

## Original article

## Prevalence and cumulative incidence of food hypersensitivity in the first 3 years of life

**Background:** Prevalence and incidence of food hypersensitivity (FHS) and its trends in early childhood 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.

**Results:** Nine hundred and sixty-nine children were recruited and 92.9%, 88.5% and 91.9% of them respectively were assessed at 1, 2 and 3 years of age. Prevalence of sensitization to foods was 2.2%, 3.8% and 4.5% respectively at these ages. Cumulatively, 5.3% [95% confidence interval (CI): 3.9–7.1] children were sensitized to a food. Using open food challenge and a good clinical history, the cumulative incidence of FHS was 6.0% (58/969, 95% CI: 4.6–7.7). Based on double-blinded, placebo-controlled, food challenge (DBPCFC) and a good clinical history, the cumulative incidence was 5.0% (48/969, 95% CI: 3.7–6.5). There is no evidence to suggest that the incidence of FHS has increased, comparing these results with previous studies. Overall, 33.7% of parents reported a food-related problem and of these, 16.1% were diagnosed with FHS by open challenge and history and 12.9% by DBPCFC and history. Main foods implicated were milk, egg and peanut.

**Conclusions:** By the age of 3 years, 5–6% of children suffer from FHS based on food challenges and a good clinical history. There were large discrepancies between reported and diagnosed FHS. Comparing our data with a study performed in the USA more than 20 years ago, there were no significant differences in the cumulative incidence of FHS.

**C. Venter<sup>1,2</sup>, B. Pereira<sup>1</sup>, K. Voigt<sup>1</sup>,  
J. Grundy<sup>1</sup>, C. B. Clayton<sup>1</sup>,  
B. Higgins<sup>2</sup>, S. H. Arshad<sup>1</sup>,  
T. Dean<sup>1,2</sup>**

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

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Dr T Dean  
School of Health Sciences and Social Work  
University of Portsmouth  
James Watson West  
2, King Richard 1st Road  
Portsmouth PO1 2FR  
UK

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## Background

The prevalence and incidence of food hypersensitivity (FHS) in children is one of the most discussed topics in allergic diseases. There are a number of reports indicating that prevalence of FHS to certain foods may vary between different countries and may have increased in recent years (1–3). Surprisingly however, only one previous study had looked at the cumulative incidence of FHS in children during the first few years of life. The most frequently quoted study performed in the USA almost 20 years ago, reported a cumulative incidence of food allergy in children (age: 1–3 years) to be 7.4% (4). A birth cohort was established on the Isle of Wight ( $n = 969$ ) to look at the prevalence and cumulative incidence of FHS during the first 3 years of life. At 1 year, 1.0% (8/763) of the infants was sensitized to aeroallergens and 2.2% (17/763) to food allergens. Cumulative incidence of FHS by 12 months was 4% on the basis of open food challenges (OFCs) and 3.2% on the basis of double-blinded, placebo-controlled, food challenge (DBPCFC).

It is well known that self-reported FHS vastly overestimates true FHS. Bock (4) determined that 28% of those who presented with possible symptoms of food allergy were truly food allergic as assessed by food challenges. In the German study 6.8% (5) of those who reported food-related problems were diagnosed with FHS and 14.9% in the study by Osterballe et al. (6).

The aim of the present study is to address key knowledge gaps with respect to FHS in young children, namely: the prevalence and cumulative incidence of FHS in the first 3 years of life (including both food allergy and nonallergic FHS), and how clinically defined FHS relates to reported symptoms of FHS.

## Methods

A whole population birth cohort was established on the Isle of Wight to study the prevalence and cumulative incidence of FHS (7). At 1, 2 and 3 years, all the children were invited to attend clinic for a medical examination, guided by a detailed

questionnaire. Information regarding any adverse reactions to food was also obtained. All children were approached to undergo skin prick testing (SPT) to a standard battery of foods (milk, egg, wheat, peanut, sesame and fish), aero-allergens (house dust mite *Dermatophagoides pteronyssinus*, cat and grass) and other allergens if identified by history as described previously (7) but not all the parents consented. Table 1 presents the information from those who consented. SPT reactions with a mean wheal diameter of 3 mm or greater than the negative control were regarded as positive.

Based on their prior history and results of the SPT during the first 3 years of life, the following children were invited for undergoing trials with food challenges.

- Those with a positive SPT to a food that they had not knowingly eaten previously.
- Those who indicated a previous adverse reaction to foods (regardless of their SPT data).

Food challenges were conducted with all the foods from 6 months of age as described previously (7), except for peanut and sesame, which were conducted once the children were 3 years old, as it is considered that infants should not be exposed to these foods in the first few years of life (H. Sampson, D. Hill, J. Hourihane, personal communication, 2003). Some were excluded from food challenges because their SPT diameter was above the 95% positive predictive levels (8).

Analysis of data

All data were doubly entered by different operators on SPSS versions 10 and 11 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 interval (CI). Comparisons between prevalence rates in this study population and an independent historical reference population was made using Fisher's exact test.

Table 1. Sensitization rates in the first 3 years of life

	1 year (n = 763) n (%)	2 years (n = 658) n (%)	3 years (n = 642) n (%)
Sensitization			
Any of the predefined allergens	20 (2.6)	54 (8.2)	76 (11.8)
Any of the predefined food allergens	17 (2.2)	25 (3.8)	29 (4.5)
Any of the predefined aero-allergens	8 (1.1)	42 (6.4)	70 (10.9)
Milk	2 (0.3)	3 (0.5)	3 (0.5)
Egg	14 (1.8)	14 (2.1)	9 (1.4)
Wheat	0	1 (0.2)	8 (1.3)*
Fish (cod)	2 (0.3)	3 (0.5)	3 (0.5)
Peanut	3 (0.4)	13 (2.0)	13 (2.0)
Sesame	2 (0.3)	5 (0.76)	9 (1.4)
House dust mite	3 (0.4)	24 (3.7)	43 (6.7)
Grass	4 (0.5)	22 (3.3)	21 (3.3)
Cat	1 (0.1)	6 (0.9)	26 (4.1)

\*All children with a positive skin prick testing (SPT) to wheat also had a positive SPT to grass and consumed wheat without any problems.

Results

The study population consisted of 969 (91% of the target population, which was 1063) children. Nine hundred (92.9%) children were seen at 1 year, 858 (88.5%) at 2 years and 891 (91.9%) at 3 years. Over the course of the 3 years, 942 (97.2%) children had been seen at either 1, 2 or 3 years, with 807 (83.3%) children seen on all three occasions. The 1-year-old data (7) has previously been published, but will be referred to in order to draw comparisons.

Sensitization rates

Sensitization rates at 1, 2 and 3 years are summarized in Table 1. Cumulatively, 5.3% (95% CI: 3.9–7.1) children were sensitized to a food. Where history indicated, the children were SPT to other allergens. At the age of 3 years, two of the children who had not been sensitized to any of the predefined food allergens were sensitized to hazel nut (1), brazil nut (2), cashew nut (1) and almond (2).

Reported symptoms of allergic diseases in the first 3 years of life

Of the 807 children seen at 1, 2 and 3 years, parents of 272 (33.7%) reported a food-related problem. At 2 and 3 years of age, 72 (8.3%) and 74 (8.3%) of the parents respectively reported one or more food-related problems in their child. Over the 3 years, cutaneous symptoms (rashes, eczema, urticaria and angioedema) were the most common symptoms, followed by gastrointestinal (diarrhoea, vomiting, constipation and colic) and respiratory symptoms (asthma, wheeze, shortness of breath, runny and itchy nose and cough). Four parents reported behavioural problems with their children at 2 years and 14 parents at 3 years. Figure 1 summarizes the reported symptoms at 1, 2 and 3 years. The foods most commonly linked with the symptoms were milk, egg, fruit (mainly strawberries and citrus fruit), tomato/tomato sauce, additives (food colours and preservatives), wheat, peanut/treenuts, fish/shell fish and soya.

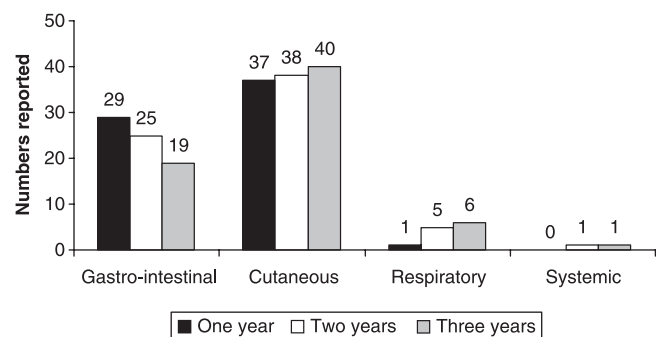


Figure 1. Reported food-related symptoms at 1, 2 and 3 years.

Diagnosis of food hypersensitivity based on food challenges  
 Selection criteria for food challenges at 2 and 3 years of age are shown in Fig. 2A and B.

Food hypersensitivity at 2 years of age

Twenty-one children fulfilled the criteria for food challenges (Fig. 2A) and underwent a total of 24 OFCs (twelve 1-day and twelve 1-week) to milk, egg, wheat and citrus fruit. Two children underwent DBPCFC only. Nine children had 10 positive OFCs [milk (5), egg (4), and wheat (1)]. Of these, four were 1-day challenges (egg) and six 1-week challenges (five to milk and one to wheat). In addition to these children, one child did not undergo a food challenge, as she was diagnosed with coeliac disease.

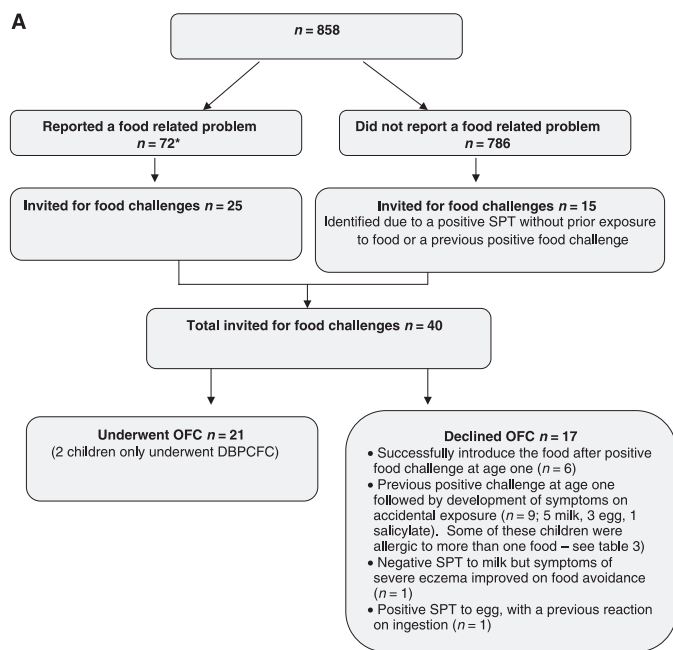
All children with a positive OFC ( $n = 9$ ) were invited to undergo DBPCFC. Additionally, two more children, whose parents had indicated their consent only for DBPCFC, underwent this type of challenge. Five children/parents declined DBPCFC for the following reasons: two children previously had positive OFC to egg and the parents regarded that as sufficient evidence; one child did not undergo a DBPCFC because of multiple

FHS and symptoms of allergic disease (wheat, egg and corn); one mother declined a DBPCFC as she decided to introduce some wheat into the child's diet despite the positive OFC (child developed a mild rash on this introduction); one mother declined the DBPCFC because of the severity of the eczema upon OFC to milk – this child was also sensitized to egg and her eczema improved on exclusion of egg, but the mother declined an egg challenge.

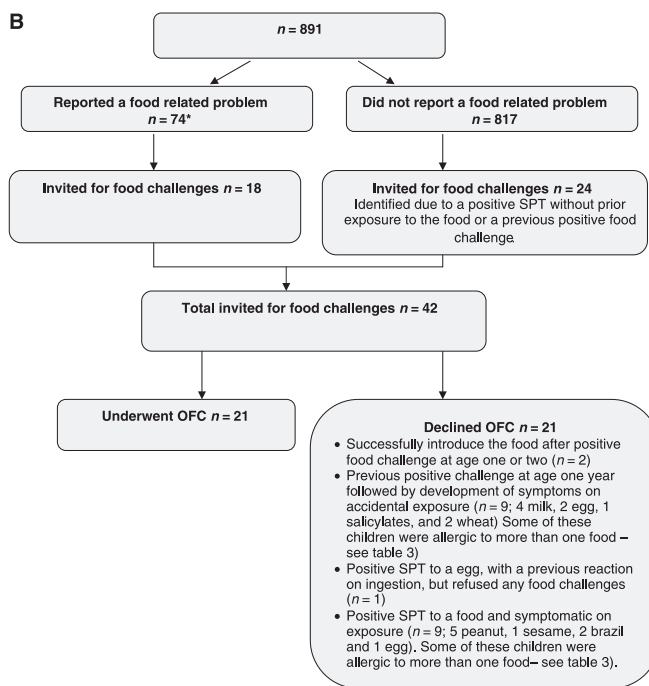
This resulted in six children undergoing six DBPCFCs (one 1-day challenge to egg and five 1-week challenges to milk) of which only one 1-week challenge to milk was positive. Only one child had a 1-day DBPCFC and this was negative. However, another 17 children were considered to be suffering from FHS: the 11 children who did not undergo OFC (Fig. 2A), one child diagnosed with coeliac disease and the five children who declined DBPCFC.

Based on those with a positive OFC and clear history, the prevalence of FHS at 2 years is 2.5% (21/858, 95% CI: 1.5–3.7). If the outcome measure is DBPCFC and a clear history, then the prevalence is 2.1% (18/858, 95% CI: 1.3–3.3).

Of the 72 children who reported adverse reactions to foods (i.e. excluding those with a positive SPT who did



\* 47 children have not been invited for food challenges. These children reported various symptoms to a variety of foods. In all these children, SPT were performed to these foods when possible and children were asked to trial the food again at home. However, all children with a positive SPT to a food, who reported an adverse reaction to that food, were challenged in hospital and not instructed to trial foods at home. In all cases subsequent exposures were tolerated well. We decided from the outset of the study not to challenge children with reported hyperactivity/behavioural problems to foods ( $n = 4$ ).



\* 56 children have not been invited for food challenges. These children reported various symptoms to a variety of foods. In all these children, SPT were performed to these foods when possible and children were asked to trial the food again at home. However, all children with a positive SPT to a food, who reported an adverse reaction to that food, were challenged in hospital and not instructed to trial foods at home. In all cases subsequent exposures were tolerated well. We decided from the outset of the study not to challenge children with reported hyperactivity/behavioural problems to foods ( $n = 14$ ).

Figure 2. (A) Selection criteria for 2-year food challenges. (B) Selection criteria for 3-year food challenges.

not report any adverse reactions to food, but had never knowingly eaten the food), only 14 (19.4%) could be verified by means of OFC and a clear history and 12 (16.7%) by DBPCFC and a clear history.

Prevalence of food hypersensitivity at 3 years of age

Twenty-one children fulfilled the criteria for food challenges and underwent 25 OFCs (twenty-four 1-day and one 1-week) to peanut, sesame, kiwi, pineapple, egg, colourings, corn and fish (Fig. 2B). Seven children had seven positive OFCs [peanut (3), sesame (1), egg (2) and pineapple (1)]. Of these, six challenges were 1-day challenges (peanut and egg) and one challenge a 1-week challenge (pineapple). In addition to these children, there was one more child who did not undergo a food challenge, as she was diagnosed with coeliac disease.

These seven children were invited to undergo DBPCFC. The parents of two children with a positive OFC to egg declined the DBPCFC as they felt the OFC was sufficient evidence of FHS, four parents declined the DBPCFC because of severity of reaction on OFC (one sesame, one egg and two peanut). Therefore, only one child had a 1-day DBPCFC, to pineapple and this was negative. However, another 26 children were considered to be suffering from FHS: the 19 children who did not undergo OFC (Fig. 2B), one child diagnosed with coeliac disease and the six children who declined DBPCFC.

Based on those with a positive OFC and clear history, the prevalence of FHS at 3 years is 3.0% (27/891, 95% CI: 2.0–4.4). If the outcome measure is DBPCFC and a clear history, then the prevalence is 2.9% (26/891, 95% CI: 1.9–4.3).

Of the 74 children who reported adverse reactions to foods (i.e. excluding those with a positive SPT who did not report any adverse reactions to food, but never knowingly eaten the food), only 15 (20.2%) could be verified by means of OFC and history or 14 (18.9%) by a DBPCFC and history. A summary of diagnosed FHS at 1, 2 and 3 years is shown in Table 2.

The cumulative incidence of FHS by 3 years of age

Over the course of the first year of life, the cumulative incidence of FHS based on OFC and a clear, convincing history was 4% (39/969) (9). Six new cases were diagnosed by 2 years of age, leading to a cumulative incidence of 4.6% (45/969). Thirteen new cases were diagnosed by 3 years of age. Therefore, using OFC and a clear, convincing clinical history as the endpoint, the cumulative incidence of FHS was 6.0% (58/969, 95% CI: 4.6–7.7) children.

Based on DBPCFC and a clear, convincing clinical history the incidence of FHS by 1 year of age was 3.2% (31/969) (9). Three new cases were diagnosed by 2 years of age, leading to a cumulative incidence of 3.5% (34/969). Fourteen new cases were diagnosed by 3 years of age. Therefore, based on DBPCFC and a clear, convincing clinical history, the cumulative incidence of FHS by 3 years of age was 5.0% (48/969, 95% CI: 3.7–6.5). Of the 807 children seen at 1, 2 and 3 years, 272 (33.7%) reported a food-related problem at 1, 2 and 3 years. Amongst those who reported a food-related problem at any time (1, 2 and 3 years), 16.1% (44/272, 95% CI: 12.1–21.1) were diagnosed with FHS by means of an OFC and history and 12.9% (35/272, 95% CI: 9.1–17.4) by means of a DBPCFC and history.

Table 2. Diagnosed food hypersensitivity (FHS) at 1, 2 and 3 years

Diagnosed FHS based on food challenge and history	A, number of children with FHS (n)	B, number of foods (n)	C, IgE-mediated reactions (n (%))	D, non-IgE-mediated reactions (n (%))	E*, Nonallergic FHS (n (%))	F, SPT not performed (n (%))
OFC 1 year	39	46	12 (26.1)	31 (67.4)	1 (2.2)	2 (4.3)
DBPCFC 1 year	31	38	12 (31.6)	23 (60.5)	1 (2.6)	2 (5.3)
OFC 2 years	21	27	12 (44.4)	9 (33.3)	1 (3.7)	5 (18.5)
DBPCFC 2 years	18	24	12 (50)	6 (25)	1 (4.2)	5 (20.8)
OFC 3 years	27	41	29 (70.7)	8 (19.5)	1 (2.4)	3 (7.1)
DBPCFC 3 years	26	40	29 (72.5)	7 (17.5)	1 (2.5)	3 (7.5)

The number of children (A) diagnosed with FHS and how many foods were involved in these reactions (B). The diagnosed FHS to each food could be either immunoglobulin E (IgE)-mediated based on a positive skin prick testing (SPT) (C), non-IgE-mediated based on a negative SPT (D) or nonallergic FHS which did not involve the immune system (E). In a number of cases, the children did not consent to SPT (F). Therefore, C + D + E + F = B.

\*Nonallergic FHS is defined as any adverse food-related problem that does not involve the immune system. This child presented with nonallergic FHS to salicylates found in berries.

OFCs, open food challenges; DBPCFC, double-blinded, placebo-controlled, food challenge.

Foods implicated in FHS

Milk and egg were the most common food hypersensitivities encountered in the first 3 years of life. We found that 80% and 50% of children outgrew their milk and egg hypersensitivity by 3 years respectively (Table 3).

## Discussion

Using OFC and a good clinical history as the endpoints, the cumulative incidence of FHS was 6.0%. Based on DBPCFC and a good clinical history, the cumulative incidence was 5.0%. The majority of the reactions produced at 1 year were nonimmunoglobulin E (IgE)-mediated (negative SPT). This changed to the majority of reactions being IgE-mediated (positive SPT) at 3 years of age. Over the 3 years, 33.7% of parents reported a food-related problem and of these, 16.1% were diagnosed with FHS by means of an OFC and history and 12.9% by means of a DBPCFC and history.

Table 3. Food hypersensitivity (FHS) to individual foods

	Number of children with FHS over 3 years (no of IgE-mediated cases)	FHS at 1 year (n)	FHS at 2 years (n)	FHS at 3 years (n)
Milk	26 (2)	22	10 (4 newly diagnosed)	4
Egg	18 (13)	16	11 (2 newly diagnosed)	9
Wheat	4 (0)	4	3	2
Gluten	1 (0)	0	1	1
Peanut	11 (11)	ND	ND	11
Sesame	5 (5)	ND	ND	5
Brazil nut	2 (2)	ND	ND	2
Corn	1 (1)	1	1	1
Fish	1 (1)	1	0	0
Tomato	1 (0)	1	0	0
Salicylate	1 (0)	1	1	1
Pineapple	1 (0)	0	0	1
Almond	2 (1)	0	0	2
Hazelnut	1 (1)	0	0	1
Cashew nut	1 (1)	0	0	1

ND, food challenges not done at 1 and 2 years.  
One additional child was diagnosed with coeliac disease at age two.

Prevalence of FHS at 2 years was 2.5% based on OFC and 2.1% based on DBPCFC. These figures were 3.0% and 2.9% at 3 years. Osterballe et al. (6) established that 2.3% of 3-year-old Danish children suffered from FHS, which is slightly lower than our figures. In our study, in children 3 years of age, the prevalence of FHS to egg, milk and peanut were 1.0%, 0.5% and 1.2%. Osterballe et al. (6) report these figures to be 1.6%, 0.6% and 0.2%, indicating slightly higher figures for egg and lower figures for peanut.

In our study, at the age of 1 year, 26.1% and 31.6% of reactions to foods (based on OFC and a history or DBPCFC and a history) were IgE-mediated as judged by SPT. In contrast, at 3 years, 67.5% and 69.3% of reactions to foods (based on OFC and a history or DBPCFC and a history) were IgE mediated. In the study by Bock (4), 28 children (age not specified) with FHS underwent SPT. Of these 25% (7/28) showed sensitization to the food, which indicates similar figures to our 1-year data, but lower figures than our 3-year data. Only one child (2%; 1/48) in our study was diagnosed with nonallergic FHS (i.e. intolerance to salicylates), in contrast with five children (16%; 5/31) in the study by Roehr et al. (5).

Adverse reactions to food were reported by 33.7% of the parents over the first 3 years of life. All children of parents who reported adverse reactions to food underwent SPT and food challenges if they consented. Those who did not react upon challenge subsequently introduced these foods safely at home. In those cases where the parents refused food challenges, and the SPT was

negative, children were followed-up until the parents reported to have introduced the food at home without any adverse reactions. Bock's study (4) reported this to be 28% by 3 years of age. Osterballe et al. (6) reported this to be 15.2% at 3 years. In our study, parental reported FHS at 3 years was much lower (8.3%).

It is well known that there is a discrepancy between reported and diagnosed FHS. In the present study, amongst those who reported a food-related problem, 16.1% were diagnosed with FHS by means of an OFC and history and 12.9% by means of a DBPCFC and history. In the study by Bock (4) 28% of those who reported a food-related problem were diagnosed by means of food challenges. These figures were 6.8% in the German study previously referred to (5) and 14.9% in the study by Osterballe et al. (6).

Foods implicated in Bock's study (4) were cows' milk, hens' eggs, soy, peanut, chocolate, corn, rice and wheat. In the study by Osterballe et al. (6), the foods most commonly implicated were hens' eggs, cows' milk and peanut. Roehr et al. (5) identified that the children mainly reacted to apple, kiwi, soy, hazelnut and wheat. The foods identified in our study were cows' milk, hens' eggs, wheat, peanut, sesame, brazil nut and fish. In addition, allergies to corn and tomato and nonallergic FHS to salicylates were identified.

In terms of the natural history of FHS, we have established that 80% of children outgrew their milk allergy by 3 years and 50% their egg allergy. Host (9) found the prognosis of cows' milk allergy is good with resolution rates of about 45–50% at 1 year, 60–75% at 2 years and 85–90% at 3 years. The remission rate in this study at the age of 3 years is slightly higher than our data.

Very importantly, in our study we were able to compare our FHS incidence rates with those of Bock (4). In this USA study conducted prior to 1987, of the 501 children enrolled into the study, 37 (7.4%) were diagnosed with FHS by means of either OFC or DBPCFC. In our study, of the 969 children enrolled into the study, 6.0% children were diagnosed with FHS based on OFC and history and 5.0% children based on DBPCFC and history. Using either the OFC or DBPCFC outcome, the difference in incidence was not statistically significant. Hence, it is concluded that the incidence of FHS has not increased over the last two decades.

Nevertheless, when considering individual foods such as peanuts, then differences in prevalence are seen in different countries (1–3). This could be due to a number of factors such as genetics, environment and eating habits.

One possible limitation of our study is that only 8.8% (83/942) of the children seen at either 1, 2 or 3 years were invited to undergo food challenges. Although a small proportion, it is similar to the proportion identified for food challenges in two previously conducted population studies (10, 11).

Another possible limitation of the study is the low levels of consent for food challenges. At 2 years, 42.5%

mothers declined an OFC and 55.6% declined the DBPCFC. At 3 years, these figures were 46.2% and 85.7%. The number of parents consenting to OFC compares well with Bock's study (4) where 44% (16/37) of the infants with positive food challenges underwent DBPCFC, but our consent rate to DBPCFC is much lower. Additionally, nine of the children not undergoing food challenges in our study were excluded because their SPT diameter was above the 95% positive predictive levels (8). A further limitation is the lack of challenges in the infants sensitized to peanut or sesame before 3 years. This could have marginally influenced the prevalence data at 1 and 2 years. It was decided that infants should not be exposed to these allergens before 3 years of age (12). Also, although rarely, negative SPTs may be observed in subjects with detectable serum-specific IgE, an issue which we have not addressed in this study.

To conclude, in this study we have found that between 5% and 6% of the children suffer from FHS. There was a large discrepancy between reported and diagnosed FHS.

The main foods implicated were cows' milk, hens' eggs and peanut. By 3 years of age, three quarters of children had outgrown their hypersensitivity to milk, and half their hypersensitivity to egg. Our data for cumulative incidence of FHS over the first 3 years of life are comparable with those of a study performed in the USA more than 20 years ago, with no significant differences.

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