

Long-lasting sensitization to food during the first two years precedes allergic airway disease

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The purpose of the study was to investigate whether the duration of sensitization to food allergens during early childhood is related to later development of IgE mediated hypersensitivity to inhalant allergens and of allergic rhinitis and asthma in 5-year-old children and whether long-lasting food-sensitization may be used to predict subsequent allergic airway diseases. Five hundred and eight children of a prospective birth cohort study with available serum samples at one and two years of age were included and followed up until five years of age. Specific sensitization to food and inhalant allergens and the occurrence of subsequent allergic airway diseases were determined. Children with a long-lasting sensitization to food allergens (persistently sensitized for more than one year) produced significantly higher total IgE and specific IgE levels than children who were only transiently food-sensitized by two years of age. Children persistently sensitized to food had a 3.4 fold higher risk of developing allergic rhinitis and a 5.5 fold higher risk of developing asthma than infants who were only transiently food sensitized. Persistent food sensitization in combination with a positive atopic family history was a strong predictor for the development of allergic rhinitis and asthma at five years of age. The risks for these children are up to 50%, and 67% respectively. Persistently detectable sensitization to food over more than one year in early childhood is a strong prognostic factor for subsequent allergic airway disease. Persistently food-sensitized children especially in atopic families have to be regarded as a high-risk group and should be considered for preventive measures against respiratory atopy.

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The search for reliable predictors to identify children at high risk for developing atopic disorders has become an important issue. No reliable predictors at birth have yet been found which might serve as a basis for primary or secondary prevention (1). Several longitudinal studies including intervention studies, however, have focused on the neonatal prediction of atopic diseases (2–6). In some of these studies the number of analyzed children was relatively small and the follow-up period short or incomplete. Predictors which satisfy public health purposes for primary or secondary prevention must be easily available and inexpensive with the best possible precision for the prognosis. This means that high risk groups should be identified and that non-atopics should not be unnecessarily alarmed and stressed with expensive and inconvenient interventions. Because of the low predictive value of the perinatal risk factors identified so far, a screening with the objective of primary prevention in

high risk groups does not seem to be promising at this time.

Allergic sensitization in infancy generally occurs first to food allergens (7–9). Sensitization to food is usually transient and most sensitized children remain asymptomatic (10, 11). What might distinguish children at risk for an allergic airway disease from non-atopics? We have reported that higher concentrations of specific IgE to hen's egg appear mostly in infants with subsequent or present inhalant allergies (12). Due to a lack of neonatal predictors, sensitization to food allergens during infancy might become a reliable predictor for the development of allergic airway diseases later in childhood and for secondary prevention strategies.

The purpose of this study is to determine whether the presence of serum IgE antibodies to food for a period of more than one year during early life, in contrast to a transient sensitization, may be used for the prognosis of subsequent allergic airway disease.

Methods

Study subjects

For a prospective multicenter birth cohort study (MAS), 1314 newborns were recruited in five German cities during 1990. A detailed description of study objects and methods is presented elsewhere (13). Briefly, 499 newborns with atopic risk factors (elevated cord blood IgE ($\geq 0.9\text{kU/l}$) and/or at least two atopic family members) and 815 newborns with none of these atopic risk factors present were included, resulting in a risk aggregated study sample. The cohort children were followed up at the ages of 1, 3, 6, 12, 18 months and 2, 3, 4 and 5 years. At each follow-up visit, parents filled out a questionnaire and gave structured interviews about the atopic symptoms and diseases of their children. Study participation rate at the fifth birthday was 76%. The study was approved by the local ethics committee.

For 508 children of our cohort, cord blood IgE and serum samples at one and two years of age were available. Our investigation was based on these subjects, who were divided into three subgroups according to their sensitization pattern to food allergens:

1. Children who had never sensitized to any of the tested food allergens by two years ($n=386$, 76%)
2. Children who were only sensitized to at least one of the tested food allergens once by two years ($n=71$, 14%). Of these 71 transiently sensitized children, 28 (39%) were sensitized on their first birthday and 43 (61%) children on their second birthday
3. Children who had been found to be persistently (twice) sensitized at both one and two years of age ($n=51$, 10%).

Laboratory methods

Serum samples were obtained from the children at birth and at 1, 2 and 5 years of age. As described previously, cord blood IgE, total serum IgE and specific IgE antibodies to hen's egg, cow's milk, soy and wheat and specific IgE to four inhalant allergens, house dust mite (Der p 1), cat dander (Fel d 1), mixed grasses and birch pollen (Bet v 1), were determined by CAP-RAST-FEIA (Pharmacia, Germany) (14). A child was considered sensitized if IgE antibody concentrations were equal to or greater than 0.35kU/l .

Definition of allergic diseases at 5 years of age

Allergic airway diseases were classified according to the questionnaires and after examination by a pediatric allergist. Period prevalences of a positive diagnosis at 5 years of age were calculated for all children followed up until 5 years of age ($n=460$).

Allergic rhinitis was defined if at least one of the following criteria was present throughout the fifth year of life:

1. Reported symptoms of blocked nose and rhinorrhea not related to infections for 2 to 8 consecutive months and /or
2. Allergic rhinitis diagnosed by the family practitioner or the study physician (considering that symptoms, see above, were not related to infections or were present especially in pollen season).

Allergic asthma was defined if at least one of the following criteria was present throughout the fifth year of life (15):

1. At least two reported episodes of wheezing or shortness of breath within the last 12 months.
2. Asthma diagnosed by the family practitioner or the study physician (considering that symptoms were not related to infections or were present especially in pollen season).

Parental atopy was assigned according to the answers parents gave to an atopy questionnaire at the birth of the study child. Parents were regarded as atopic if they reported at least one of the following atopic disorders or relevant symptoms: Atopic eczema, allergic rhinitis or asthma, allergy against food, house dust mites or cats. 'Identical parental atopy' was present if at least one parent reported an allergic manifestation (allergic rhinitis or asthma) corresponding to the allergic airway disease of the study child.

Statistical methods

Point prevalences for specific sensitization to food and inhalant allergens were calculated. They were defined as the proportion of sensitized children at a specified time point in the total group of analyzed children. In addition, we calculated the risk of developing an allergic airway disease as the proportion of diseased children in the groups of children with the different levels of sensitization to food allergens. The roles of food sensitization and other atopic parameters for the prognosis of allergic airway diseases were evaluated on the basis of the observed risks. If sensitization to food or the presence of the other factors is interpreted as a 'diagnostic test' of the future occurrence of allergic airway diseases, the risk of developing these diseases corresponds to the 'positive predictive value' (probability that a subject with a positive test result is affected).

The statistical analysis was performed using spss/pc, SPSS Inc., USA, and BMDPDYN statistical software package, BMDP Statistical Software Inc., USA. Pearson's chi-squared test was used for categorical data and Mann-Whitney U test or Kruskal-Wallis test for continuous nonparametric

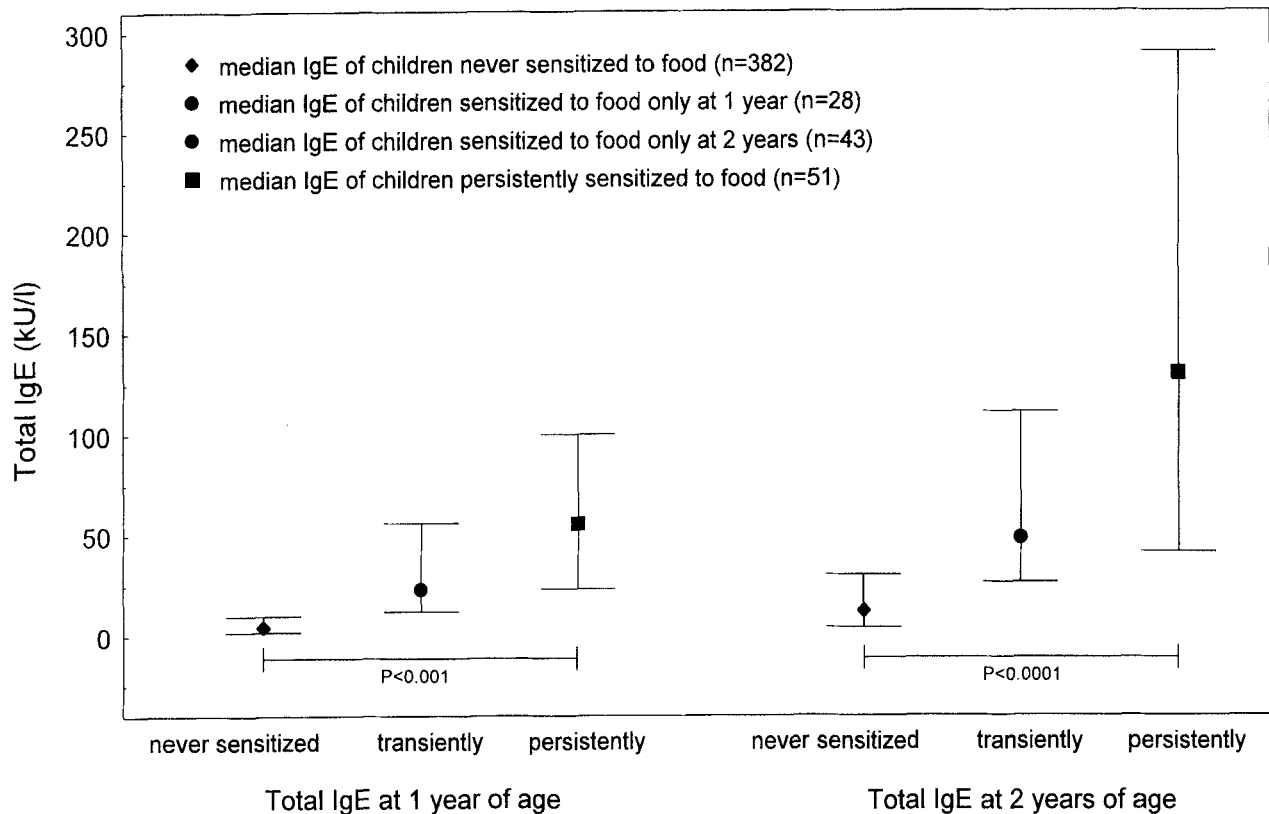


Fig. 1. Total IgE in subgroups of never, transiently and persistently food-sensitized children at 1 and 2 years of age (median, 25th and 75th percentile).

(IgE antibody levels and allergen concentrations) data analysis.

Results

Point prevalences for sensitization to at least one of the four tested food allergens throughout the first two years of life are shown in Table 1. Sensitization rates to hen's egg were highest, followed closely by

cow's milk. Relatively few children were sensitized to wheat and soy. Sensitization rates to the four tested inhalant allergens increase markedly by age (Table 1).

Comparison of the three subgroups of never, transiently and persistently food-sensitized children

General characteristics of the three analyzed subgroups in terms of sex, low birth weight, duration of breast feeding, atopic family history and home environmental conditions are listed in Table 2. No significant differences were found between the three groups. The overall MAS cohort did not differ from the analyzed group in this study regarding these characteristics.

Immunological parameters. To determine immunological differences in children according to their sensitization pattern to food allergens, the three subgroups were tested for differences in respect to total IgE and specific IgE levels and the appearance of sensitization to inhalant allergens. The group of transiently sensitized children, however, includes subjects who are negative for specific IgE at any one of the two time points. Therefore, the comparisons were performed only for those transiently sen-

Table 1. Prevalences of sensitization to food allergens and inhalant allergens at one, two and five years of age

Age	Sensitization to food allergens				
	Hen's egg	Cow's milk	Wheat	Soy	At least one of 4 food allergens
1 year (n=508) [†]	10.6%	7.3%	2.8%	2.6%	15.6%
2 years (n=508) [†]	12.6%	10.3%	4.5%	3.2%	18.5%
	Sensitization to inhalent allergens				
	Cat and/or Mite	Birch and/or Grasses	At least one of 4 inhalant allergens		
1 year (n=363) [‡]	2.4%	2.0%	4.3%		
2 years (n=363) [‡]	6.2%	8.3%	13.2%		
5 years (n=363) [‡]	13.8%	23.1%	27.3%		

[†] children with available blood samples at 1 and 2 years of age

[‡] children with available blood samples at 1, 2 and 5 years of age

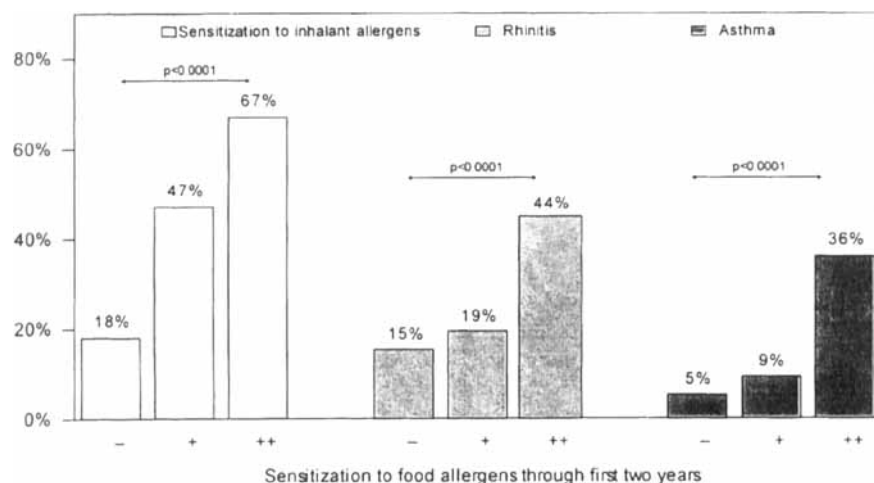


Fig. 2. Prevalences of sensitization to inhalant allergens (5th year) and allergic rhinitis and asthma (5th year) in subgroups of never (-), transiently (+) and persistently (++) food-sensitized children.

sitized children who were actually sensitized at the respective time point: The total IgE levels at one and two years of age differed significantly. The highest IgE responses were found in the group of persistently food-sensitized children ($p < 0.001$, Fig. 1). Children persistently sensitized to hen's egg had significantly higher specific IgE to this allergen at the ages of one and two than transiently sensitized children ($p < 0.005$).

Sensitization rates to inhalant allergens at 5 years of age also varied significantly between the three groups ($p < 0.0001$, Fig. 2). 18% in never (-) sensitized, 47% in transiently (+) and 67% in persistently (++) sensitized children). Approximately the same differences were observed between the three subgroups if they were stratified for parental atopy ($p < 0.0001$). Sensitization rates in children with no atopic parents were lower (8% in never (-) sensitized, 47% in transiently (+) and 67% in persistently (++) sensitized children) in comparison to children

with at least one atopic parent (26% (-), 51% (+), 80% (++)).

Allergic airway diseases. Of the children included in the analysis, 18.1% developed allergic rhinitis and 8.7% developed asthma at age five. The appearance of allergic airway diseases differed significantly among the children according to the sensitization pattern to food allergens (Fig. 2). Children with a long-lasting sensitization to food allergens developed allergic rhinitis or allergic asthma significantly more often than children only transiently or never sensitized to food ($p < 0.0001$). Infants with a long-lasting sensitization to food had a 3.4 fold higher risk (represents odds ratio) of developing allergic rhinitis and a 5.5 fold higher risk of developing asthma than infants who were only transiently food-sensitized. The risk was even higher if persistently food-sensitized children were compared to never food-sensitized: a 4.7 fold risk of developing allergic rhinitis and a 10.6 fold risk of developing asthma.

Table 2. Characteristics of study subgroups

	Sensitization pattern to food			p-value†
	never (n=386)	transient (n=71)	persistent (n=51)	
Male	48%	52%	61%	0.22
Low birth weight (< 10th percentile)	11%	13%	8%	$p = 0.71$
Parental atopy				
(at least one atopic parent)	51%	62%	65%	0.06
Breast feeding more than 4 months	54%	57%	62%	0.51
Parental smoking at 18 months	46%	52%	41%	0.49
Pets in household at 18 months	29%	32%	24%	0.66
Mite allergen exposure				
by 18 months (median)	226 ng/g	227 ng/g	380 ng/g	0.29
Cat allergen exposure				
by 18 months (median)	65 ng/g	54 ng/g	64 ng/g	0.99

† test for differences between the three groups according to the sensitization pattern

Prediction of allergic airway diseases

In order to compare the predictive capacity of the evaluated atopic parameters, the risks or probabilities of developing an allergic airway disease at five years of age are listed in Table 3. Predictive discrimination by single parameters is relatively small. In the absence of these factors, the risk of developing an allergic airway disease was only slightly lower. The observed risks were higher only in the case of persistent food sensitization. The combination of atopic family history and long-lasting food sensitization resulted in a better predictive capacity: a 48% risk of developing allergic rhinitis and a 45% risk of developing allergic asthma. The risks were higher for identical atopic family history: 50% and 67%, respectively (Table 3). Adding detectable cord

Table 3. Risk or positive predictive value (in %) of developing allergic rhinitis and asthma at five years of age depending on cord-blood (CB)-IgE, atopic family history and sensitization to food throughout the first two years of life. If the respective criterion is present ('positive'), the risk corresponds to the positive predictive value (see methods).

Prevalence of allergic airway disease in the 460 analysed children: Rhinitis Asthma			
Possible predictors at birth		18.1%	8.7%
no detectable CB-IgE (<0.35 kU/l)	n=299	16%	6%
detectable CB-IgE (≥0.35 kU/l)	n=141	19	12
no atopic family history (none atopic parent)	n=210	12	5
atopic family history† (at least one atopic parent)	n=250	23	12
atopic family history (both parents atopic)	n= 62	37	13
Sensitization to food allergens (first two years of life)			
never sensitized to food	n=351	15	5
transiently sensitized to food	n= 63	19	9
persistently sensitized to food	n= 45	44	36
Combinations of predictors‡			
no atopic family history and never food-sensitized	n=169	10	4
family history and transiently food-sensitized	n= 39	26	13
family history and persistently food-sensitized	n= 29	48	45
no identical atopic family history and never food-sensitized	n=205	10	4
identical family history and transiently food-sensitized	n= 31	26	8
identical family history and persistently food-sensitized	n= 26	50	67

†quite similar values for identical family history

‡additional detectable cord blood IgE does not increase the risk values

blood IgE to the combination of these two predictive factors did not improve the precision of the prognosis.

The ratio of the false positives and the true positives can be used as an index for the 'goodness' of the prognosis. It reflects the proportion of incorrectly versus correctly predicted allergic airway diseases. The lower the index, the less the proportion of incorrect predictions; the index would be zero for perfect prognosis, i.e. no incorrectly predicted cases. For the group of persistently sensitized children with a positive family history, the ratio was 1.1 : 1 in the case of rhinitis and 1.2 : 1 in the case of asthma. The proportions were even better (<1) if identical family history was used as prognostic criterion.

Because persistent food sensitization has proved to be a very strong predictor, we calculated the validity parameters of the prognosis. The reported risks of developing an allergic airway disease correspond with the positive predictive values (see Methods). The validity parameters sensitivity and specificity of the prognosis are only reported for the group

of persistently sensitized children. In the case of allergic rhinitis, sensitivity was 24% and specificity 93% and in the case of asthma sensitivity was 40% and specificity 93%. In combination with a positive atopic family history, the sensitivity and specificity in the case of allergic rhinitis were 42% and 92% and in the case of asthma were 65% and 92%, respectively.

Discussion

The association of allergic sensitization and subsequent development of allergic diseases has been analyzed in many studies (4, 16, 17). However, study designs have varied widely. The few longitudinal studies were mostly risk-aggregated cohorts or interventional trials of food allergen avoidance. In some studies, small sample sizes with follow-up problems may have limited the validity and generalizability of the results. In the prospective MAS, the natural course of IgE responses to food allergens of approximately 500 children was followed up throughout early childhood. The subsequent occurrence of allergic airway diseases could also be determined up to the fifth birthday.

Food-sensitized children seem to be more prone to subsequent sensitization to inhalant allergens (18, 19). Since sensitization can be regarded as predisposing for the development of allergic diseases (20–22), one important point of interest is: How can children who will develop inhalant allergies be distinguished from children who remain asymptomatic? The results of a study of 86 female children suggested that only higher specific IgE levels, especially to hen's egg, discriminated atopsics from non-atopsics). We confirmed these observations in a former analysis of our cohort, determining specific IgE levels above 2.0 kU/l as a risk factor for subsequent sensitization to inhalant allergens). In the present study, we have focused not only on the IgE levels but also on the duration of the sensitization to food allergens. Our observations considered also the occurrence of only transient sensitization (development of tolerance?) and the early onset. Children with a long-lasting and early sensitization to food allergens produced significantly higher total serum IgE levels and specific IgE levels to hen's egg than children not or only transiently food sensitized. Those infants with a long-lasting sensitization to food allergens had a 3.4 fold higher risk of developing allergic rhinitis and a 5.5 fold higher risk of developing asthma than only transiently food-sensitized children. The differences in risks are still more pronounced if persistently food-sensitized children were compared with those never sensitized.

The main question in this study was whether the presence and duration of food-sensitization can be

used for the prognosis of allergic airway diseases. Long-lasting sensitization to food in combination with a positive family history turned out to be a strong prognostic criterion. Its determination helps to identify children who are most likely to develop an allergic airway disease.

Besides sensitization to food, other commonly suggested parameters as cord blood IgE and atopic family history were also analyzed for predictive purposes. Recent studies have generally reported a poor predictive capacity of cord blood IgE (23–25). Also in this study cord blood IgE as single parameter and combined with the other evaluated parameters cannot be recommended for prediction of atopy. The best prediction resulted for the group of children who had a long-lasting sensitization to food allergens and a positive family history of atopy or better still an identical family history. An accurate prediction must be made as early as possible in order to effectively apply preventive measures. It could be argued that the second birthday is already too late to implement preventive measures. Testing for sensitization to food allergens before the age of 12 or 24 months, however, might substantially decrease the sensitivity of this valuable predictor. The dilemma between a timepoint as early as possible for the application of secondary preventive measures but low sensitivity and a timepoint too late for interventions remains unsolved. In general, the risks or the positive predictive values presented in this study may be rather underestimated, since the children are only followed up until the fifth birthday. Some of the children as yet unaffected may develop an allergic airway disease in later years, resulting in higher predictive values.

The specificity values for the prediction of allergic airway disease which are already very high in our study may even be higher if the prevalence of food sensitization is lower in the general population than in our risk-enriched cohort. These good values correspond to a small quotient of the false positive to the true positive test results. In other studies this quotient as an index for the 'goodness' of the prognosis is not reported. But it may easily be calculated from the reported values and compared to our results. The small values of this index for cases with persistent food-sensitization and positive family history indicate the utility of preventive measures in this high risk group. The proportion of children who might unnecessarily be subjected to preventive measures (the false positives) is relatively small. The consideration of these prognostic factors enables a differentiated prognosis and determination of different risk groups for planning effective prevention studies and program.

We found distinct differences in respect to immunological parameters between children never or

only transiently food sensitized and children who were persistently food sensitized during early childhood. Also, the subsequent occurrence of allergic airway diseases is much higher in those children. Persistent sensitization to food has proved to be a strong prognostic factor, and in the absence of better predictors, the determination of persistently food-sensitized children in early childhood, especially in atopic families, is suitable to identify children at risk of allergic airway disease. This group can be considered for preventive measures whereas never and only transiently food-sensitized children can be excluded from questionable, inconvenient and expensive interventions.

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