   |
| Gender                   |     |                                       |      |                                |     |                               |     |                               |     |
| Male                     | 586 | 475                                   | 81.1 | 30                             | 5.1 | 43                            | 7.3 | 38                            | 6.5 |
| Female                   | 496 | 430                                   | 86.7 | 20                             | 4.0 | 32                            | 6.5 | 14                            | 2.8 |
| Parental atopy           |     |                                       |      |                                |     |                               |     |                               |     |
| Yes                      | 604 | 494                                   | 81.8 | 31                             | 5.1 | 45                            | 7.5 | 34                            | 5.6 |
| No                       | 474 | 408                                   | 86.1 | 19                             | 4.0 | 29                            | 6.1 | 18                            | 3.8 |

No sensitization, no sensitization at 2 and 6 years; Early onset, sensitization only at 2 years; Late onset, sensitization only at 6 years; Persistent, sensitization at 2 and 6 years; Sensitization, allergen-specific IgE-antibodies  $\geq 0.35$  kU/L; fx5, mix of common food.

**Table 5.** Doctor-diagnosed food allergy (DDFA) in relation to sensitization phenotypes to common food allergens

| Sensitization phenotypes | Prevalence<br>DDFA at 6 years |      |        | New onset after second year<br>DDFA at 6 years only |      |       |
|--------------------------|-------------------------------|------|--------|-----------------------------------------------------|------|-------|
|                          | $n/N$                         | %    | $P^*$  | $n/N$                                               | %    | $P^*$ |
| Fx5                      |                               |      |        |                                                     |      |       |
| No sensitization         | 31/896                        | 3.5  | <0.001 | 24/873                                              | 2.8  | 0.036 |
| Early onset              | 7/49                          | 14.3 |        | 5/48                                                | 10.4 |       |
| Late onset               | 4/74                          | 5.4  |        | 3/73                                                | 4.1  |       |
| Persistent               | 9/50                          | 18.0 |        | 2/49                                                | 4.1  |       |
| Hen's egg                |                               |      |        |                                                     |      |       |
| No sensitization         | 41/996                        | 4.1  | <0.001 | 30/972                                              | 3.1  | 0.143 |
| Early onset              | 6/45                          | 13.3 |        | 2/44                                                | 4.6  |       |
| Late onset               | 0/13                          | 0.0  |        | 0/13                                                | 0.0  |       |
| Persistent               | 4/15                          | 26.7 |        | 2/14                                                | 14.3 |       |
| Cow's milk               |                               |      |        |                                                     |      |       |
| No sensitization         | 42/992                        | 4.2  | 0.006  | 30/966                                              | 3.1  | 0.140 |
| Early onset              | 4/32                          | 12.5 |        | 2/32                                                | 6.3  |       |
| Late onset               | 1/25                          | 4.0  |        | 0/25                                                | 0.0  |       |
| Persistent               | 4/20                          | 20.0 |        | 2/20                                                | 10.0 |       |
| Peanut                   |                               |      |        |                                                     |      |       |
| No sensitization         | 42/1005                       | 4.2  | <0.001 | 32/981                                              | 3.3  | 0.817 |
| Early onset              | 1/9                           | 11.1 |        | 0/9                                                 | 0.0  |       |
| Late onset               | 4/42                          | 9.5  |        | 2/41                                                | 4.9  |       |
| Persistent               | 4/12                          | 33.3 |        | 0/11                                                | 0.0  |       |

\* $P$ -values from Fisher's exact test.

Fx5, mix of common food.

**Table 6.** Logistic regression analysis describing the association between doctor-diagnosed food allergy (DDFA) and sensitization phenotypes to fx5 (fx5 = mix of common food)

|             | OR (95%CI)                     |                                                      |
|-------------|--------------------------------|------------------------------------------------------|
|             | Prevalence<br>DDFA at 6 years* | New onset after second year<br>DDFA at 6 years only* |
| Fx5         |                                |                                                      |
| Early onset | 4.65 (1.9–11.2)                | 4.11 (1.5–11.3)                                      |
| Late onset  | 1.59 (0.6–4.7)                 | 1.52 (0.5–5.2)                                       |
| Persistent  | 6.13 (2.7–13.7)                | 1.51 (0.4–6.6)                                       |

\*No sensitization was used as reference category.

OR, crude odds ratio; CI, confidence interval; fx5, mix of common food.

time-point sensitization to predict the report of the doctor's diagnosis of food allergy. The German Multi-Centre Allergy Study (MAS) was the first study analysing the natural course of sensitization to food allergens during the first 6 years of life [11]. They found similar to our results that the prevalence of IgE sensitization to egg and milk decreased with age [12]. Beside this, the sensitization to at least one food allergen remained stable during the first 6 years, whereas our data show a small increase in food allergen sensitization (fx5 positive). This increase is probably due to peanut sensitization, which was not measured in the MAS cohort. Another birth cohort in Sweden (BAMSE) describes a slightly different pattern of

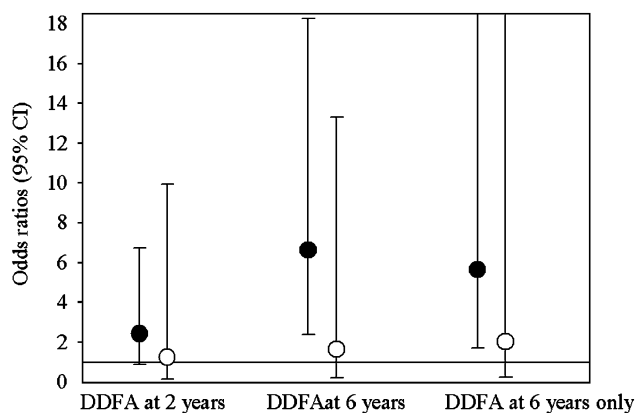


Fig. 1. Association between early onset of food sensitization to fx5 and doctor-diagnosed food allergy (DDFA) stratified for parental atopy.

food sensitization with a higher proportion of the total population being sensitized to food, and only about half as many to milk and egg compared with our study [13, 14]. This discrepancy is likely because of different age groups of the studies. In the latter study, food-specific IgE were measured in 4- and 8-year-old children.

Our classification of food sensitization reflects the course of the measured food-specific IgE. Thus for egg and milk, the early onset phenotype and for peanut sensitization, the late onset phenotype is the most frequent. This is in line with several other studies indicating that the natural course of sensitization to specific food allergens is very different [15, 16]. Response to egg or milk allergens mainly shows an early manifestation, but most children outgrow their sensitivity by the first years of life. On the other hand, peanut sensitization seems to develop at a later date in childhood. This is reflected in the positive results for fx5, which showed most frequently, a late onset. Nevertheless, the number of children with an early onset and a persistent phenotype should not be underestimated.

The main question in this study is whether onset and duration of food sensitization can be used for the prognosis of food allergy in childhood. Several studies indicate that sensitization to food and inhalant allergens are associated with allergic diseases in childhood and it may also provide indications to the severity of these diseases [17–19]. Additionally, it was shown that quantitative measurements of food-specific IgE to milk, egg and fish allergens are useful to estimate food allergy in children [20, 21]. Transient sensitization to food allergens is a common and a known phenomenon in childhood, [22] and it was demonstrated that transient sensitized children seem to have a lower risk to develop allergic diseases in later life than permanently sensitized children [23]. Furthermore, early sensitization to food allergens should be regarded as a risk factor for the development of food allergy and other allergic diseases [17, 24, 25]. These

outcomes are consistent with our results. Thus, we could indicate that an early onset of food allergen sensitization at the age of 2 years increases the risk of DDFA at 6 years of age. However, it has to be considered that some children with an early onset of food allergen sensitization had no sensitization at the age of 6 years. This might indicate that in this case, the early onset of food allergen sensitization is rather associated with non-allergic food allergy than with IgE-mediated food allergy. Additionally, persistent food allergen sensitization is associated with DDFA at 6 years. Persistent sensitization was defined as specific IgE at two points of time. Thus, it indicates the ongoing sensitization to food allergens independently from the development of this sensitization, as for example the occurrence of pollen-related cross-reactivities to foods. Sensitization to egg, milk and peanut allergens shows similar result, but because of the small numbers in these subgroups, they have to be considered with caution and no multivariate analysis was possible. The analysis of higher levels of specific IgE (at least 0.7 kU/L) showed as well that persistent food allergen sensitization is a risk factor for DDFA at the age of 6 years. But there was no association between an early onset of food allergen sensitization and DDFA at 6 years. This indicates that the degree of sensitization has an influence on the risk of later food allergy. Thus, the level of food-specific IgE is important, if you use specific IgE measurements as a diagnostic tool. However, we could not demonstrate that this risk increased with increased levels of specific IgE, because the prevalence of this higher level of sensitization was too low to be convincing. When looking at the characteristics of the study population, boys and children with parental atopy show conspicuously more often a persistent phenotype. This indicates that male gender and a family history of atopy probably increase the risk for persistent sensitization to food allergens and might, therefore, be a potential risk factor for the development of food allergy, as shown above. However, the strongest risk for the development of food allergy has proved to be early food sensitization, especially in children with a history of parental atopy. Thus, the determination of food sensitization in early childhood, especially in atopic families, might be suitable to identify children at a high risk of food allergy. But, such a screening for IgE to foods bears several challenges for the health care system, too. Thus up to now, there are no adequate and safe ways to prevent food allergy and many children sensitized to food allergens will never show any symptoms to these foods. Hence, it is difficult to provide correct advice to these sensitized children. The parents should be assured that their children may, but not necessarily will develop food allergy. Furthermore, they should be informed about possible symptoms and the children should not avoid foods that they can eat without symptoms. Additionally, the identification of food sensitization in children may have a

negative impact on their quality of life. They are stigmatized and will always remain uncertain, whether they will develop a food allergy or not. Nevertheless, the early detection of high-risk population is an important part of our health care system. It offers the possibility to evaluate individual health risks more precisely and vulnerable people can be observed carefully for the development of clinical symptoms, so that further diagnostic and an adequate therapy can be started as soon as possible.

The main advantages of this study are the prospective study design, its large study population, and the highly time-resolved collection of data. It is one of few longitudinal and population-based investigations on this topic, offering the possibility to examine sensitization at two different points of time in early life. Therefore, we could evaluate whether the onset and duration of sensitization to specific food allergens in early childhood is related to the later development of food allergy.

However, this study also has its limitations. We did not perform any food challenges within this study. Instead, we used the parental report on DDFA as the outcome, which might lead to an overestimation in comparison with DBPCFC-based estimates [26–28]. As only the parental statement on DDFA is at our disposal, we have no further information on what kind of diagnostic this diagnosis is based on. Therefore, it might refer to all food-related problems, including allergic and non-allergic mechanisms [29]. However, a Finnish study found that the validity of questionnaire-obtained information on childhood food allergy was good to excellent, based on a comparison between parental reports and hospital records [30]. Although there are some limitations in the comparability of this Finnish study to our study, it describes an example for the validation of parent-reported food allergies. Furthermore, we had no information to which foods children with DDFA showed allergic reactions. Thus, we could not examine the association between sensitization to specific food allergens and symptomatic food allergy to these foods. Additionally, the prevalence of sensitization was rather low, which is reflected in the broad confidence intervals. This potential lack of reliability has to be considered when discussing the implications of our findings. Finally, it has to be considered that a complete follow-up was available for only 35% of the children who were recruited at birth. However, it is really a challenge to take blood samples at two different points of time in a population-based birth cohort. Thus, a second measurement of specific IgE at 6 years in 55% of children with a first measurement at 2 years is a fair result. Nevertheless, it has to be considered that in longitudinal studies, drop outs are usually selective and not at random. Thus, the final analysis overrepresents boys, children with a family history of atopy and children with a higher level of parental education compared with the subject group with incomplete data. However, the prevalence of DDFA

and of sensitization to common food allergens did not differ between our analysis population and the drop outs after the second year follow-up. This again reflects that the potential bias of the disease-selective drop out is presumable small.

## Conclusion

The determination of onset and duration of food sensitization might be a strong prognostic criterion for the development of food allergy. Thus, persistent sensitisation at 2 and 6 years of age and an early onset of sensitization at the age of 2 years, but not late onset, pointed out to be a strong risk factor for food allergy at the age of 6 years. Therefore, the measurement of specific IgE antibodies against food allergens (fx5) in young children with atopic predisposition could be used to identify children who are at a high risk to develop symptomatic food allergy later on. However, the clinical importance of this early detection of high-risk children has to be challenged critically. Thus until today, there are no adequate ways of preventing the development of food allergy and many children identified will never show food allergy symptoms, despite being sensitized. Nevertheless, identifying children at risk to develop food allergy early in life offers the possibility to observe these children continuously for the development of clinical symptoms, and to start an adequate diagnostic and therapy as soon as possible.

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