

Food allergy and non-allergic food hypersensitivity in children and adolescents

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Summary

Background Previous studies have shown a 10-fold discrepancy of self-reported food-induced symptoms and physician-diagnosed food hypersensitivity. Little information is available on the prevalence of food hypersensitivity in unselected paediatric populations. No data were available for German children.

Objective To study the perception of food-induced symptoms in the paediatric population, to investigate the allergens accused, to objectify patients' reports, and to identify subgroups at risk of having food-induced allergy (FA) or non-allergic food hypersensitivity (NAFH) reactions.

Methods This paper presents the data of the paediatric group (0–17 years) of a representative, randomly sampled, cross-sectional population-based survey studying 13 300 inhabitants of the German capital city Berlin regarding food-related symptoms. Instruments included mailed questionnaires, structured telephone interviews, physical examination, skin-prick tests, specific serum IgE and standardized, controlled and blinded oral food challenges.

Results Two thousand three hundred and fifty-four individuals were contacted by mailed questionnaire, 739 (31.4%) responses could be fully evaluated. Four hundred and fifty-five (61.5%) participants reported symptoms related to food ingestion, 284 (38.4%) affirmed reproducible symptoms in the standardized telephone interview. One hundred and eighty-four (24.8%) individuals were fully examined. Reproducible symptoms to food were found in 31 (4.2%) children and adolescents: 26 (3.5%) showed symptoms of FA and five (0.7%) of NAFH. The oral allergy syndrome was most often observed. Foods most commonly identified by oral challenges were apple, hazelnut, soy, kiwi, carrot and wheat.

Conclusion: The perception of food-related symptoms is common among children and adolescents from the general population. Self-reports could be confirmed in around one out of 10 individuals, still resulting in 4.2% of proven clinical symptoms. However, most reactions were mild and mainly because of pollen-associated FA, while NAFH reactions were less common. Severe IgE-mediated FA was observed in individuals with pre-existing atopic disease, who should be fully investigated for clinically relevant FA.

Keywords adolescents, allergy, children, DBPCFC, food allergy, food challenge, food hypersensitivity, IgE, non-allergic food hypersensitivity, prevalence, skin prick test

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Introduction

Adverse reactions to food are among the most frequent health complaints of our time. The term 'allergy' has entered the common vocabulary and is uncritically used to describe discomfort following exposure to 'something that does not harm most people' [1]. In this report, the term food allergy (FA) is used to describe clinical symptoms, which are mediated by the immune system and non-allergic food hypersensitivity (NAFH) to describe those which are not [2, 3]. The term food hypersensitivity represents the umbrella term for both reaction

patterns [2]. Food-allergic individuals are at risk of developing life-threatening IgE-mediated systemic reactions upon ingestion of the particular allergen [4–6]. These patients need to cautiously eliminate all offending foods from their diet [7], requiring detailed product information to minimize the risk of accidental ingestion of allergens [8].

Food-induced hypersensitivity symptoms are publicly far more frequently perceived (20–30%) [9–14] than recognized by the medical profession (2–8%). Sloan and Powers studied the public perception of adverse reactions to foods in United States of America [14]. They found that complaints of FA were expressed by a third of all studied households, resulting in a restricted diet. Such elimination diets are commonly introduced without consulting a physician [15, 16]. However, disquietingly, elimination diets can be cost intensive and may put the individual at risk of severe malnourishment [16–20].

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In England, Young and colleagues studied a population by mailed questionnaire and selected food challenges to investigate the prevalence of perceived food-related symptoms [10]. Their study substantiated the prevalence of FA symptoms in approximately 1.4–1.8% for the total population and an estimated 6–8% prevalence of FA in the paediatric population. This report further ascertained the wide discrepancy between the public perception of food allergic reactions and challenge proven FA. Results from other studies showed comparable results for nations with so called 'Western lifestyle', with prevalence rates of FA in children and adolescents ranging between 2.0% [21] and 4.6% [13]. So far, no prevalence data have been available for the German paediatric population.

The Prevalence of Adverse reactions to Nutrients – an Epidemiological study (PANE study) surveyed a representative German population regarding self-reported FA/NAFH reactions [22]. In this paper, we present the data for the paediatric population (children and adolescents) of the PANE study.

Methods

Study design

An extensive cross-sectional, population-based study was undertaken to study the prevalence of adverse food reactions in Germany. The study was carried out in the capital city of Berlin between October 1998 and December 2000. At the time, Berlin had a total population of 3 398 822; the German population comprised of 2 967 168 citizens, while 431 654 of the inhabitants were non-German citizens. The study was initiated and funded by the German Ministry of Health and was approved of by the Humboldt University ethics committee and by the Berlin Data Protection Commissioner.

With reference to the data provided by Young et al. [10], the overall prevalence of self-reported adverse reactions to foods was estimated at 20% of the normal population. Therefore, it was calculated that a total PANE sample size of 4000 persons would be sufficient to report an expected prevalence rate of 2% with a 95% confidence interval smaller than [1.5–2.5]. Further calculating a reply rate of 30–40%, a random sample of 15000 persons of all districts and age groups with German citizenship was drawn from the Berlin population register. The PANE database of 13 300 persons was created by further repeated random sub-sampling. For the analysis of the distribution of food hypersensitivity reactions in the paediatric population, we approached all subjects of the PANE database from 0 to 17 years. A total of 2354 male and female individuals were selected for this study.

Questionnaires

A questionnaire was designed with the questions adapted to the age groups 0–14, 14–18 and adults and evaluated in 50 patients of the University Departments of Dermatology and Pediatrics. Questions were about perceived connections between food ingestion and itching, eczema, urticaria (URT), angio-oedema, rhinitis, asthma, gastro-intestinal (GI) symptoms, headache and other symptoms. In addition, questions were asked about the existence of atopic diseases, the existence of the above-named symptoms without the

perceived relation to food ingestion, possible risk factors such as smoking, household size and status of education. Space was provided to quote the suspected food(s) and the actual symptoms evoked. The degree of clinical reactions, age of onset of the reaction, current dietary habits and/or other methods of treatment were elicited. In addition, questions regarding the patients' history, possible risk factors such as smoking, atopic disorders and treatment, and the general attitude towards food safety were included. The questions regarding the status of education were taken directly from the German National Health Survey Questionnaire to enable the statistical comparison. After the initial contact by mailed questionnaire, further standardized questionnaires were used in the telephone interview, the physical examination and food challenge procedures.

Patient contact and evaluation

The initial questionnaire was distributed by posted mail. Upon response to the questionnaire, individuals with a suspicion of adverse reactions related to food ingestion were contacted by telephone and interviewed using a structured questionnaire. The possibility of food hypersensitivity was not considered if the subject would only report a 'one off' adverse encounter but could not confirm reproducible symptoms to any given type of food. Depending on the subject's history and his or her certainty about the reproducibility of symptoms, the individuals were invited to visit the Departments of Pediatric Pneumology and Immunology of the Charité Children's Clinic or Dermatology for further assessment of the reported complaints. A thorough medical history and physical examination, including the cutaneous, respiratory, cardiovascular and GI systems was obtained. Every individual was tested for specific sensitization using skin-prick tests (SPTs) and blood was taken for specific IgE analysis. All participants were examined by the same investigators with a specialist training in paediatric allergy (C. C. R. for children 0–14 years, S. R. for adolescents 15–17 years).

Laboratory evaluations

Patients' sera were analysed for concentrations of total IgE and specific IgE concentrations to dietary allergens (cow's milk (CM), hen's egg (HE), wheat, fish, carrot and soy), as well as inhalative phadiatop (Sx1), latex and profilin, determined by FEIA using the Pharmacia CAP-System (Pharmacia Diagnostics, Freiburg, Germany). The detection limit was 0.35 kU/L IgE and children were regarded as sensitized if the specific IgE was above the detection limit.

Skin prick test

The number of SPTs were chosen according to age. Children under the age of 8 years were tested with six common nutritional allergens (CM, HE, wheat, soy, carrot and peanut) plus the allergens accused by the patient. Children older than 8 years were diagnosed according to the standardized protocol of the adult part of the study population (plus those proposed by the individual patient). Fresh foods were applied to the patient's volar forearm, for example, fresh CM milk containing 3.5% fat, native HE egg (white of egg and yolk), wheat powder (Kröner, Ibbenbüren, Germany) dissolved in

water (1 g/10 mL) and soy milk, fresh carrot and roasted peanut. Prick tests were performed using a 1 mm single peak lancet (ALK, Copenhagen, Denmark), either as prick test or prick-to-prick test. Reactions were read after 15 min, the SPT was assessed as positive if the weal was >3 mm and $>60\%$ of that induced by histamine without reaction of the negative control (NaCl 0.9%). As positive control 10 mg/mL histamine dihydrochloride (ALK and Bencard, Germany) was used. Patients were advised to avoid antihistamines and topical steroids for 72 h before the test.

Food challenges

All patients with a history of reproducible symptoms following the ingestion of food were subjected to an oral food challenge with the allergen in question. Further, all patients with a positive SPT or IgE and an ambiguous history of food hypersensitivity to that particular food were challenged. This accounted for those subjects in whom (1) a reaction to the allergen was unknown to the subject, (2) the subject was uncertain whether sensitization resembled clinically active disease and (3) the subject insisted on a perceived reaction to an allergen irrespective to the lack of specific sensitization. The foods selected for challenges were those most probable to elicit a positive reaction according to the history. Food challenges were performed as double-blind, placebo-controlled food challenges (DBPCFC) whenever possible. If DBPCFC could not be performed secondary to refusal of the patient, challenges were performed as single-blind food challenges.

The studied individuals were asked to eliminate the allergens in question, depending on the clinical symptoms: 3 days for typical immediate-type reactions, like URT, and 7 days for eczema. For this, they received detailed instructions by a nutritionist how to omit hidden sources of suspected food items from the diet and how to keep a diary in order to certify that the diet was followed properly. The elimination diet was followed by DBPCFC at the clinic. Randomization and preparation of the challenges were carried out by the clinical dietician (I. E.). For DBPCFC, food items were blinded by the nutritionist using Sinlac[®] (Nestle, München, Germany; ingredients: rice flour, carob, saccharose, natrium citrate, potassium chloride, natrium phosphate, vitamins, zinc sulphate), orange flavour (SHS International, Liverpool, UK), carotene, cereal flakes and/ or pure cacao powder. Blinding was confirmed by tasting the panels. Briefly, successive doses (0.1, 0.3, 1.0, 3.0, 10.0, 30.0 and 100 mL) of fresh pasteurized CM milk containing 3.5% fat, soy milk and wheat powder (Kröner, Ibbenbüren, Germany) dissolved in water (total amount of 10 g of wheat protein) or placebo (Sinlac[®] or Neocate[®], SHS, Liverpool, UK) were administered. Raw HE egg (white of egg and yolk) was given in a similar regimen except that the highest dose was omitted. Apple and nuts were administered in Sinlac[®]. The time interval between doses was 20 min. Children were advised to avoid antihistamines 72 h prior to provocation.

In addition, 50 persons of the total PANE population sample with no history of adverse reactions to food were asked to participate in an open food-challenge test in the form of a three-course meal. This included the following food allergens: wheat, rye, oat, egg, soy milk, crab, codfish, milk, apple, carrot, celery, peanut, hazelnut, guar gum, carrageen

and carob, as well as the mixture of food additives that were given in capsules.

A physician with specialist training in paediatric allergy supervised all food challenges. Challenges were scored positive if a single or a combination of the following clinical reactions to the challenge were noted: oral discomfort, allergic rhinoconjunctivitis (ARC), angio-oedema, URT, vomiting, diarrhoea, abdominal pain, exacerbation of atopic dermatitis (AD), wheezing, bronchial asthma (BA) or cardiovascular shock. The full emergency equipment including drugs (adrenaline, antihistamines, glucocorticosteroids and β -agonists) was at hand at all times. The challenge was stopped if clinical symptoms occurred or the highest dose was reached. Individuals were observed for 120 min for immediate reactions. Late-phase reactions were assessed via telephone call after 24 and 48 h, in case of a late reaction, patients were asked to come to the study centre for a clinical evaluation.

Statistical analyses

Descriptive statistical analyses were performed using SPSS for Windows software (Version 8.0, SPSS, Chicago, IL, USA). Prevalence rates with exact 95% confidence intervals were computed with STATA 6.0. The robustness of the results with regard to potential response bias was analysed and documented for all age groups in the primary study [22]. In the main study an assessment and correction for response bias was made by comparison of the study data with the Berlin Micro Census data of 1999. A weighted analysis for all age groups of the main study data was performed with regard to age, sex and educational status and has recently been published [22].

The robustness of the reported prevalence rates with regard to incomplete data, i.e. individuals who had returned the questionnaire but failed to answer our phone calls or to attend personal clinical investigation, was analysed by a comparison of two approaches. Firstly, prevalence rates were calculated by including individuals with no missing information. Secondly, a simple imputation algorithm based on a multinomial model was used to predict the health status for individuals with incomplete data from the available questionnaire data. Both approaches resulted in nearly identical prevalence rates.

Results

Studied individuals

We studied a total of 2354 children aged 0–17 years. The mean age was 9.2 years. The male/female ratio was 52:48. Two age groups were defined: Group 1 (children 0–14 years) 1923 subjects (81.6%) and Group 2 (adolescents 15–17 years) 431 subjects (18.3%).

Response rate

A total of 739 (31.4% (95% confidence interval 0.29–0.33)) individuals returned the questionnaire (Fig. 1). The response rates were equally distributed throughout both groups: 598 (31.1%) of Group 1 (mean age of 7.3 years) responded to the questionnaire and 141 (32.7%) of Group 2 (mean age 16.0

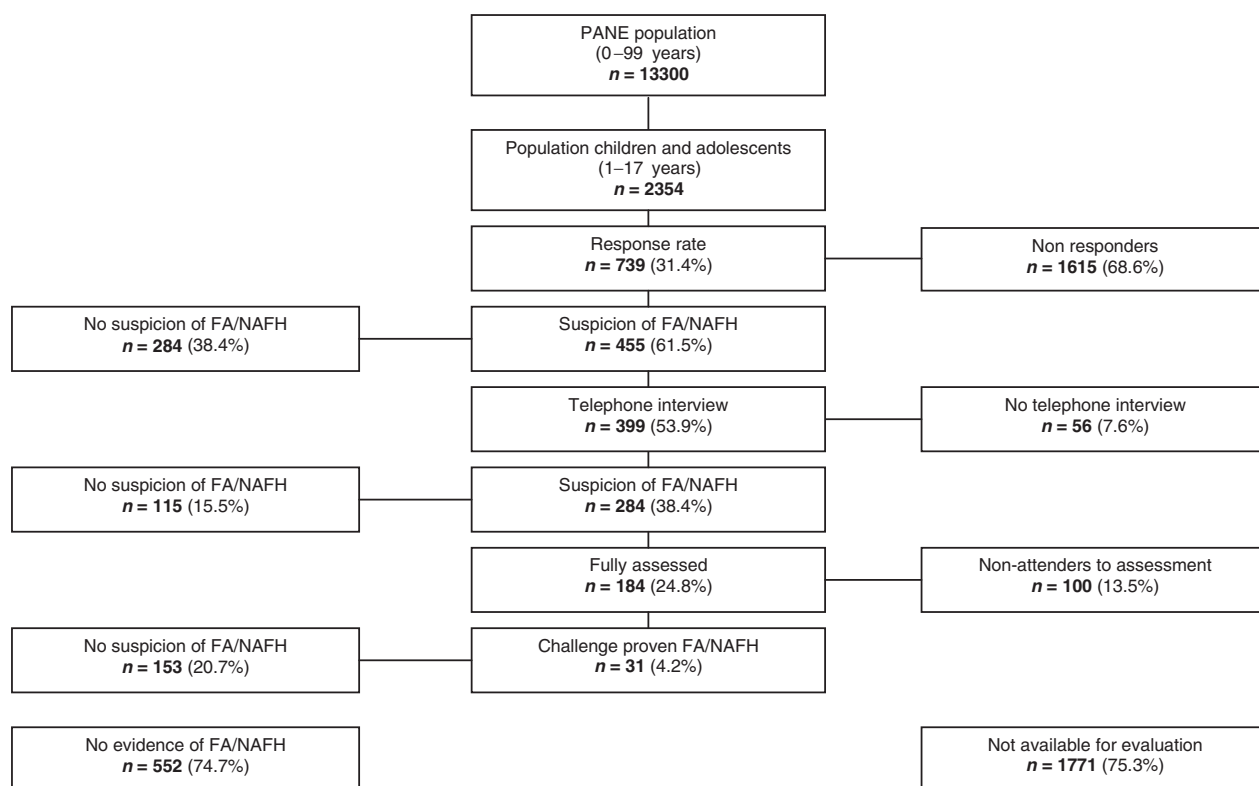


Fig. 1. Prevalence of Adverse reactions to Nutrients – an Epidemiological study (PANE study) flow diagram illustrating the study process.

years) responded. The sex ratio was equally distributed in Group 1 (58% boys and 42% girls) but showed a slight female predominance in age Group 2 (44% boys and 56% girls). The majority of questionnaires (97.7%) were completed by, or jointly with, the subject's parents.

Complaints of food reactions

Symptoms of food reactions indicative of FA and/or atopic disorders related to FA (AD, BA, ARC and URT) were mentioned by 455 (61.5% (95% confidence interval 0.58–0.65)) individuals (Fig. 1). Most subjects reported adverse reactions to a single food ($n = 134$), 49 to two foods, 23 to three foods and 15 to four or more foods.

A quarter ($n = 116$; 25.4%) had previously sought advice from a healthcare professional, mostly a private paediatrician. In total, 585 complaints secondary to ingestion of one or more foods were made in the mailed questionnaire. Symptoms related to the ingestion of food were chiefly eczematous (22.7%), GI (17.9%) or symptoms of oral discomfort (14.1%) (Table 1).

Fruits, in particular acidic fruits (kiwi, oranges and grapefruit) were most frequently mentioned as causing symptoms of oral discomfort, pruritic or eczematous, urticarial or GI reactions. Adverse reactions to apple and pear ranked second and were described to arouse similar sensations, followed by reactions attributed to the ingestion of vegetables (carrots, potatoes, tomatoes), and fruit (peach, nectarine, plum, cherries, pineapple). The distribution of allergens accused of causing adverse food reactions is shown in Fig. 2.

Three hundred ninety-nine subjects (53.9%) identified by the postal questionnaire were interviewed on the telephone.

Table 1. Reactions to common foods mentioned in mailed questionnaire

Reactions (1–17 years)	<i>n</i>	%
Eczema	133	22.7
Gastrointestinal (nausea, vomiting, diarrhoea)	105	17.9
Oral discomfort (tingling of lip, tongue or palate)	83	14.1
Urticaria	62	10.5
Allergic rhino-conjunctivitis	51	8.7
Headache	49	8.3
Angio-oedema	44	7.5
Vertigo	13	2.2
Shortness of breath	11	1.8
Other	34	5.8
Total	585	100

After the telephone contact, 284 (38.4%) subjects remained suspicious of having experienced reproducible adverse reactions to food. No suspicion of FA or NAFH could be found in 115 (15.5%) subjects upon specific questioning. Those who could not be contacted by telephone were sent two consecutive letters explaining the intentions of our study and were requested to contact us by telephone. No response after repeated contact could be obtained from 56 (7.6%) children and were thus lost for analysis (Fig. 1).

Clinical assessment

Two hundred eighty-four (38.4% (95% confidence interval 0.35–0.42)) individuals were invited to the allergy clinic for further evaluation of their perceived food hypersensitivity. A total of 184 (24.8% (95% confidence interval 0.22–0.28))

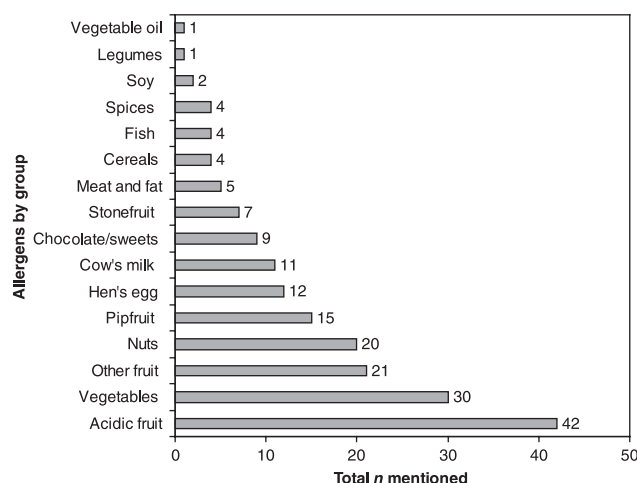


Fig. 2. List of allergens suspicious of causing food allergy/non-allergic food hypersensitivity (FA/NAFH) (after telephone interview).

children could be fully assessed, while 100 (13.5%) individuals did not attend the examination and were lost for analysis. Seventy-eight percent of children fully assessed in our study were suffering from atopic disease. The distribution of foods accused of causing adverse reactions at the clinical assessment is listed in Fig. 2. Attendance to the clinical examination was not equally distributed within the age groups: Group 1 (0–14 years) showed a high attendance rate ($n = 153$; 83.1%) whereas only a third of individuals from Group 2 (15–17 years) attended the full examination ($n = 31$; 16.8%).

Skin prick test

SPTs were positive in 97 (52%) subjects. SPTs to carrots were found positive in 18 (9.7%) individuals, to each apple and hazelnut in 17 (9.2%), to soy in 10 (5.4%), to wheat or peanut in eight (4.3%). SPT to HE was positive in four cases (2.2%) and only one SPT was positive to CM (0.5%). The number of SPTs performed and the outcome per allergen are listed in Table 2. Analysis of the reactivity to SPT by age group revealed that 46% of Group 1 and 65% of Group 2 reacted to SPT testing with food items.

Immunoglobulin E antibodies and specific sensitization

A total of 170 blood samples (92%) could be obtained for evaluation of total and specific IgE levels. Of the 139 blood samples analysed from Group 1, the mean value for total IgE was 189 kU/L (ranging from <0.35 to >2000 kU/L). In Group 2, the mean was 209.0 kU/L (ranging from <0.35 to 1414 kU/L). Evidence of specific IgE antibodies to common nutritional allergens were found in 31 (20%) children of Group 1, while 60 (39%) children showed elevated IgE levels to common inhalant allergens. Of 31 adolescents with elevated IgE levels, three individuals (10%) showed specific IgE antibodies to common food allergens and 23 (74%) to inhalant allergens.

Food challenges

A total of 78 oral food challenges were carried out. Half of the challenges ($n = 39$) were performed as DBPCFC, whereas

Table 2. Results of SPT to native allergens

Substance	SPT total, <i>n</i>	SPT positive, <i>n</i>	SPT positive (%)
Histamine	177	177	100
NaCl 0.9%	177	0	0
Carrot	170	18	11
Apple	68	17	25
Hazelnut	60	15	25
Soy	175	10	6
Potato	48	10	21
Wheat	172	8	5
Peanut	175	8	5
Walnut	49	5	10
HE	177	4	2
Herring	43	1	0.6
CM	177	1	0.5
Shrimp	43	0	0

SPT, skin prick test; HE, hen's egg; CM, cow's milk.

the remaining half of the challenges were carried out in single-blind or open fashion depending on the patients' compliance. Forty-eight (61.5%) food challenges were assessed as positive in 31 individuals. The most commonly tested foods were acidic fruits, vegetables, apples and nuts. The commonest clinical reaction to food challenges was the oral allergy syndrome (OAS) ($n = 32$; 66.6%), followed by urticarial reactions ($n = 6$, 12.5%) (Fig. 3). Multiple reactions to one allergen were observed (OAS, AD, BA or URT). Two (4.2%) individuals reacted severely to soy and necessitated anti-allergic medication. The pattern of reactivity and the foods responsible for FA reactions are shown in Table 3. None of the 50 individuals challenged in the three-course provocation meal showed a clinical reaction.

Confirmed food allergy/non-allergic food hypersensitivity

Of the examined 184 subjects, 31 (16.8% (95% confidence interval 0.03–0.06)) were found to have reproducible symptoms to foods, comprising 4.2% of the study population (31/739). Of these, 23 (77.4%) were individuals from Group 1 (0–14 years) and eight (22.6%) from Group 2 (15–17 years). Eighty-four percent ($n = 26$ (95% confidence interval 0.02–0.05)) of these individuals had specific antibodies to the given allergens and were classified as food allergic: 19 (83.2%) from Group 1 and seven (85.7%) from Group 2. The foods most commonly found to evoke allergic symptoms were apple, hazelnut, kiwi, carrot and soy. All but one reaction (URT) in Group 2 were OAS. The remaining five individuals (16% (95% confidence interval 0.002–0.015); Group 1 $n = 4$, Group 2 $n = 1$) showed reproducible symptoms (two OAS, three URT, one ARC) despite no evidence of specific sensitization (specific IgE or positive SPT) and were classified as NAFH to the particular food. Therefore, one individual showed NAFH reactions to two foods (tomato, satsuma) (Fig. 3).

Individuals without evidence of food allergy/non-allergic food hypersensitivity

One hundred fifty-three (83.1%) of the 184 individuals examined showed no clinically relevant symptoms to foods, not even in oral challenges. This group was assessed for age,

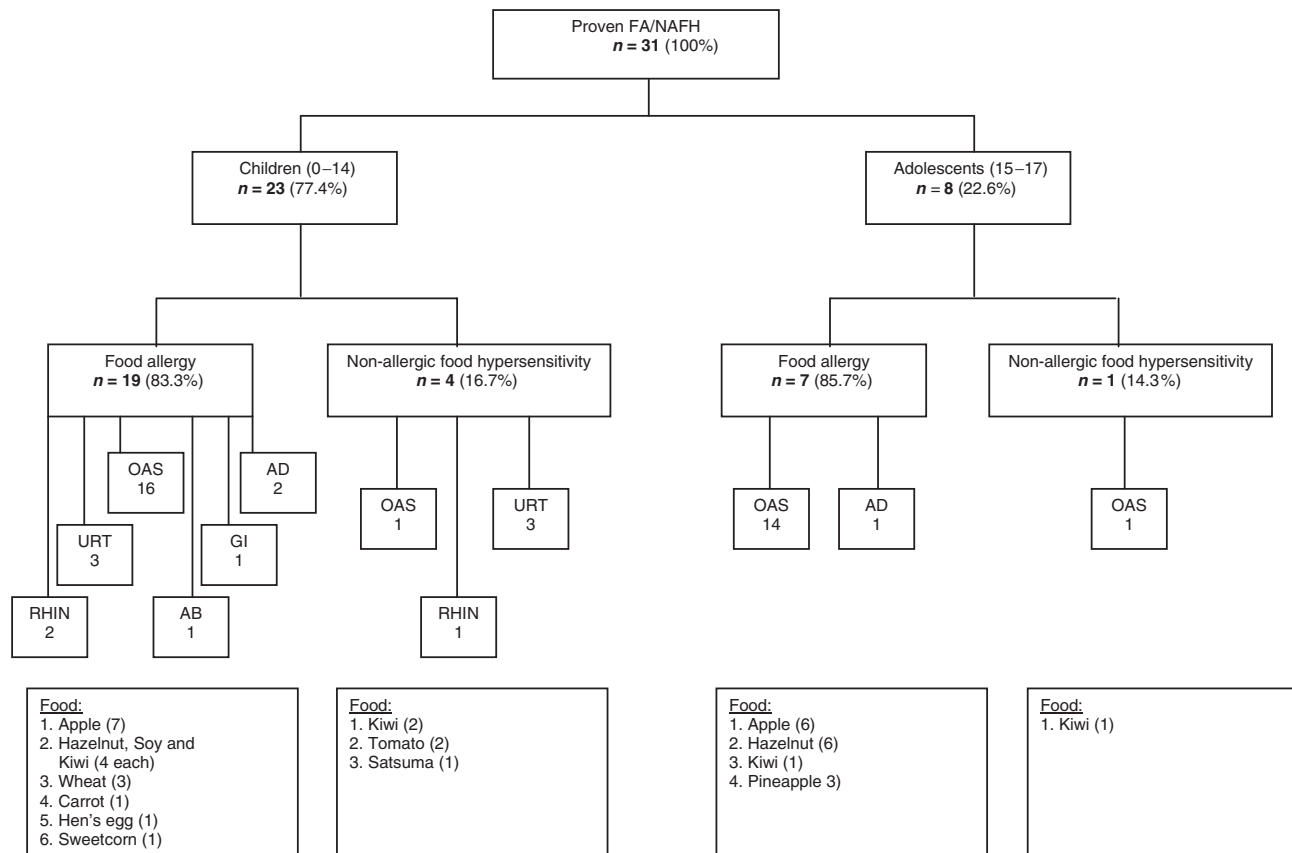


Fig. 3. Result of allergy testing food allergy/non-allergic food hypersensitivity (FA/NAFH) and offending allergens.

Table 3. Food allergy reactions

	OAS	AD	ARC	URT	GI	BA	Total reactions
Apple	12		1				13
Hazelnut	10						10
Soy	1			1	1*	1*	4
Kiwi	4			1			5
Wheat	1	1	1				3
Pineapple	2			1			3
Carrot	1			1			2
Sweetcorn	1						1
HE		1					1
Total	32	2	2	4	1	1	42

OAS, oral allergy syndrome; AD, atopic dermatitis; ARC, allergic rhinoconjunctivitis; URT, urticaria; GI, gastrointestinal; BA, bronchial asthma; HE, Hen's egg.

*Severe reactions, requiring medical intervention.

sex, allergens alleged of causing symptoms, type of symptom noted, medical history and mother's education. No statistically significant difference was found comparing these to the reacting children.

Discussion

A representative sample of 2354 randomly chosen German children and adolescents was surveyed regarding the self-

perception of food hypersensitivity reactions. Thirty-one percent completed mailed questionnaires and were evaluated. Of these, 284 (38.4%) reported reproducible adverse reactions to foods or were suffering from diseases related to FA/NAFH. In total, 184 of 284 could be fully examined and subjected to food challenges. FA/NAFH was proved in 31 (4.2%) of all children and adolescents: 26 (3.5%) were classified as FA and five (0.7%) as NAFH. FA reactions were predominantly attributed to pollen-associated foods and commonly presented as OAS, but severe reactions were seen to soy. NAFH occurred mainly to acidic fruits and most often presented as URT. The prevalence of self-perceived FA/NAFH in this cohort was nearly 10 times that of physician-proven FA/NAFH. Individuals with severe reactions had pre-existing atopy syndrome.

The studied group represents the largest homogenous yet randomly chosen paediatric population reported, where perceived reactions to food have been individually investigated. Every child or adolescent with suspected hypersensitivity reactions to foods in the questionnaire was interviewed by telephone to assess active FA/NAFH. This approach allowed to control for over- and under-representation secondary to recall errors or ill beliefs of FA/NAFH. Through this screening process, a third of the presumed food reactions were excluded prior to the physical examination and testing on the grounds of lacking reproducibility of symptoms. SPT- and serum-specific IgE analyses were used as screening instruments for specific sensitization only, because these tests cannot be accepted as a proof of clinically active

FA [23, 24]. Solely rigorous food challenge procedures were used to diagnose FA/NAFH. Every effort was made to challenge each individual with the particular allergen stated.

Few cross-sectional studies have specifically assessed the prevalence and distribution of FA/NAFH in unselected paediatric populations. Some form of oral challenges was used in part of those studies, but rigorous, patient-centred food challenges were not elemental [12, 13, 21, 25–27]. Population-based studies showed a prevalence of perceived FA/NAFH of 16–28% in the general population [10, 13, 26, 28]. This stands in contrast to the prevalence rates of 2–8% for medically recognized food allergies in the paediatric population [9, 11–13, 21, 25, 27, 29]. In this study, having paid particular attention to choosing a representative population, we found the prevalence rate of FA/NAFH to be 4.2% among German children and adolescents, with a high rate of IgE-mediated reactions and a low rate of NAFH symptoms. This may be because of the age distribution of our study population in favour of older children with typical pollen-associated food-allergic symptoms.

Analysing the discrepancy between the high rate of self-reported food reactions and challenge proven symptoms as found in our cross-sectional study, one might consider several possible explanations [30]. On the one hand, it is well known and could again be shown in our study that objective clinical symptoms can be reproduced in only a small proportion of subjective reports, probably because of a strong tendency of individuals to causally relate situations of the daily life with ingested foods. On the other hand, patients may have become tolerant to several reported food allergens in the interim period, and may therefore be negative in oral challenges performed later in life (as is overt for CM and HE allergy, which is lost by around 80% of children at school age [31, 32]). In our view, the first argument seems more valid, because besides the fact that reproducible symptoms were predominantly IgE mediated, the array of presumed reactions to food span from 'retro-sternal burning sensations at consumption of spring water' to 'pruritus on caput after soda water', illustrating the extent of ill-perceived food-related symptoms.

While studies investigating the pattern and distribution of food allergies in young children so far have found a predominance of four major allergens, CM, HE, wheat and soy [32, 33], peanut is currently heralded as a new major allergen particularly in the USA and in Great Britain (suspected prevalence 0.6% and 0.5%, respectively) [34, 35]. Peanut was not perceived as a major offending allergen in the studied group. None of the children with positive SPT to peanut (5%) reacted clinically to peanut challenge. Our data show that peanut is not a major food allergen in Germany. This supports the conclusion voiced by Madsen several years ago that peanut is not a major food allergen in many European countries so far [36] – with the exception of France and the UK.

Pollen-associated IgE-mediated food reactions accounted for the majority of symptoms. In both age groups, and particularly in Group Two, the OAS was the predominantly observed symptom. The allergens most commonly causing adverse reactions during food challenges were birch pollen-associated allergens, suggesting an element of cross-reactivity. The lack of differences between the two groups may be

because of the mean age resulting in quite a high mean age in Group 1 (7.3 years). Therefore, pollen-associated food allergies also played a major role in Group 1. Other authors have observed similar reactions in school-age children [23, 37]. Asthmatic symptoms were rare, as were GI symptoms. Two subjects (2% of challenges) with a clearly recognized atopic history reacted severely to soy, an allergen with proven cross-reactivity to birch pollen. Both had severe clinical symptoms (BA and vomiting) and received anti-allergic medication post-challenge, preventing the progression to possible serious anaphylaxis [38].

In conclusion, the perception of food-related symptoms is common among children and adolescents from the general population. While self-reports could be confirmed in around one out of 10 individuals, clinically proven symptoms could still be found in 31 individuals (4.2%). However, most reactions were mild and mainly because of pollen-associated FA, while NAFH reactions were less common. Severe IgE-mediated FA was observed in individuals with pre-existing atopic disease, who should be fully investigated for clinically relevant FA.

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References

- 1 May CD. Food sensitivity – facts and fancies. *Nutr Rev* 1984; 42:72–8.
- 2 Johansson SGO, O'B Hourihane J, Bousquet J et al. A revised nomenclature for allergy. An EAACI position paper from the EAACI nomenclature task force. *Allergy* 2001; 56:813–24.
- 3 Niggemann B, Reibel S, Roehr CC et al. Predictors of positive food challenge outcome in non-IgE-mediated reactions to food in children with atopic dermatitis. *J Allergy Clin Immunol* 2001; 108:1053–8.
- 4 Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal food-induced anaphylaxis in children. *N Engl J Med* 1992; 327:380–4.
- 5 Yunginger JW, Sweeney KG, Sturmer WQ et al. Fatal food-induced anaphylaxis. *JAMA* 1988; 260:1450–2.
- 6 Macdougall CF, Cant AJ, Clover AF. How dangerous is food allergy in childhood? The incidence of severe and fatal allergic reactions across the UK and Ireland. *Arch Dis Child* 2002; 86: 236–9.
- 7 Niggemann B, Wahn U, Sampson H. Proposals for standardization of oral food challenge tests in infants and children. *Pediatr Allergy Immunol* 1994; 5:11–3.
- 8 Brett GM, Bull VJ, Morgan MR. Identification of hidden allergens within foods. *Allergy* 1998; 53 (46 Suppl.):109–10.
- 9 Eggesbo M, Halvorsen R, Tambs K, Botten G. Prevalence of parentally perceived adverse reactions to food in young children. *Pediatr Allergy Immunol* 1999; 10:122–32.
- 10 Young E, Stoneham MD, Petrukevitch A, Barton J, Rona R. A population study of food intolerance. *Lancet* 1994; 343:1127–30.

- 11 Høst A. Adverse reactions to foods: epidemiology and risk factors. *Pediatr Allergy Immunol* 1995; 6 (Suppl. 8):20–8.
- 12 Høst A, Halken S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life. Clinical course in relation to clinical and immunological hypersensitivity reaction. *Allergy* 1990; 45:587–96.
- 13 Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first three years of life. *Pediatrics* 1987; 79:683–8.
- 14 Sloan AE, Powers MA. A perspective on popular perception of adverse reactions to foods. *J Allergy Clin Immunol* 1986; 78:127–33.
- 15 Eggesbo M, Botten G, Stigum H. Restricted diets in children with reactions to milk and egg perceived by their parents. *J Pediatr* 2001; 139:583–7.
- 16 Niggemann B, Grüber C. Side-effects of complementary and alternative medicine. *Allergy* 2003; 58:707–16.
- 17 Henriksen C, Eggesbo M, Halvorsen R, Botten G. Nutrient intake among two-year-old children on cow's milk-restricted diets. *Acta Paediatr* 2000; 89:272–8.
- 18 Roesler T, Barry P, Bock SA. Factitious food allergy and failure to thrive. *Arch Pediatr Adolesc Med* 1994; 148:1150–5.
- 19 Davidovits M, Levi Y, Avramovits T, Eisenstein B. Calcium-deficiency rickets in a four-year old boy with milk allergy. *J Paediatr* 1993; 122:249–51.
- 20 Robertson DA, Ayers RC, Smith CL. Adverse consequences arising from misdiagnosing food allergy. *Br Med J* 1988; 297: 719–20.
- 21 Schrandt JJ, van den Bogart JP, Forget PP, Schrandt-Stumpel CT, Kuijten RH, Kester AD. Cow's milk protein intolerance in infants under 1 year of age: a prospective epidemiological study. *Eur J Pediatr* 1993; 152:640–4.
- 22 Zuberbier T, Edenharter G, Worm M et al. Prevalence of adverse reactions to food in Germany – a population based study. *Allergy* 2004; 59:338–45.
- 23 Bircher AJ, van Melle G, Haller E, Curty B, Frei PC. IgE to food allergens are highly prevalent in patients allergic to pollens with and without symptoms of food allergy. *Clin Exp Allergy* 1994; 24:367–74.
- 24 Roehr CC, Reibel S, Zeigert M, Sommerfeld C, Wahn U, Niggemann B. Atopy patch tests, together with determination of specific IgE levels, reduce the need for oral food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 2001; 107:548–53.
- 25 Hill DJ, Hosking CS, Heine RG. Clinical spectrum of food allergy in children in Australia and South-East Asia: identification and targets for treatment. *Ann Med* 1999; 31:272–81.
- 26 Aardoom HA, Hirasing RA, Rona RJ, Sanavro FL, van den Heuvel EW, Leeuwenburg J. Food intolerance (food hypersensitivity) and chronic complaints in children: the parents' perception. *Eur J Pediatr* 1997; 156:110–2.
- 27 Jakobsson I, Lindberg T. A prospective study of cow's milk protein intolerance in Swedish infants. *Acta Paediatr Scand* 1979; 68:853–9.
- 28 Altman DA, Lawrence T, Chiaramonte LT. Public perception of food allergy. *J Allergy Clin Immunol* 1996; 97:1247–51.
- 29 Kivity S, Dunner K, Marian Y. The pattern of food hypersensitivity in patients with onset after 10 years of age. *Clin Exp Allergy* 1994; 24:19–22.
- 30 Nichaman M, McPherson S. Estimating prevalence of adverse reactions to foods: principles and constraints. *J Allergy Clin Immunol* 1986; 78:148–54.
- 31 Sampson HA. Epidemiology of food allergy (review). *Pediatr Allergy Immunol* 1996; 86:S42–50.
- 32 Crespo JF, Pascual C, Burks AW, Helm RM, Esteban MM. Frequency of food allergy in a pediatric population from Spain. *Pediatr Allergy Immunol* 1995; 6:39–43.
- 33 Niggemann B, Sielaff B, Beyer K, Binder C, Wahn U. Outcome of double-blind, placebo-controlled food challenge tests in 107 children with atopic dermatitis. *Clin Exp Allergy* 1999; 29:91–6.
- 34 Sicherer SH, Munoz-Furlong A, Burks W, 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; 103:559–62.
- 35 Tariq SM, Stevens M, Matthews S, Ridout S, Twiselton R, Hide DW. Cohort study of peanut and tree nut sensitization by age of 4 years. *Br Med J* 1996; 313:514–7.
- 36 Madsen C. Prevalence of food allergy/intolerance in Europe. *Environ Toxicol Pharmacol* 1997; 4:163–7.
- 37 Fuglsang G, Madsen C, Saval P, Osterballe O. Prevalence of intolerance to food additives among Danish school children. *Pediatr Allergy Immunol* 1993; 4:123–9.
- 38 Reibel S, Röhr C, Ziegert M, Sommerfeld C, Wahn U, Niggemann B. What safety measures need to be taken in oral food challenges in children? *Allergy* 2000; 55:940–4.