Prevalence and cumulative incidence of food hypersensitivity in the first 10 years of life

Carina Venter1,2, Veeresh Patil1, Jane Grundy1, Gillian Glasbey1, Roger Twiselton1, Syed Hasan Arshad1 & Taraneh Dean1,2

1The David Hide Asthma and Allergy Research Centre, St. Mary’s Hospital, Newport, Isle of Wight, UK; 2School of Health Sciences and Social Work, University of Portsmouth, Portsmouth, UK

To cite this article: Venter C, Patil V, Grundy J, Glasbey G, Twiselton R, Arshad SH, Dean T. Prevalence and cumulative incidence of food hypersensitivity in the first 10 years of life. Pediatr Allergy Immunol 2016; 27: 452–458.

Keywords
food allergy; food hypersensitivity; food intolerance; incidence; prevalence

Abstract

Background: Prevalence, incidence and natural history of food hypersensitivity (FHS) and its trends in an unselected cohort of older children are unclear.

Methods: A birth cohort born on the Isle of Wight (UK) between 2001 and 2002 was followed up prospectively. Children were clinically examined and skin prick tested at set times and invited for food challenges when indicated. At 10 years of age, children were also invited for a blood test.

Results: A total of 969 children were recruited at 12 weeks of pregnancy, and 92.9%, 88.5%, 91.6% and 85.3% were assessed at 1, 2, 3 and 10 years. Prevalence of sensitization to any allergen over 10 years was 186 of 969 (19.2%; 95% CI: 16.8–21.8) and 108 of 969 (11.2%; 95% CI: 9.3–13.2) children were sensitized to at least one predefined food allergen. Excluding wheat (due to cross-reactivity with pollen), 40 of 969 (4.1%; 95% CI: 3.1–5.3) children were sensitized to a predefined food allergen. Using food challenges and/or a good clinical history, the cumulative incidence of food hypersensitivity (FHS) in the first decade of life was 64 of 947 (6.8%, 95% CI: 5.2–8.4), while the prevalence of FHS at 10 years was 30 of 827 (3.6%, 95% CI: 2.5–5.1). The vast majority, 25 of 827 (3.0%, 95% CI: 1.8–4.2), suffered from IgE-mediated food allergy, while 5 of 827 (0.6%, 95% CI: 0.07–1.3) had non-IgE-mediated food allergy/food intolerance.

Conclusions: By the age of 10 years, 6.8% of children suffered from FHS based on food challenges and a good clinical history. There was a large discrepancy between reported and diagnosed FHS.

Food hypersensitivity (FHS) is the umbrella term for food allergies (FA) [IgE and non-IgE mediated] and non-allergic food hypersensitivity as currently defined by the European Academy of Allergy and Clinical Immunology (EAACI) and the World Allergy Organization (1).

Very few studies are available with the majority of these focusing on IgE-mediated food allergies only. An EAACI systematic review reported food allergy rates based on a clinical history/food challenge of 1.1–1.2% in 6-year-olds and 1.4–2.3% in 11- to 17-year-olds. Based on food challenge only, these figures were 0.4–4.2% in 6- to 10-year-olds and 0.1–5.7% in 11- to 17-year-olds (2).

We have previously reported FHS in 6-, 11- and 15-year-old cohorts on the Isle of Wight (IOW). At 6 years of age (3), the prevalence of FHS based mainly on open food challenge (OFC) outcomes and positive skin prick test (SPT) responses plus a history of adverse reactions was 20 of 798 (2.5%) (95% CI 1.5 to 3.8). In the older children, we found that the prevalence of FHS was 18 of 775 (2.3%) in the 11-year-old cohort and 17 of 757 (2.3%) in the 15-year-old cohort (4).

The aim of this study was to address key knowledge gaps with respect to FHS in older children, namely the prevalence, cumulative incidence and natural history of FHS in the first 10 years of life (including both FA and non-allergic FHS), and how clinically defined FHS relates to reported symptoms of FHS. In this study, we will continue to use the term FHS in order to compare our data with previous studies from the IOW, using the same methodology. However, our focus is primarily on IgE-mediated food allergies.
Methods

A whole population birth cohort was established on the Isle of Wight to study the prevalence and cumulative incidence of FHS (5). At 1, 2 and 3 years, cohort children were invited to attend the clinic for a medical examination guided by a detailed questionnaire. At 10 years, visits to the schools were performed for SPT upon consent. Information regarding any adverse reactions to food was obtained using a standardized questionnaire (3, 4). SPT was performed using ALK Abello diagnostic extracts (6). Lupin flour (only performed at 10 years) and sesame allergens were obtained from Stallergens. SPT reactions with a mean wheal diameter of 3 mm or greater than the negative control were regarded as positive.

Based on their history and SPT results at 10 years of age, the following children were excluded: 1 Those with a previous SPT to a food that they had not knowingly eaten previously; 2 Those who indicated a previous adverse reaction to foods (regardless of their skin prick test data); and 3 Those with a previous diagnosis of a food allergy, without any recent exposure with a clear reaction.

The following children were excluded: 1 Those with a previous diagnosis of food allergy based on a food challenge where the SPT size increased significantly; 2 Those with a previous diagnosis of a food allergy, where consultation with the allergist indicated that a food challenge would be too risky; and 3 Those with a SPT size above the 95% predictive values with a history of a clinical reaction (6).

Food challenges were performed using the PRACTALL (7) guidelines for IgE-mediated food allergy. To diagnose non-IgE-mediated food allergy, a normal daily amount was given to the individual, based on the information of the National Diet and Nutrition Survey (UK) until the child showed a reaction or a maximum period of 7 days (8). To minimize any bias, food challenges were performed blinded where possible, but always when looking for delayed/subjective symptoms.

Symptoms for IgE- and non-IgE-mediated FHS were classified according to the NICE guidelines (9), that is we diagnosed immediate-type symptoms based on the symptoms listed by the NICE guidelines occurring within 2 h of ingestion of the foods. Delayed symptoms were diagnosed based on the symptoms listed by the NICE guidelines occurring 2 h up to 7 days after ingestion of the food.

Ethics permission

Ethical approval for the study was obtained from the NRES South Central – Southampton B Research Ethics Committee (REF 10/H0504/11).

Analysis of data

Data were double-entered by different operators on SPSS versions 20 and 21 and were compared and verified (SPSS Inc, Chicago, IL, USA). Frequency tables were produced at each time point from which prevalence rates were computed for each allergen together with 95% confidence intervals. Numbers indicating loss of follow-up were clearly stated. Missing data were handled by showing the relevant denominator in each instance. Reasons for loss of follow-up or missing data were as follows: family declined any further involvement in the study; children declined to provide a blood sample or undergo skin prick tests; families/children declined food challenges due to previous reactions (defined as assessment by a paediatric allergist and symptoms in agreement with the UK NICE guidelines) (9) or positive oral challenges; and families moved out of area. Confidence intervals were calculated using the Clopper–Pearson test. To rule out selection bias at 10 years, we used the following methodology: A family history of allergic disease was defined as a first degree relative (mother, father or sibling) with a ‘yes’ answer to any of the validated ISAAC questions (10).

We compared (using a 2 × 2 table and Fisher’s exact test) those who completed the FAIR recruitment questionnaire with a positive answer to a family history of allergic disease vs. those who completed the 10-year questionnaire with a positive answer to a family history of allergic disease. We then compared those who consented to SPT at one year who reported a family history of allergy to those who consented to SPT at 10 years with a reported family history of allergy. We measured education level by comparing the mothers in the consenting families at one and 10 years with higher (college/university) and high school/less.

Results

The study population consisted of 969 (91% of the target population of 1063) children; 827 of 969 (85%) children were seen at 10 years. Over the course of the 10 years, 725 of 969 (74.8%) children were seen at one, two, three and 10/11 years of age, and 947 of 969 (97.7%) children were seen at any time point. We have therefore used 947 as our denominator for FHS over 10 years.

To rule out selection bias at 10 years, we compared reported family history of allergy at recruitment vs. those seen at 1 year (752/900 [83.3%]) and those seen at 10 years (691/827 [83.4%]), and there was no difference between the two groups (p = 0.99). The same applied to those consenting to SPT at 1 year (637/736 [86.5%]) and 10 years (490/588 [83.6%]; p = 0.64). We also compared maternal education between those seen at 1 year (558/900 [62%]) and 10 years (527/827 [63.6%]); p = 0.75 with no difference.

Sensitization rates

Sensitization rates at three and 10 years are summarized in Table 1. Cumulatively over the period of 10 years, 40 of 969 (4.1%; 95% CI: 3.19–5.32) children were sensitized to a predefined food allergen.

Where history indicated, children were skin prick tested to other allergens. At the age of 10 years, five children who were not sensitized to any of the predefined food allergens were
sensitized to hazel nut (3), brazil nut (4), cashew nut (3), pistachio (3), walnut (1), almond (1) and tomato (1).

**Reported symptoms of allergic disease in the first 10 years of life**

Over the 10-year period, 203 of 947 (21.4%) children or parents reported a food-related problem; 77 of 827 (9.3%) children reported a food-related problem to 107 foods, to the question ‘do you have any food related problems’. On further questioning of the 77 of 827 (9.3%) participants, it was noted that a number of children/parents interpreted this question as food-related aversion/dislike and 23 children were excluded for these reasons. Of the 54 remaining participants followed with further phone calls and history taking by the study clinical and specialist allergy dietitian, 1 child showed no improvement on the elimination diet (wheat) and was therefore not indicated to undergo a food challenge; 2 further children declined the intervention (reported GI symptoms but did not want to trial an elimination diet); 3 children were suffering from a FHS at 10 years of age, based on skin/serum testing and recent history; and 3 10 children declined food challenges but were included in prevalence data if they were considered to be still allergic based on skin/serum testing and recent history.

One hundred and sixty-two children were avoiding a food related avoidance without giving any reason, a further 15 children were invited to be further investigated based on reported symptoms suggestive of FHS: 9 underwent food challenges, 2 children declined intervention/challenges, another 2 children reported that the problem resolved naturally, and 2 children showed no improvement on an exclusion diet (Figure 1).

**Diagnosis of food hypersensitivity based on food challenges at 10 years**

Overall, 37 food challenges were performed in 32 children (23 in those reporting food allergy and 9 in those reporting food avoidance). These challenges were as follows: 11 one-day OFC, 10 one-day DBPCFC, 5 one-week OFC and 11 one-week DBPCFC. Of these, 6 one-day OFC, 3 one-week OFC and 2 one-week DBPCFC were positive.

We invited all children for food challenges, but some declined. We have therefore concluded that the following children were suffering from a FHS at 10 years of age, based on the following criteria: 1 6 positive OFC 1 day; 2 peanut, 2 brazil nut, 1 sesame and 1 egg; 2 3 positive OFC 1 week: 2 wheat and 1 milk; 3 2 positive DBPCFC 1 week: 1 wheat and 1 egg;
4 6 positive SPT plus clear history: 3 peanut (SPT 5, 6 and 8 mm), 2 sesame (SPT 5 and 6 mm) and 1 hazelnut (SPT 6 mm);
5 6 SPT above the 95% predicted values (>8 mm): 5 peanut and 1 brazil nut;
6 2 still avoiding the food and report reactions on recent accidental ingestion: 2 egg (refused SPT but 5 and 5 mm at last follow-up);
7 2 positive food challenges for delayed type symptoms in the past who refused further food challenges: 2 milk; and
8 3 children diagnosed with coeliac disease.

Two of these children, one with a peanut allergy and one with an egg allergy, did not initially report a problem but were picked up from further questioning and challenges and were diagnosed with a food allergy.

Of these 30 children, 9 had more than one food allergy, leading to 30 children allergic to 50 foods.

Based on those with a positive food challenge and/or clear history (i.e. objective symptoms on consumption of the allergen), the prevalence of FHS at 10 years is 30 of 827 (3.6%, 95% CI: 2.54 to 5.15). Of the 77 of 827 (9.3%) children who initially reported adverse reactions to foods, only 23 of 77 (29.9%) could be verified by means of a food challenge and/or a clear history.

Dividing the children into those with IgE-mediated and non-IgE-mediated food allergy, 25 children suffered from IgE-mediated food allergy: 25 of 827 (3.0%, 95% CI: 1.8–4.2), and 5 children suffered from non-IgE-mediated food allergy: 5 of 827 (0.6%, 95% CI: 0.07–1.3). We did not rule out that these children might have suffered from food intolerances.
The cumulative incidence of FHS by 10 years of age

The cumulative incidence of food hypersensitivity over 10 years was 64 of 947 (6.7%, 95% CI: 5.2 to 8.4). Between 3 and 10 years of age, 9 of 947 children (0.95%, 95% CI: 0.3 to 1.6) outgrew their food hypersensitivity (egg 4, milk 3, sesame 1, peanut 1) and 12 of 947 (1.3%, 95% CI: 0.6 to 2.0) children developed new food hypersensitivities (peanut 2, egg 1, wheat 2, sesame 2, gluten 2, milk 1, tree nuts 2) (Table 2).

Foods implicated in FHS

Milk and egg were the most common food hypersensitivities encountered in the first 10 years of life, although peanut was the most prevalent allergen at 10 years (Table 2).

Table 2 FHS to single foods

| Number of children | FHS at 3 years (n) | FHS at 10 years (n) |
|--------------------|--------------------|---------------------|
| with FHS over 10 years (no of IgE-mediated cases) | IgE vs. non-IgE |                          |
| Milk 26 (2) | 4 | 3 (0.36%) (1 outgrew) |
|   | | 1*:2 (both with diarrhoea and bloatedness; also to cheese) |
|   | | * had negative SPT using solution but positive SPT using pasteurized milk |
| Egg 19 (13) | 9 | 6** (0.73%) (4 outgrew and 1 newly diagnosed) |
|   | | ** only two children consented to SPT at 10 years had positive results. Three children had positive SPTs during the first 10 years of life but refused SPT on the day. One child became sensitized after egg avoidance. |
| Wheat 6 (1) | 2 | 4 (0.48%) (2 newly diagnosed) |
|   | | 1:3 (main symptoms included constipation/diarrhoea; coeliac disease ruled out) |
| Gluten 3 (0) | 1 | 3 (0.36%) (2 newly diagnosed) |
| Peanut 13 (13) | 11 | 12 (1.5%) (1 outgrew peanut allergy and 2 new onset) |
| Sesame 7 (7) | 5 | 6 (0.73%) (1 outgrew sesame allergy and 2 new onset)* |
| Brazil nut 4 (4) | 2 | 4 (0.48%) (2 new onset) |
| Corn 1 (1) | 1 | 0 |
| Fish 1 (1) | 0 | 0 |
| Tomato 1 (0) | 0 | 0 |
| Salicylate 1 (0) | 1 | 0 |
| Pineapple 1 (0) | 1 | 0 |
| Almond 2 (1) | 2 | 2 |
| Hazelnut 3 (3) | 1 | 3 (0.36%) (2 new onset) |
| Cashew nut 3 (3) | 1 | 3 (0.36%) (2 new onset) |
| Pistachio 3 (3) | 3 (0.36%) |
| Walnut 1 (1) | 1 | 1 (0.12%) |

*In Table 1, only one child showed a positive SPT to sesame. The six children with sesame allergy had SPT of 4.5, 2.5 and 1.5 mm and 3 refused SPT at 10 years of age, but were still clinically allergic.

**Out of the 6 children with egg allergy, only two children consented to SPT at 10 years and showed positive results. Three children had positive SPTs during the first 10 years of life but refused SPT on the day. One child became sensitized after egg avoidance.

Discussion

To our knowledge, this is currently the only cohort in the world providing this kind of information. The prevalence of FHS at 10 years was 30 of 827 (3.6%, 95% CI: 2.54 to 5.15), while the cumulative incidence of food hypersensitivity over a 10-year period was 64 of 947 (6.7%, 95% CI: 5.20 to 8.4); 25 of 827 (3.0%, 95% CI: 1.8–4.2%) suffered from IgE-mediated food allergy and 5 of 827 (0.6%, 95% CI: 0.07–1.3%) from non-IgE-mediated food allergy/food intolerance.

Sensitization to food allergens

Sensitization rates to milk were relatively low. No child was sensitized to milk using the SPT solution, but one child showed...
a positive prick–prick to milk and was clinically milk allergic. Mustafayev et al. (11), reported a sensitization rate of 1.1% in 10- to 11-year-olds in Turkey, and Ronchetti et al. (12), reported sensitization rates of 0.5% in 9-year-olds and 2% in 13-year-olds in Italy.

In this cohort, 2 of 588 (0.34%) children were sensitized to egg. Ronchetti et al. (12), reported egg sensitization of 0% in 6- to 9-year-olds in Italy and 1% in 13-year-olds.

In our cohort, 14 of 588 (2.4%) children were sensitized to peanut at 10 years of age. Sensitization rates to peanuts in the previous two cohorts were 3.7% (11 year) and 2.7% (15 year) (4). Mustafayev et al. (11), reported a 0.7% prevalence of peanut sensitization in 10- to 11-year-old Turkish children, while Nicolaou et al. (13), reported 5.1% sensitization in 8-year-olds from the UK.

Clinical Allergy

We have diagnosed 3 of 827 (0.36%) children with a clinical reaction to cow’s milk, but only one child was sensitized and showed signs of IgE-mediated CMA (0.12%). Other studies in this age group have reported IgE-mediated CMA varying from 0.1% (Mustafayev et al. (11), and Orhan et al. (14),) up to 13.3% (Wan et al. (15),).

At 10 years of age, 6 of 827 (0.73%) were egg allergic, and all were IgE mediated. Based on OFC and a good clinical history, Mustafayev et al. (11), reported 0.1% egg allergy in 10- to 11-year-olds and Orhan et al. (14), reported 0.9% egg allergy in Turkish children.

Over the course of the 10 years, 13 of 947 (1.4%) children were diagnosed with peanut allergy, and 12 of 827 (1.5%) children were allergic at 10 years, similar to Nicolaou et al. (13), who diagnosed 1.9% of 8-year-olds in the UK with a peanut allergy. In our earlier cohorts, we have found that 7 of 775 (0.9%) at 11 years and 6 of 757 (0.8%) at 15 years were peanut allergic.

In our 10-year-old follow-up, 6 of 827 (0.73%) children were clinically allergic to sesame. In our other cohorts, we have found that 0 of 775 11-year-olds and 1 of 757 (0.013%) 15-year-olds were sesame allergic (4).

We have found 4 of 827 (0.48%) children with wheat allergy at the age of 10 years. We could not find any other studies reporting wheat allergy at 10 years of age.

Reported vs. diagnosed food allergy

It is well known that there is a discrepancy between reported and diagnosed FHS. At 10 years of age, 77 of 827 (9.3%) parents reported a food-related problem, and of these, 23 of 77 (29.9%) were diagnosed with FHS. The EAACI systematic review reported 1.6–24.2% of self-reported rates of food allergy at 6–17 years of age (2). Brugman et al. (16), reported 7.2% of self-reported rates of food allergy in children in the Netherlands aged 4–15 years.

Foods implicated

In a German study by Roehr et al. (17), the authors identified that the children mainly reacted to apple, kiwi, soya, hazelnut and wheat. The foods identified in our study were cows’ milk, hens’ eggs, wheat, peanut, sesame and tree nuts.

One possible limitation of the study is the low uptake of food challenges. We do however feel that all those children considered to be food allergic at 10 years of age were questioned by an experienced allergy dietitian/allergist, have been seen over the years at the David Hide Asthma and Allergy Centre and have clear histories of reactions plus positive SPT results in the case of IgE-mediated food allergies. The findings of our study do not represent food allergy data across the world, but according to the UK census data, is representative of the South of England, and our data with the recently published cow’s milk allergy data from Southampton/Winchester (18).

To conclude, in this study we have found that 64 of 947 (6.8%) of children suffer from FHS over the first decade of life. There was a large discrepancy between reported and diagnosed FHS. The main foods implicated were cows’ milk, hens’ eggs and peanut. A large number of children seem to outgrow their allergies to milk and egg by 10 years, with smaller numbers for peanut and sesame. New onset food allergies at 10 years of age were found for most foods studied.

Acknowledgment

The authors gratefully acknowledge the cooperation of the children and parents who have participated in this study. All parents consented and children provided assent for the study. We also thank Linda Terry and Lisa Matthews for their considerable assistance with many aspects of this study.

Funding

Carina Venter was funded by a National Institute for Health Research Post-Doctorate research award. This article/paper/report presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. The sponsor and funder played no role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. The researchers acted independent of the funders (NIHR UK).

References

1. Johansson SG, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol 2004: 113: 832–6.

2. Nwaru BI, Hickstein L, Panesar SS, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. Allergy 2014: 69: 62–75.

3. Venter C, Pereira B, Grundy J, Clayton C, Arshad H, Dean T. Prevalence of sensitisation, reported and objectively assessed food hypersensitivity amongst 6-year-old children – A population based study. Pediatr Allergy Immunol 2006: 17: 356–63.

4. Pereira B, Venter C, Grundy J, Clayton CB, Arshad SH, Dean T. Prevalence of...
sensitisation to food allergens, reported adverse reaction to foods, food avoidance and food hypersensitivity amongst teenagers. J Allergy Clin Immunol 2005: 116: 884–92.

5. Venter C, Pereira B, Grundy J, et al. Incidence of parentally reported and clinically diagnosed food hypersensitivity in the first year of life. J Allergy Clin Immunol 2006: 117: 1118–24.

6. Venter C, Pereira B, Voigt K, et al. Prevalence and cumulative incidence of food hypersensitivity in the first 3 years of life. Allergy 2008: 63: 354–9.

7. Sampson HA, Gerth van Wijk R, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol 2012: 130: 1260–74.

8. Smithers G, Gregory J, Coward WA, Wright A, Elsom R, Wenlock R. British National Diet and Nutrition Survey of young people aged 4 to 18 years: feasibility study of the dietary assessment methodology. Abstracts of the Third International conference on Dietary Assessment Methods. Eur J Nutr 1998: 32: S2. S76.

9. NICE. Diagnosis and assessment of food allergy in children and young people in primary care and community settings. Clinical Guideline 116. NICE, 2011. Available at: www.nice.org.uk/guidance/cg116

10. von Mutius E. Epidemiology of asthma: ISAAC–International Study of Asthma and Allergies in Childhood. Pediatr Allergy Immunol 1996: 7(Suppl. 9): 54–6.

11. Mustafayev R, Civelek E, Orhan F, Yuksel H, Boz AB, Sekerel BE. Similar prevalence, different spectrum: IgE-mediated food allergy among Turkish adolescents. Allergol Immunopathol (Madr) 2013: 41: 387–96.

12. Ronchetti R, Jesenak M, Trubacova D, Pohanka V, Villa MP. Epidemiology of atopy patch tests with food and inhalant allergens in an unselected population of children. Pediatr Allergy Immunol 2008: 19: 599–604.

13. Nicolaou N, Poorafshar M, Murray C, et al. Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. J Allergy Clin Immunol 2010: 125: 191–7.

14. Orhan F, Karakas T, Cakir M, Aksoy A, Baki A, Gedik Y. Prevalence of immunoglobulin E-mediated food allergy in 6-9-year-old urban schoolchildren in the eastern Black Sea region of Turkey. Clin Exp Allergy 2009: 39: 1027–35.

15. Wan KS, Chiu WH. Food hypersensitivity in primary school children in Taiwan: relationship with asthma. Food Agric Immunol 2012: 23: 247–54.

16. Brugman E, Meulmeester JF, Spee-van der Welke A, Beuker RJ, Radder JJ, Verloo- Vanhorick S. Prevalence of self-reported food hypersensitivity among school children in The Netherlands. Eur J Clin Nutr 1998: 52: 577–81.

17. Roehr CC, Edenharder G, Reimann S, et al. Food allergy and non-allergic food hypersensitivity in children and adolescents. Clin Exp Allergy 2004: 34: 1534–41.

18. Schoemaker AA, Sprickelman AB, Grimshaw KE, et al. Incidence and natural history of challenge-proven cow’s milk allergy in European children – EuroPrevall birth cohort. Allergy 2015: 70: 963–72.