

Prevalence of sensitization reported and objectively assessed food hypersensitivity amongst six-year-old children: A population-based study

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There is a paucity of information on food hypersensitivity (FHS) in young children and there are even fewer population-based studies in this area. The aim of the study was to determine the prevalence of parentally reported FHS, and objectively diagnosed FHS amongst six-year-old children and to establish the rates of sensitization to key allergens. This population-based cohort study recruited 798 6-year-olds resident on the Isle of Wight (UK). Sensitization rates, reported rates of FHS and objectively assessed FHS was established using food challenges. A total of 94 (11.8%) 6 yr olds reported a problem with a food or food ingredient. The rate of sensitization to the pre-defined panel of food allergens was 25/700 (3.6%). Based on open food challenge and/or suggestive history and skin tests, the prevalence of FHS was 2.5% (95% CI 1.5–3.8). Based on double-blind challenges, a clinical diagnosis or suggestive history and positive skin tests, the prevalence was 1.6% (95% CI 0.9–2.7). The rates of perception of FHS are higher than the prevalence of sensitization to main food allergens and the prevalence of FHS based on food challenges. Milk, peanut and wheat were the key food allergens amongst those with positive challenges.

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An increasing prevalence of manifestations of allergy in the form of asthma, allergic rhinitis and atopic dermatitis has been seen in recent years (1). There are, however, a very limited number of studies, which have investigated the prevalence of food hypersensitivity (FHS) and its trends in Europe and USA (2–7). The prevalence of FHS in the community and its changes over time are very dependent upon public awareness, diagnostic approaches as well as the eating habits of that community. It is not clear, however, whether the increased prevalence represents a real increase, an increase in awareness or an improvement in diagnosis (1). The few studies that have investigated perceptions of FHS and how these relate to

proven FHS, have shown large discrepancies between the two (2, 6, 8–10).

Food allergy accounts for a significant proportion of anaphylaxis and severe allergic reactions in children (11, 12). Hence, it is of paramount importance that we have robust population-based epidemiological data regarding food problems and sensitization to key food allergens in this age group, upon which any population recommendations and education programmes can be based. The aim of this study therefore, was to establish the prevalence of sensitization to food allergens, reported adverse reaction to foods and food avoidance as well as objectively assessing rates of FHS using food

challenges amongst all six-year-old children living on the Isle of Wight.

Methods

The study was carried out between September 2003 and August 2004. The target population for the study was all 6 yr old (with birth dates between 1 September 1997 and 31 August 1998) who were resident on the Isle of Wight at the time of the study. Ethical approval for the study was obtained from the Isle of Wight, Portsmouth and South East Hampshire Local Research Ethics Committee (Ref.: 09/01). The target population was approached via the schools after discussions with the Isle of Wight Education Authority and all head teachers. All schools consented to participate in the study. The schools comprised 52 Primary Schools (47 state, three independent and two special needs schools). In order to ensure confidentiality and data protection the schools posted the study information, a consent form, a self-administered questionnaire and a pre-paid envelope to the parents/guardians of all eligible pupils who were asked to reply directly to the Allergy Centre. Approximately 2 wk after initial contact reminders were sent to the non-responders.

The reported prevalence of adverse reactions to food and numbers of foods avoided were established using a questionnaire that was completed by the parents. Parents were asked to describe any symptoms experienced. Questions regarding food related problems included 'Does your child currently have a problem with any of the following foods? Milk, egg, peanut, tree nuts (e.g. almond, brazil), wheat, fish, sesame and other'.

'If yes to any of the above foods, can you describe the problem'.

All those consenting to participate were offered skin prick tests (SPT) to a pre-defined panel of food allergens (milk, egg, wheat, cod fish, peanut and sesame) and aeroallergens (house dust mite, cat and grass pollen). In addition, they were offered skin tests to other allergens reported to be a problem. We used standardized extracts of food allergens and, in the case of fruits and vegetables, offered prick-to-prick testing to the fresh product. Parental presence during testing was accommodated.

Skin prick tests were conducted with commercial extracts of technically optimized standard allergens (Soluprick SQ allergens-ALK Allergologisk Laboratorium A/S, Horsholm, Denmark). Two experienced allergy nurses performed all the SPTs. The wheal was measured after transfer to paper from the skin with translucent tape. The

mean diameter was calculated from the largest wheal diameter and the diameter orthogonal to it. Results were expressed as positive if mean diameter was 3 mm or more in the presence of a negative control and a positive histamine reaction after 12–15 min. The families of sensitized children were offered appropriate advice.

All data obtained were double entered onto SPSS (Version 10.0; SPSS Inc, Chicago, USA) by separate operators, compared and verified before analysis.

Two members of the research team screened the questionnaire information regarding reported current problems with food and food avoidance. Those who reported an adverse reaction to a food were contacted. Children with an appropriate history were questioned in detail to ascertain which foods were implicated in producing the symptoms. If there was any suggestion of a food related problem amongst those avoiding a food, but who did not report a problem with that food, the parents were contacted by the research dietitian for a detailed assessment.

Children with a history suggestive of adverse reaction to a food irrespective of the result of skin test, or those with a positive skin test and no definite prior exposure to the relevant food allergen were later invited for food challenges.

Prior to the food challenges the dietitian advised families and parents regarding avoidance of the offending food or ingredient for at least 4 wk and in the case of food additives, 2 days prior to the challenge (13). Oral challenges were performed following an algorithm developed according to the history in terms of dose and timing where available. Challenge protocols were developed based on current available literature. As there are no agreed international protocols the draft protocols were circulated to experts in UK, Europe and USA. A consensus was reached and protocols established for the diagnosis of FHS with immediate and delayed symptoms. Patients typically experienced similar reactions to their initial reaction on re-exposure to a food (14). Challenges were designed to mimic each child's initial reaction using the total amount of food at least as previously caused the reaction in a setting mimicking the time-frame reported for reactions (1 day in hospital for immediate and 1 wk at home for non-generalized late reactions).

One-day challenge protocols were based on the consumption of the equivalent of 8–10 g of dried food (15), unless the history clearly indicated a different approach. All food for challenges was freshly prepared for each individual child, taking into consideration the range of food each child would prefer as a vehicle.

If negative, the parent was asked to give the child further doses of the food at home as higher or repeated doses have been reported to lead to clinical symptoms not observed during single point oral challenges (13).

One-week challenges were based on normal daily consumption for the specific age group, unless the history clearly indicated otherwise. A normal portion was defined as an amount indicated by the history or as a normal portion for that age group calculated by means of the National Diet and Nutritional Survey (16). Foods used for the double-blind placebo-controlled food challenges (DBPCFC) were tested for blindness by the study team, and an independent group of parents and children.

The children underwent open challenges and only those with a positive reaction were invited to participate in a DBPCFC unless the open challenge had resulted in a severe reaction or there was a history of anaphylaxis. Those with a history of immediate symptoms had day case challenges on the Paediatric Day Unit, whilst those with delayed symptoms and negative SPT had home food challenges. Dietary management of food hypersensitivities is important to avoid unnecessary restriction and appropriate exclusion (17). Children with positive challenges were offered dietary advice. The full details of the challenge protocols have been discussed elsewhere (6).

Results

The target eligible population comprised 1440 6 yr old, calculated based on school attendance. The final response rate was 798 (55.4%, 95% CI 52–58), 403 boys. There was no difference in response between the respondents and non-respondents in terms of sex, age or area of residence. The response pattern did not differ between the state and independent sector pupils. A sample of non-responders ($n = 103$) was contacted and the majority reported lack of interest as the main reason for non-participation.

Reported rates of adverse reaction to foods

Parents of 94 (52 boys) six-year-old children reported that their child had a current problem with a food/food ingredient, with 30 children reporting problems with more than one food or food ingredient. Hence, the prevalence of reported adverse reactions to food amongst this cohort was 11.8% (94/798, 95% CI 9.6–14.2) (Fig. 1). There was no significant difference between males and females. Sixty-eight of ninety-four

* Statistically significant difference between the rate of sensitization of those who either did or did not report a problem with a food $\chi^2 = 40.0$; $p = 0.00$

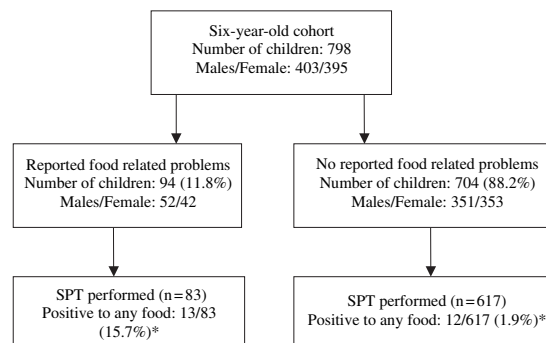


Fig. 1. Reported adverse reactions to food in relation to sensitization and food challenge outcome.

(72.3%) 6 yr olds who reported a current problem were avoiding one or more foods; these did not necessarily include the food to which they reported an adverse reaction.

Wide ranges of foods or food ingredients were implicated in reported adverse reactions in the children (Table 1). The most frequent problems parents reported as being associated with consuming these foods were behavioural (hyperactivity and dislike) and gastrointestinal (abdominal pain, vomiting and diarrhoea). Other problems were wheeze, urticaria or other rashes, rhinitis, collapse or mucosal swelling.

Prevalence of sensitization

A total of 700 six-year-old children (87.8% of respondents) consented to be SPTed. The rate of sensitization to any allergen tested was 125/700 (17.8% 95% CI 15.9–20.1), with 118 sensitized to one or more of the aeroallergens tested (house dust mite 76, grass 60 and cat 48). In addition to this, one child was tested to other aeroallergens on request and was found to be positive to horse.

Table 1. Major foods/ingredients reported to cause problems

Food	Number (%) reporting problem
Milk and dairy	38 (40%) (29 to milk)
Peanut	15 (16%)
Egg	15 (16%)
Additives and colourings	13 (14%)
Tree nuts	11 (12%)
Wheat	10 (11%)
Strawberry	6 (6%)
Sesame	5 (5%)
Fish	2 (2%)
Other*	59 (63%)

A total of 94 children reported a problem with some food and of these 30 reported a problem with more than one food.

*A variety of other food and food ingredients were reported to cause problems including tomatoes, meat, other fruits and fruit juices and fizzy drinks.

The rate of sensitization to any of the pre-defined food allergen panel was 7.7% (54/700). However, large numbers were asymptotically sensitized to both grass and wheat. Cross reactivity between grass and wheat allergen is well established in subjects with asymptomatic sensitization to wheat (18). All those who had a positive reaction to wheat and grass were assessed for possible problems by the study physician and if they consumed wheat (in various forms) without any problem the reaction was regarded as cross reactivity. Only three 6 yr old were sensitized to wheat alone. If subjects with a history of grass pollen allergy who are sensitized to grass and wheat are removed, the true rate of sensitization to any pre-defined food allergen dropped to 3.6% (25/700, 95% CI 2.3–5.2). The individual rate of food sensitization to the pre-defined panel of allergens is shown in Fig. 2. In addition, 12 6 yr old were tested to one or more other food allergen based on their histories [almond (six), banana (one), cocoa (one), green bean (one), red/green/yellow/orange pepper (four), strawberry (one), tomato (one), walnut (six), brazil nut (six), green pea (one), hazel nut (five), cashew (five), pecan (five)]. Of these, four children were sensitized (one to banana, one to green bean and green pea, one to almond and one to hazelnut).

Of the 94 6 yr old who reported problems with any food 83 underwent SPT (Fig. 1). Of these, 25 were sensitized to any allergen with 13 sensitized to the pre-defined food allergen panel. Amongst the 94 only 12 (13% 95% CI 6.8–21.2) had a positive SPT to the food they reported a problem to. These 12 children had a history, which was suggestive of Type-I reaction and the majority were sensitized and reported a reaction to peanuts. In contrast, amongst those who did not report any problem with a food ($n = 704$), 617 consented to be SPTed and only 12 children (1.9%) had a positive SPT to the pre-defined

food allergens (Fig. 1). This was a statistically significant difference ($\chi^2 = 40.0$; $p = 0.00$).

Food challenges

Although 94 children reported a problem with various food or food substances, only 28 were regarded as eligible for food challenges. Sixty-six were not eligible for a variety of reasons. These included inconsistent history where, after consultation with the research dietitian, it was actually revealed that they ate the food frequently in a variety of forms without any reactions. Another reason was children tolerating foods from the same food groups in their diet, e.g. does not drink full fat milk, but eats yoghurt, cheese and semi-skimmed milk frequently etc. Another three children were identified by means of their SPT result. Of the 31 children invited for food challenges, 12 declined food challenges because of a variety of reasons. These included previously diagnosed food allergy ($n = 5$), previous reaction and positive skin test ($n = 1$), mother with allergy to that food, child SPT positive to that food and no prior exposure ($n = 1$) and simple refusal ($n = 5$). Based on the criteria in the methods section, the remaining 19 children underwent a total of 21 open challenges (13 one-day and 8 one-week challenges) to foods including milk ($n = 4$), peanut ($n = 6$), wheat ($n = 3$), egg ($n = 2$), fish ($n = 1$), chocolate ($n = 1$), sesame ($n = 2$), almond ($n = 1$) and banana ($n = 1$). Of these, 10 children had a positive reaction: milk (four), peanut (two), wheat (two), chocolate (one), sesame (one) and banana (one). One child had a positive open food challenge OFC to both sesame and peanut. Amongst the children who had a negative OFC, one child (challenged to fish) was known to be allergic to peanut, milk and wheat. The 10 children with positive OFC were then invited to undergo DBPCFC but four declined, either for personal reasons or severity of reaction on open challenge. The remaining six children underwent DBPCFC and three had a positive reaction to milk ($n = 2$) and wheat ($n = 1$) (Table 2).

To calculate the rate of FHS with a focus on open food challenge we included those children who had a positive open food challenge ($n = 10$), one child with a history of inadvertent reaction with positive skin test, those with hospital diagnosis ($n = 5$) plus one child who was known to be allergic to peanut, milk and wheat but was negative on OFC to fish. We were also aware that a further six children did not consent to undergo food challenges. If we apply the same rate of positive challenge rate to this group as observed

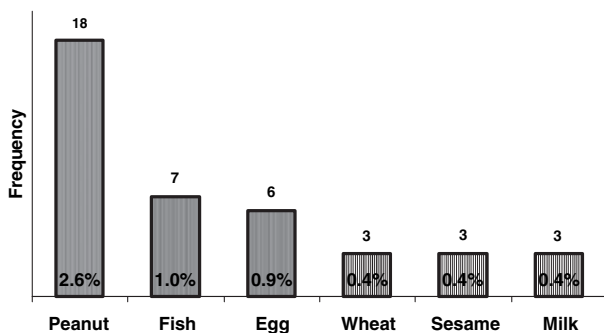


Fig. 2. Frequency of sensitization to the pre-defined food allergen panel in 700 six-year-old children.

Table 2. Food Challenges, symptoms and skin prick test (SPT) data

No.	Food	Open challenge	DBPCFC	Symptoms of positive challenge	SPT (mm)
1	Milk	<i>Positive</i>	<i>Negative</i>	Eczema/diarrhoea	0
2	Milk	<i>Positive</i>	<i>Positive</i>	Nasal congestion	0
3	Wheat	<i>Negative</i>	n.a.	—	0
4	Milk	<i>Positive</i>	<i>Positive</i>	Rash/diarrhoea	0
5	Sesame	Negative	n.a.	—	3.5
6	Banana	Positive	Declined	Projectile vomiting/abdominal pain	4
7	Wheat	<i>Positive</i>	Declined	Diarrhoea/abdominal pain	0
8	Milk	Simple refusal	n.a.	—	0
9	Peanut	Negative	n.a.	—	5
10	Almond	Known allergic, declined challenge	n.a.	—	5.5
11	Peanut	Negative	n.a.	—	5.75
12*	Fish	Negative	n.a.	—	4.75
13	Peanut	Positive	Declined	Angioedema	8.25
14	Peanut	Known peanut allergic, declined challenge	n.a.	—	8.5
	Milk	declined challenge			8
15	Wheat	<i>Positive</i>	<i>Positive</i>	Eczema	0
16	Peanut	Known peanut allergic, declined challenge	n.a.	—	5
	Brazil nut	declined challenge			11.5
17	Peanut	Negative	n.a.	—	4
18	Peanut	Positive	Declined	Vomiting	5.75
	Sesame	Positive	Declined	Urticaria and angioedema	2.75
19	Egg	Negative	n.a.	—	3.75
20	Chocolate	<i>Positive</i>	<i>Negative</i>	Diarrhoea	—
21	Milk	Simple refusal	n.a.	—	0
22	Hazelnut	Positive SPT, family history, no prior exposure	n.a.	—	3.25
23	Milk	<i>Positive</i>	<i>Negative</i>	Diarrhoea/abdominal pain	0
24	Peanut	Negative	n.a.	—	8.25
	Almond	Negative			3
25	Milk	Simple refusal	n.a.	—	0
26	Peanut	Known peanut allergic, declined challenge	n.a.	—	7.5
	Egg	declined challenge			6
27	Peanut	Known allergic, declined challenge	n.a.	—	7
28	Additives	Simple refusal	n.a.	—	—
29	Egg	Positive SPT and previous reaction on exposure	n.a.	—	4.25
30	Milk	Simple refusal	n.a.	—	0
31	Egg	<i>Negative</i>	n.a.	—	0

Challenges in italic were one-week challenges.

DBPCFC, double-blind placebo-controlled food challenges.

*This child was known to be allergic to peanuts, milk and wheat.

with the 19 who did undergo OFC (i.e. 10/19, 53%) amongst them there will be three children with FHS. This leads to a total of 20 (20/798) children. Therefore the prevalence of FHS based mainly on OFC outcomes and history was 2.5% (95% CI 1.5–3.8).

To calculate the rate of FHS with a focus on DBPCFC we included the three children with a positive DBPCFC + 5 (prior hospital diagnosis) + 2 (applying a 50% rate to the four who declined to undergo DBPCFC) + 1 (history of inadvertent reaction with positive skin test)/798 = 1.4% (95% CI 0.7–2.5).

However, we do know that six declined challenges altogether. To compensate for this we estimated that three of them could have been positive if they underwent OFC (based on the rate that was positive on OFC). If we further assume that these three would have undergone

DBPCFCs, it is likely that two (50% based on the rate that was positive on DBPCFC) could have been positive. This then leads to a total of 13 and FHS rate of 1.6% (95% CI 0.9–2.7).

Discussion

This study is the first population-based study of unselected six-year-old children in the United Kingdom establishing reported food problems, and sensitization, objectively assessing FHS. Most of this study was conducted within the schools in the presence of the parents, which raised awareness and offered the opportunity of education. A total of 94 (11.8%) 6 yr olds reported a problem with a food or food ingredient. Our previous study (6) with cohorts of 11- and 15-year-old children reported a similar prevalence rate of perceived FHS (11.6% and

12.4%, respectively). The rate of sensitization to the pre-defined panel of food allergens amongst this cohort of 6 yr old was 3.6% (95% CI 2.3–5.2). Based on open food challenge and/or suggestive history and positive skin tests, the prevalence of FHS was 2.5% (95% CI 1.5–3.8). Based on double-blind challenges, a clinical diagnosis or suggestive history and positive skin tests, the prevalence was 1.6% (95% CI 0.9–2.7). We believe that this cohort of children on the Isle of Wight is representative of English children, though the results may not necessarily be applicable to children in other countries.

These estimates are likely to be conservative estimates. We did not for example assess the prevalence of unrecognized reactions to food. Indeed parents may under report food reactions just as well as over reporting them. A true prevalence estimate needs to address both aspects and we did not investigate this as it was beyond the scope of the project.

Additionally a number of children who reported a problem with a food were excluded from challenges primarily because they ate the food in a variety of forms without any reactions or because they were tolerating other foods from the same food group. It could be argued that children may react differently to food items belonging to the same food group, as processing and cooking can alter the antigens.

There are only a handful of other published studies specifically looking at prevalence of FHS amongst children. In the USA, 480 consecutive children born into a paediatric clinic were recruited at a routine two-week appointment. The researchers determined that 8% (cumulative incidence) of the children (0–3 yr) of the 28%, who presented with possible symptoms of food allergy, were truly food allergic as assessed by food challenges (7).

In the Netherlands, in a cohort of 1039 children aged 5–6 yr the reported rate of FHS was 11.4% although only 39% of the cohort was assessed. Within this cohort, 91.5% of the parents who perceived their child to have FHS restricted the child's diet (19). In our cohort the reported rate of FHS was 11.8%, which is very similar to the rate reported in the Netherlands. Another population-based study in the Netherlands demonstrated that the prevalence of self-reported adverse reactions to foods among school children (aged 5–15 yr) was 7.2%, with food additives and chocolate being the commonest foods avoided.

In a German study by Roehr et al. (5), questionnaires were sent to 2354 (0–17 yr) children and the investigators had a response rate of

31.4%, which is considerably lower than our response rate. A total of 78 oral food challenges were carried out (mixture of DBPCFC and open and single blind food challenges) with 48 positive food challenges amongst 31 children. Based on this the researchers concluded that the prevalence of proven FHS was 4.2%. This is a higher rate than found in our study, but it has to be remembered that in the German study a wide age range (0–17) was involved and it is not clear whether the majority of their proven cases were very young children (0–4 yr) as it is well established that FHS is higher during infancy and early childhood. Nevertheless we both found a similar discrepancy between reported and proven FHS. The foods most commonly implicated were apple, kiwi, soy, hazelnut and wheat, although challenges were performed to a much wider range of foods.

Rance et al. (4) conducted a questionnaire-based survey in Toulouse (France) schools to determine the prevalence of food allergies among school children. Three thousand and five hundred questionnaires were distributed in 150 classes in eight schools and 2716 (77.6%) children responded. Based on these questionnaires, 182 (6.7%) children were considered to be truly food allergic. The point prevalence was 6.8% for the children aged 6–10 yr. The main foods reported as causing adverse reactions were cow milk, eggs, kiwis, peanuts, fish, tree nuts and shrimp. One should however take into account that these figures are based on reported FHS and not confirmed by food challenges.

The main weakness of our study is the response rate of 55.4%. This is indeed a problem with most population-based prevalence studies. We addressed this limitation by sampling the non-responders and found that they were not significantly different to the responders. It is possible that this low response could have led to a selection bias with only atopic individuals or those with a food related problem being more likely to respond. If, however, selection bias was a major issue, we would expect a high rate of atopy in the responders. Approximately 18% of the cohort was atopic, which is similar to a previously reported population study of similar aged children from the Isle of Wight where the response rate was high (84%) and 19.6% were found to be atopic (20).

We believe that this cohort of children on the Isle of Wight is representative of English children, though the results may not necessarily be applicable to children in other countries. Geographical variance in prevalence of self-reported FHS and differences in the foods reported to

cause hypersensitivity has been documented (3, 21). Although we feel that results from this cohort will be applicable to 6 yr old in the UK as a whole one needs to be aware that this estimate is likely to be a conservative estimate.

Peanut and tree nut allergy has been a cause for concern for a while, with 16% of allergic reactions occurring in school or day care (22). Sensitization to peanuts at the age of 4 yr in a study of 1218 children on the Isle of Wight has previously been shown to be 13/981 (1.3% 95% CI 0.6–3.9) of those who had SPT (23). Amongst this cohort although the sensitization rate was considerably higher (2.6%, 95% CI 1.4–7.6), the difference was not statistically significant ($p = 0.075$).

It is difficult to compare our sensitization rates with other studies. Firstly there are no other population-based studies that have specifically SPTed 6 yr old. There are a few studies, which have looked at sensitization data amongst children of varying ages only if they had reported a problem (5) and they used prick-to-prick technique with free foods. We had ethical approval to use standardized allergen extract and only use prick to prick when this is not available. In addition by using identical commercial allergen extracts (and same operators) we were able to compare the results from this cohort directly with previous cohorts on the Isle of Wight. We are however aware that evidence suggests skin testing with fresh foods may have higher sensitivity and specificity (24, 25).

Discrepancy in self-reported food-induced symptoms and physician diagnosed FHS has been reported by others to be 10-fold in children and adolescents (5). In our study, despite 94 (11.8%) children having reported food-related problems, a much smaller proportion were diagnosed to have FHS on the basis of food challenges and inclusion of those with a physician's diagnosis or clinical reaction or inadvertent exposure coupled with sensitization.

Conclusion

In conclusion, this study revealed that reported food problems are common in six-year-old children but the rate of sensitization to food allergens and FHS diagnosed by food challenge is low.

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