

**T07023: Prevalence and incidence of food allergies and food intolerance– a prospective birth cohort study to establish the incidence and a concurrent cross-sectional study of whole population cohorts at 1,2,3,6,11 and 15**

## **Final Technical Report**

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**1. Title**

Project Code           **T07023**

Project Title           **Prevalence and incidence of food allergies and food intolerance – a prospective birth cohort study to establish the incidence and a concurrent cross-sectional study of whole population cohorts at 1,2,3,6,11 and 15**

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## **2. Executive Summary**

Food hypersensitivity (FHS) is believed to affect 1.5% of adults and 6–8% of children (1-4). Very few studies regarding population prevalence of FHS have been published, and not all of them used the gold standard method for diagnosis of food allergy: the Double Blind Placebo Controlled Food Challenge (DBPCFC), particularly for the diagnosis of non-IgE mediated allergy. Even fewer studies have addressed the prevalence of FHS in children. The most quoted study was performed in the USA more than 20 years ago and determined that 7.6% (cumulative incidence) of the children (0-3 years) were truly food allergic (1). In a recent German study (3), 4.2% of children (0 – 17 years) were found to suffer from FHS.

It was therefore the aim of this study to 1) investigate the prevalence and incidence of FHS in children, looking primarily at the cumulative incidence of FHS over the first three years of life and the prevalence of FHS in older children and teenagers (6, 11 and 15 years) and 2) establish temporal changes in sensitisation to foods and FHS over the last two decades.

To recruit the birth cohort, all pregnant women with an estimated delivery time 1 September 2001– 31 August 2002 were approached at antenatal clinics to participate in this study. For the school cohorts, the target population was approached via the schools after discussions with the Isle of Wight Education Authority and all head teachers for primary, middle and high schools. Children in the birth and school cohorts were approached for skin prick tests (SPT) to a standard battery of food allergens (milk, egg, wheat, peanut, sesame, and cod fish), aero-allergens (house dust mite *Dermatophagoides pteronyssinus*, cat and grass) and other allergens as identified by history. Children were identified for food challenges taking into account their reported history and SPT result. Challenge protocols were designed by the research dietitian based on procedure manuals, guidance papers, current research literature and consultation with experts in food allergy.

For the birth cohort, a total of 969 pregnant women were recruited for the study (91% of the target population). Over the course of the three years 942 (97.2%) children were seen at either one, two or three years, with 807 (83.3%) children seen at one, two and three years. At one, two and three years, the rate of sensitisation to any food allergen was 1.9%, 3.8% and 4.5%. Over the course of the three years 5.3% children had a positive SPT to any food in the predefined panel.

Adverse reactions to food were reported by 7.2 % parents at 12 months of age, 8.4% at two years and 8.3% at three years. Of the 807 children seen at one, two and three years, 272 (33.7%) reported a food related problem. Based on OFC and a good clinical history, the prevalence of FHS was 3.8% at one year, 2.5% at two years and 3.0% at three years. Based on DBPCFC and a good clinical history, the prevalence of FHS was 3.0% at one year, 2.1% at two years and 2.9% at three years. Cumulative, by 3 years of age, 6.0% of children were diagnosed with FHS based on OFC and history and 5.0% children based on DBPCFC and history. Overall the foods implicated in this study were milk, egg, peanut, corn, potato, tomato, salicylates and wheat.

Only 16.1% of children who were seen at one, two and three years and reported a food related problem were diagnosed with FHS by means of an OFC and history and 12.9% by means of a DBPCFC and history.

Comparing the information of the three year olds with children (aged four years) born 12 years earlier on the Isle of Wight, the results indicated that there was no increase in sensitisation to food allergens ( $p=0.3$ ) or in the prevalence of peanut allergy ( $p=0.1$ ) (based on OFC results from both studies). Very importantly, in our study we were able to compare our FHS incidence rates with that of Bock (2). In this USA study, 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% (58/969, CI: 4.6 – 7.7) children were diagnosed with FHS based on OFC and history and 5.0% (48/969, CI: 3.7 – 6.5) children based on DBPCFC and history. Using either the OFC or DBPCFC outcome, the difference in incidence was not statistically significant ( $p=0.30$  for OFC and  $p=0.06$  for DBPCFC).

For the school cohorts, 3.6% (6 year olds), 5.1% (11 year olds) and 4.9 % (15 year olds) had a positive SPT to any of the food allergens. A total of 94 (11.8%) six-year-olds reported a problem with a food or food ingredient, 11.6% eleven- and 12.4% fifteen-year-olds. Based on open food challenge and/or suggestive history and positive skin tests, the prevalence of food hypersensitivity was 2.6% in the six year old cohort. Based on double blind challenges, a clinical diagnosis or suggestive history and positive skin tests, the prevalence was 1.6%. The corresponding figures were 2.3% and 1.4% for the eleven year olds and 2.3% and 2.1% for the fifteen year olds. Amongst the school cohorts the foods most commonly implicated in FHS were milk and milk products, peanut, wheat, banana, sesame, tree nuts, egg, shellfish, gluten (coeliac disease), green beans, kiwi, tomato and additives. FHS was confirmed by OFC and a

good clinical history in only 21% (20/94) six year olds, 20% (18/90) eleven year olds and 18% (17/94) of the fifteen-year-olds who reported a food problem.

The key findings from this study therefore indicate that, reported adverse reactions to foods are common in all age groups, but rates of diagnosed FHS are low. Looking at the rates of FHS in each age group, the FHS rate ranged between 1.4% based on DBPCFC and a good clinical history at age 11 years and 3.0% based on DBPCFC and a good clinical history at one year. Additionally, considering the birth cohort, we have found that sensitisation to foods and diagnosed FHS have not increased over the last two decades. In the light of the discrepancy between reported and diagnosed FHS, the major implication of this study is the need for accurate diagnosis to prevent children being on unnecessary restricted diets. This may be associated with inadequate nutrition at this important period of growth and development. This has an important implication as there are a limited number of Allergy Specialists and Allergy Centres available in the UK. Community dietitians and GPs are often left with having to make a clinical diagnosis of FHS without the possibility of performing SPT or food challenges. They very often also do not know how to interpret specific IgE levels. This study therefore highlights the need for more allergy trained health professionals in order to rule out FHS in about 20% of the UK population who claims to suffer from FHS as well as managing FHS in about 1.5 – 3.8% of the UK population who are truly clinically allergic.

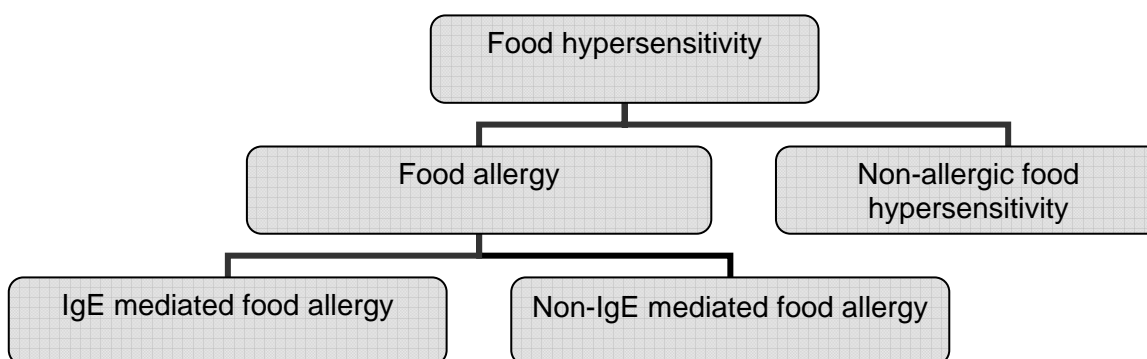
### **3. Glossary and Abbreviations**

IgE	Immunoglobulin E
FHS	Food hypersensitivity
OFC	Open food challenge
DBPCFC	Double blind placebo controlled food challenge
SPT	Skin prick test
CI	Confidence Interval
HDM	House Dust Mite

#### **4. Aims and Objectives of the investigation**

A European Academy of Allergy and Clinical Immunology task force (5) has recently suggested that any adverse reaction to food should be called food hypersensitivity (Fig. 1). When immunological mechanisms have been demonstrated, they suggest that the appropriate term is food allergy. Where the role of IgE is confirmed, it is suggested that it is known as IgE-mediated food allergy. They suggest that other reactions, previously sometimes referred to as 'food intolerance' should be referred to as non-allergic food hypersensitivity. Severe, generalised allergic reactions to food are classified as anaphylaxis (5).

**Figure 1: Proposed nomenclature for food hypersensitivity.**



The term food hypersensitivity (FHS) will be used throughout this report.

This research aimed to establish the incidence of FHS in a birth cohort at the age of one, two and three years. We also established the prevalence of FHS in six, eleven and fifteen year old children on the Isle of Wight. Additionally we will compare our findings with a previously established prevalence and incidence of FHS in children.

FHS is believed to affect 1.5% of adults and 6–8% of children (1-4) and is more common in atopic individuals (6). Cows' milk, eggs, peanut and tree nuts, soy and wheat are among the most common food allergens in infants and children (7-13). Peanut and tree nuts (14) as well as fish and shellfish (15) are reported to be the most common food allergens in teenagers and adults. Oral allergy syndrome is also frequently reported in this older group (16).



FHS is the most common cause of anaphylaxis in children in western countries, and more specifically the United Kingdom (17;18). Of these foods, peanut is reported as the most common food causing severe IgE mediated reactions in children and adolescents in the USA and Europe (19;20) and milk in the UK (21).

The few studies which have addressed the prevalence of FHS have mainly investigated adult populations (4;22) or have been hospital based studies where the population rate has been extrapolated from assessment of children referred to paediatric clinics for a general health check (1). Recently, one population based study has been published looking at the prevalence of food allergy in both adults and children (3).

The prevalence studies conducted in adults comprise information from Dutch, United Kingdom and German populations. Jansen and colleagues looked at the prevalence of food allergy/intolerance assessed by DBPCFC in a random sample ( $n = 1483$ ) of an adult Dutch population and estimated the true prevalence to be 2.4% (4). Of the 1483 adults who completed an initial questionnaire, only 37 eventually underwent food challenges. The research team aimed to replicate the history in terms of dose needed and challenge duration. However, the DBPCFCs were performed with freeze dried foods rather than actual ones. Some of the challenges were performed openly, but repeated in a double blind placebo controlled fashion if the challenge was positive. Interestingly, the foods or ingredients leading to adverse reactions in this study population included pork, white wine, menthol, kiwi, additives and glucose. They did not include any of the 12 major allergens as identified by the European Union (23). Another point to notice is the omission of a confidence interval for the estimated true prevalence, which raises the question of whether this may be very wide, indicating a wide range of values within which there is a 95% chance that the values are correct.

The main UK prevalence data quoted widely is that of the High Wycombe study conducted in the late 1980's. This study reported a population prevalence rate between 1.4–1.8%, looking at eight different food allergens including milk, egg, wheat, soya, citrus, fish/shellfish, nuts and chocolate (22). In this study, questionnaires were sent to 15,000 households (7,500 in the Wycombe Health Authority and 7,500 nationwide). More than half (52.7%) of the individuals from Wycombe and 41.6% of the nationwide sample responded. Following an algorithm, 93 study participants were identified for food challenges. Out of 93 people there were five children under the age of 10 and ten people between the ages of 10 and 30 that underwent food challenges. Although only

18 people had a positive food challenge, 71 people were considered food allergic, based on food challenge outcome or a positive skin test plus a reliable history. This study has three major limitations. Firstly only a few foods were investigated in the study. Secondly the foods used for the DBPCFC were tinned processed food specially prepared for the study not mimicking the real food exposure. Prolonged challenges (3-7 days) were used as indicated by the history. Thirdly, the challenge dose used in the study is not indicated. This is a problem as too small challenge doses may lead to false negative food challenges.

A recent cross-sectional survey (1999 – 2000) from Germany reported that 34.9% of people experienced an adverse reaction to food at some point in their life (3). The point prevalence of adverse reactions to food confirmed by DBPCFC in the Berlin population was calculated as 3.6% and in the adult population 3.7% (18-79 years). Two and a half percent of the reactions were IgE-mediated and 1.1% non-IgE-mediated. Females were more frequently affected (60.6%) than males. Based on a general health data for the adult German population, the estimated prevalence of FHS was calculated as 2.6%. The most common foods implicated were nuts, fruit, vegetables, ethanol, milk, flour and cocoa.

Prevalence studies in children are less readily available. In a USA study published in 1982, 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 years) out of the 28% who presented with possible symptoms of food allergy, were truly food allergic as assessed by food challenges (1). This study utilised open and/or DBPCFCs over a one-day period using a standard dose of dried, rather than fresh, food. This implies that delayed symptoms or symptoms triggered by larger dosages of food could be missed.

In the German study previously referred to (3), 4.2% of children (0 – 17 years) were found to suffer from FHS as assessed by DBPCFC. In this study questionnaires were sent to 2354 children and 739 responded. This was a very poor response rate (32%), which could have led to selection bias. A total of 78 oral food challenges were carried out. Half of the challenges ( $n=39$ ) were performed as DBPCFC and the rest as a single-blind or open food challenge depending on the patients compliance. Forty-eight food challenges were considered positive in 31 children. The foods most commonly implicated were apple, kiwi, soy, hazelnut, and wheat, although challenges were performed to a much wider range of foods. As the challenges were performed by

mixing a standard amount of food, or dried food, in a milk-based drink, one could argue that some of the challenges did not contain sufficient amounts of food to elicit a reaction. Challenges were however performed over 3-7 days depending on the history and the nature of the symptoms, which enabled the researchers to diagnose patients with delayed onset symptoms. In addition, Osterballe et al. diagnosed 2.3% of 3 year old children with FHS using OFCs (24).

Rance et al (25) conducted a questionnaire-based survey in Toulouse schools to determine the prevalence of food allergies among schoolchildren. 3500 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 main foods reported as causing adverse reactions were cows' milk, eggs, kiwis, peanuts, fish, tree nuts, and shrimp. One should however take into account that these figures are based on reported food hypersensitivity and not confirmed by food challenges.

The few studies looking at FHS to cows' milk as a single food show that about 2.5% of children suffer from cows' milk allergy (1;13;26-29), but not all these reported reactions were confirmed by means of food challenges. Milk hypersensitivity data range from 1.1% in Spain (26), 2.1% in Denmark (13), 2.2% in the USA, (1), 2.3% in the Netherlands (27), 2.5% in the UK (28) to 7.5% in Canada (29). This wide range in prevalence rates may be due to different populations studied and diagnostic techniques used, particularly the differences in food challenge procedures. The prognosis of cows' milk allergy is good with remission rates of about 45-50% at 1 year, 60-75% at 2 years and 85-90% at 3 years (30). It is most likely to persist in those with a strong family history of atopy, IgE mediated reactions and other food allergies (such as egg, soy, peanut or citrus fruits) (27;31;32).

Population prevalence for soya allergy has not been widely studied, but it is estimated to be 0.3-0.4% and is commonly outgrown (1). In a study by Bock et al only three out of 480 (0.6%) children who presented with suspected soya milk allergy were confirmed to be positive by food challenges (7).

About 0.2% (1) -1.1% (33) of children suffer from egg allergy and tolerance is usually achieved by five years. However, in about 20% of cases, it will persist into adulthood (34). Deaths related to egg allergy have been reported (35).

Peanut is reported as the most common food causing severe IgE mediated reactions in children and adolescents in the USA and Europe (19;20). It is estimated that 0.8% children in the USA (14) and 1.5% children in the UK (36) suffer from peanut allergy. In the UK, about six deaths, usually in young people, occur each year as a result of peanut anaphylaxis and many other near-fatal episodes occur (37;38). In a study performed by Lack and colleagues (39), 49 children out of 13,971 reported a history of adverse reactions upon ingestion of peanut and 29 of the 36 children who underwent DBPCFC had a positive challenge. Peanut allergy may resolve in 20% of cases, especially in those children developing peanut allergy at a young (< 2 years) age (40). It has been suggested that it may recur (41). Allergy to tree nuts affects about 0.5% of the USA population (14) and it is thought not to be outgrown.

Seafood allergy is potentially severe, but the prevalence of this group of food allergies is relatively unknown. A recent survey in the USA estimated the prevalence of seafood allergy as 2.3% for any seafood allergy, 2% for shellfish, 0.4% for fish, and 0.2% for fish/shellfish(15). Seafood allergy was more commonly reported in adults than in children. Individuals with a fish allergy, are often allergic to more than one type of fish or shellfish (42-44) and this allergy is not generally outgrown (45).

Adverse reactions to wheat are commonly encountered in both paediatric and adult allergy clinics, but epidemiological data is unavailable. Kiwi and sesame allergy have recently been reported to cause adverse food reactions in adults and children, also causing food induced anaphylaxis (11;16;46;47). In recent years reactions to mustard, celery and sulphite have been reported but population prevalence data is not available.

Allergic reactions to fruit and vegetables are commonly reported in adults (48) and children (1) and the symptoms experienced can range from mild oral symptoms to more severe systemic reactions, depending on the protein the individual reacts to.

To summarise, very few studies regarding population prevalence of FHS have been published. Although the data obtained is helpful in giving an indication on the number of people suffering from FHS, all these studies have their limitations regarding the method of diagnosis, in particular the food challenge procedures used.

It was therefore the aim of this study to investigate the prevalence and incidence of FHS in children under the following objectives:

### **Objectives to establish the incidence data**

Incidence quantifies the number of new cases of food allergy and food intolerance over a defined period of time. Incidence rates have an advantage over prevalence rates in being uninfluenced by duration of the disease.

- 01 Establish the cumulative incidence of sensitisation to foods (as defined by skin prick test data) by 3 years of age using the birth cohort (all children born on the Island between September 2001 and August 2002).
- 02 Establish the cumulative incidence of reported food allergy and food intolerance in the above cohort.
- 03 Establish the cumulative incidence of food allergies and food intolerance confirmed by open challenges followed by DBPCFCs if positive to open challenge.

### **Objective to establish the prevalence data**

The prevalence of food allergy and food intolerance is the proportion of the population who suffer from these conditions at a particular point in time. The prevalence is influenced by two variables: the duration of condition and the acquisition of new cases.

- 04 Establish the population prevalence of sensitisation to foods amongst the six whole population cohorts of children aged 1, 2, 3, 6, 11 and 15 years.
- 05 Establish the reported prevalence of food allergies and food intolerance amongst these six cohorts.
- 06 Establish the prevalence of food allergies and food intolerance in these six cohorts confirmed by open food challenges followed by DBPCFCs if positive to open challenge.

Objective to establish the temporal changes of both the incidence and prevalence data using the existing 1989 Island birth cohort as a comparator.

The study approach and the results for each objective are described below. However, in order to ensure the flow of the data, the results will be presented as:

- Prevalence and incidence of sensitisation, reported FHS and diagnosed FHS in the birth cohort at one, two and three years.
- Prevalence of sensitisation, reported FHS and diagnosed FHS in the six, eleven and fifteen year old cohorts.

## **5) THE BIRTH COHORT**

### 5.1 Study Approach

#### 5.1.1 Recruitment of the birth cohort

All pregnant mothers with an estimated delivery time 1 September 2001– 31 August 2002 were approached (Appendix 1) at antenatal clinics to participate in this study. Following consent (Appendix 2), information regarding family history of allergy (parental or sibling), parental smoking, social class and household pets was obtained by means of a standardised questionnaire (Appendix 3).

At three, six and nine months information regarding feeding practices, immunisation status and reported symptoms of atopy were obtained using a standardised questionnaire administered by telephone (Appendices 4-6). Most questions were based on the ISAAC questionnaires (49).

Two members of the research team screened this information and those parents who reported their child having an adverse reaction to a food were contacted. Children with an indicative history were invited to attend the Allergy Centre where a more detailed history was taken to ascertain which foods were implicated in producing the reported symptoms. Information regarding description of symptoms, time of onset and duration of reaction, quantity of food required to elicit symptoms and the number of times the reaction has occurred was obtained. In addition they were skin prick tested to the suspected foods at the time they presented.

At one, two and three years of age, all the children were reviewed at clinic for a medical examination guided by a detailed questionnaire (Appendices 7, 8 and 9). The questionnaire covered symptoms of atopy, feeding and weaning practices, immunisation history and environmental factors.

#### 5.1.2 Skin prick tests

Children in each of the birth and school cohorts were approached for skin prick tests (SPT) to a standard battery of food allergens (milk, egg, wheat, peanut, sesame, and cod fish), aero-allergens (house dust mite *Dermatophagoides pteronyssinus*, cat and grass) and other allergens as identified by history (Appendix 10). SPTs were conducted with commercial extracts of standard food and aeroallergens (Soluprick SQ allergens-ALK Allergologisk Laboratorium A/S, Horsholm, Denmark). In the case of

fruits and vegetables a prick-to-prick test was offered to the fresh product (all prick-to-prick testing was performed at the Allergy Centre). Histamine and physiological saline were used as positive and negative controls respectively. Two experienced allergy nurses performed all the SPTs. The wheal was measured after being transferred to paper from the skin with translucent tape. Measurement was undertaken in a standard fashion, measuring the largest wheal diameter and the diameter orthogonal to it. The mean wheal diameter was calculated. Results were expressed as positive if the mean diameter was 3 mm or more in the presence of a negative control and a positive histamine reaction after 12-15 minutes.

Children who were sensitised to various allergens were offered appropriate advice. The results were communicated to the parents who were given an opportunity to discuss concerns if they wished.

#### 5.1.3 Food challenges

Two members of the research team (the research dietitian and research fellow/research nurse) screened the questionnaire information for both the birth cohort and school children regarding reported current problems with food and 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.

Based on their given history and SPT results the following children were invited for food challenges.

- Those with a positive SPT that never knowingly had the food or large amounts of the food previously.
- Those who indicated a previous adverse reaction to foods (regardless of their SPT data) who improved on an exclusion diet.

Children were excluded from food challenges where there was a clear history of anaphylaxis to a specific food; when suffering from ongoing disease such as seasonal allergy during the season when they were affected; if they were taking medication that could influence the challenge result or patients who were considered unsuitable for the challenge on the day of the challenge e.g. infants with a temperature, flare-up of eczema etc. Food challenges were conducted with all foods except peanuts and sesame in the birth cohort as it was considered (following discussions with leading

international Allergists) that these young children should not be exposed to these foods in any form during infancy (50).

Prior to the food challenges, children and parents were advised by the research dietitian to avoid the offending food for at least four weeks prior to the challenge and in the case of food additives, two days prior to the challenge (51). Following consent (Appendix 11) a supervised open challenge was performed. When IgE mediated reactions were suspected either by SPT result or history, challenges were performed in a hospital setting.

Challenges were performed at home when the history clearly indicated delayed development of symptoms and the SPT was negative. Some of these home challenges started at hospital and were continued at home. Reactions during home challenges were recorded by parents on food and symptom diaries and verified by the research team.

Challenges were performed following an algorithm adhering to the history in terms of dose and timing. All foods for challenges were freshly prepared for each child, taking into consideration the range of food each child would prefer. Challenge protocols were developed based on current available literature. Since there are no agreed international protocols the draft protocols were circulated to experts in the UK, Europe and USA. [Dr Jonathan Hourihane (UK), Professor Stephan Strobel (UK), Professor Johannes Foster (Germany) Professor David Hill (Australia), and Professor Hugh Sampson (USA).] A consensus was reached and protocols established and used for the diagnosis of immediate (one-day challenge protocols) (51) (Appendices 12-14) and delayed (one-week challenge protocols) (52-55) (Appendices 15–16) symptoms. One-day challenge protocols were based on the consumption of a total of 8-10g of dried food (56), unless the history clearly indicated otherwise. We therefore calculated how much food we needed to give in order to provide 10g of a dried product e.g. 100 ml of semi-skimmed milk = 89.8 g of water thus contains 10.1g of a dried product (57).

At the end of a negative challenge the child was expected to consume a normal portion of the food. If the child refused the food at the time, the parents were asked to give a normal portion of the food to the child at home, on the same day (58). 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 (59;60).



One-week challenge procedures were based on normal daily consumption for the specific age group, unless the history indicated otherwise. Normal daily consumption was calculated by means of:

- National Diet and Nutritional Survey (59;60)
- Portion sizes indicated by the Clinical Paediatric and Dietetics (61)
- Portion sizes calculated from the Food Portion Size Handbook (62)
- In order to determine the amount of food that should be consumed when using baked or cooked food for the food challenge:
  - *Dietplan 5* recipe analysis was used to determine the amount of wheat, milk, egg etc. that should be taken in baked/cooked food or
  - Product information from manufacturers was used to calculate amount of wheat, milk, egg present in manufactured foods in order to set guidelines with adequate amounts of the challenge foods.

All 'eligible for challenge' children were invited for an OFC first and only those with a positive reaction were invited to participate in a DBPCFC. Some children were excluded from DBPCFC due to the severity of the reaction upon open challenge. We aimed to perform the DBPCFC within six weeks of the open challenge to exclude the possibility of children in the birth cohort outgrowing their FHS. Foods used for the DBPCFC were tested for blindness by the study team, parents and a different group of children. If immediate symptoms of food allergy were suspected, the same challenge dosages for the DBPCFC as for the open challenge was used, except if the patient reacted to the first dose used during the OFC. In this case, in some instances we started with half the dose to which the patient reacted (Appendices 17-18). The dose given for delayed symptoms was the same as that used during the 1- week OFC (Appendices 19–20).

Those with a negative response to the food challenges were recommended to eat the food normally. Those with a positive challenge were given dietary advice on continued avoidance of the food and followed up every 3-6 months. All information obtained during history taking and during the food challenges were recorded on the challenge forms and transferred by the dietitian on to food challenge outcome forms for data entry and analysis (Appendices 21–30). Parents were phoned one month after the challenge by the dietitian to enquire whether they had introduced the food into the child's diet in the case of a negative challenge.

Statistical analysis - All data obtained was double entered onto SPSS (v10.0; SPSS Inc, Chicago, USA) by two separate operators, compared and verified before analysis.

## 5.2 Results

### 5.2.1 Characteristics of participants

The target population consisted of 1063 pregnant women with delivery dates between 1<sup>st</sup> September 2001 and 31<sup>st</sup> August 2002. A total of 969 pregnant women were recruited for the study (91% of the target population). Reasons for non-consent/recruitment included lack of interest (56), moving from the Island (12), stillbirths (6), missed opportunities to recruit (11), language issues (4) and antenatal complications (5). Characteristics of the recruited infants are shown in Table 1.

**Table I: Characteristics of recruited infants (n=969)**

<b>Male gender</b>	500 (51.6%)
<b>First child</b>	401 (41.4%)
<b>Exposure to ETS in the first year of life</b>	421 (43.5%)
<b>Reported history of FHS*</b>	
- Family history of FHS	322 (33.2%)
- Maternal history of FHS	189 (19.5%)
- Sibling with FHS	122 (21.5%)
<b>Method of feeding at 3 months of life</b>	
Exclusively breast fed	198 (20.4%)
Breast and formula fed	128 (13.2%)
<b>Exposure to pets (cat/dog) during the first year of life</b>	534 (55.1%)
<b>medium/high socio-economic status (based on maternal level of education)</b>	589 (60.8%)

\* Defined as any reported symptoms to a food or ingredient (does not include dislike of foods)

At 3, 6, 9 and 12 months, 927 (95.6%), 912 (94.1%), 900 (92.9%) and 900 (92.9%) follow up questionnaires were completed respectively. At two years 858 (88.5%) questionnaires were completed and 891 (92%) at three years. Over the course of the 3 years 942 (97.2%) children were seen at either one, two or three years, with 807 (83.3%) children seen at one, two and three years.

### 5.2.1 Sensitisation to food and aero-allergens

#### 5.2.1.1 Prevalence of sensitisation at one year

A total of 763 infants were skin prick tested at one year of age. Lack of parental consent was the main reason that other infants were not tested. The rate of sensitisation to any of the predefined allergens tested was 2.6% (20/763, 95% confidence interval (CI): 1.6 to 4). The rate of sensitisation to the predefined aero-allergens (house dust mite, cat and grass) was 1.1% (8/763, CI: 0.45 to 2). Three infants to house dust mite, 4 to grass and 1 to cat. SPT to other aeroallergens were carried out in 4 infants based on indicated history (3 dog and 1 alternaria). One infant had a positive SPT to dog. The rate of sensitisation to any of the predefined food allergens (milk, egg, fish, peanut, sesame and wheat) was 1.9% (17/763, CI: 1.3 to 3.5). Fourteen infants were sensitised to egg, 3 to peanut, 2 to milk, 2 to fish and 2 to sesame. Three infants were sensitised to more than one food.

Where history indicated, the infants were skin prick tested to other foods. Sixteen infants were skin prick tested to other foods (corn, rice, potato, raspberry, maize, strawberry, plaice, tuna, tomato, orange, lemon, crab, cocoa, wheat gluten and chocolate). Only one had a positive skin prick test to corn, potato and rice in addition to egg.

We further investigated the predictors of sensitisation. Within this relatively small cohort, gender, position in sib-ship and family history of atopy were significantly associated with sensitisation to either food allergens or aeroallergens (Table 2).

**Table 2: Sensitisation to allergens in relation to gender, sib-ship position and family**

Predictor Factor	RR (95% C.I.)	P value
<b>Male Gender</b>		
Any allergen	1.48 (0.62 – 3.54)	0.38
Any food allergen	1.67 (0.63 – 4.48)	0.36
Any aeroallergen	1.14 (0.31 - 4.21)	0.84
<b>First born</b>		
Any allergen	1.72 (0.73 to 4.04)	0.26
Any food allergen	2.37 (0.89 – 6.34)	0.77
Any aeroallergen	1.61 (0.44 – 5.96)	0.47
<b>Family history</b>		
Any allergen	3.96 (0.54 – 29.21)	0.14
Any food allergen	3.17 (0.42 – 23.65)	0.23
Any aeroallergen	(infinite)	0.18
<b>Maternal history</b>		
Any allergen	2.94 (0.99 – 8.66)	0.39
Any food allergen	2.25 (0.74 – 6.83)	0.14
Any aeroallergen	5.53 (0.7 – 44.0)	0.68

5.2.1.2 Sensitisation in the two year old cohort

A total of 658 children were skin prick tested at two years of age. The rate of sensitisation to any of the predefined allergens tested was 8.2% (54/658, CI: 6.2 – 10.6). The rate of sensitisation to the predefined aero-allergens was 42/658 (6.4%, CI:

4.6 – 8.5; 24 children were sensitised to HDM, 6 to grass and 22 to cat). 11 SPT to other aeroallergens were carried out in 4 children based on indicated history (tree mix [1], dog [3], rabbit [1], alternaria [2], weeds [1], rapeseed [1], cladosporium [1], nettle [1], mould [1]). Three children who were already sensitised to some of the predefined allergens were also sensitised to dog (2) and another child to rabbit and Cladosporium.

The rate of sensitisation to any of the predefined food allergens (milk, egg, fish, peanut, sesame and wheat) was 25/685 (3.8%, CI: 2.5 – 5.6). Fourteen children were sensitised to egg, 13 to peanut, 5 to milk, 3 to fish, 1 to wheat, and 5 to sesame. Eight children were sensitised to more than one food.

Where history indicated, the children were skin prick tested to other foods. Overall 10 children were skin prick tested to other foods (barley, cocoa, kiwi (2), prawn (2), soya, strawberry (2), tomato, walnut, almond, brazil nut, grape, lobster, onion, orange, crab, mussel, tuna and salmon). None of the children were sensitised to these foods.

#### 5.2.1.3 Sensitisation in the 3 year cohort

A total of 642 children were skin prick tested at three years of age. The rate of sensitisation to any of the predefined allergens tested was 11.8% (76/642, CI: 9.4 – 14.6). The rate of sensitisation to the predefined aero-allergens (HDM, Cat and Grass) was 70/642 (10.9%, CI: 8.6 – 13.6; 43 children were sensitised to HDM, 26 to grass and 21 to cat). 10 SPT to other aeroallergens were carried out in 7 children based on indicated history (tree mix [3], dog [4], rat [1], alternaria [1], cladosporium [1]). Two children who were already sensitised to some of the predefined allergens were also sensitised to dog (2), alternaria (1) and tree pollen (1). Two children not sensitised to any aero-allergen in the predefined panel were sensitised to dog (1) and rat (1).

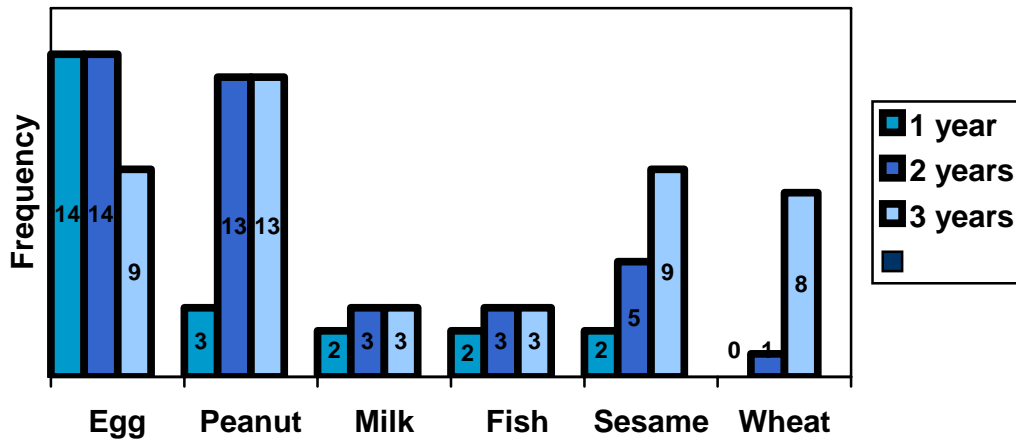
The rate of sensitisation to any of the predefined food allergens (milk, egg, fish, peanut, sesame and wheat) was 29/642 (4.5%, CI: 3.1 – 6.4). Nine children were sensitised to egg, 13 to peanut, 3 to milk, 3 to fish, 8 to wheat, and 9 to sesame. Of the 8 children sensitised to wheat, all 8 children had a positive SPT to grass. When the wheat/grass cross-reactors are removed, sensitisation rates to the predefined food allergens are 3.6% (23/642). Nine children were sensitised to more than one food.

Where history indicated, the children were skin prick tested to other foods. Overall 7 children were skin prick tested to other foods (cashew nut (5), coconut (2), strawberry (2), walnut (4), hazelnut (4), brazil nut (4), pecan nut (4), and almond (4). Two children

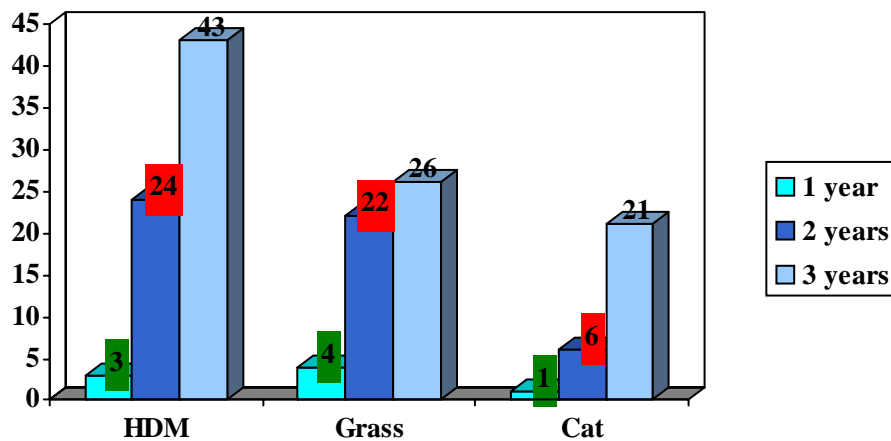
who were not sensitised to any of the predefined food allergens were sensitised to hazel nut (1), brazil (2), cashew nut (1) and almond (2).

Figures 2 and 3 summarise the sensitisation data over all three years.

**Figure 2: Sensitisation to food allergens over all three years**



**Figure 3: Sensitisation to aeroallergens over all three years**



**5.2.1.4 Cumulative incidence of sensitisation over all three years**

Over the course of the three years 814 children underwent SPT. 5.3% (43/814, CI: 3.9 – 7.1) children had a positive SPT to any food in the predefined panel, 10.6% (86/814, CI: 8.5 – 12.9) children were sensitised to any of the predefined aeroallergens and 12.0% (98/814, CI: 9.9 – 14.5) children were sensitised to any allergen. Table 3 summarises the sensitisation to individual food allergens over all 3 years.

**Table 3: Sensitisation to individual foods over all three years**

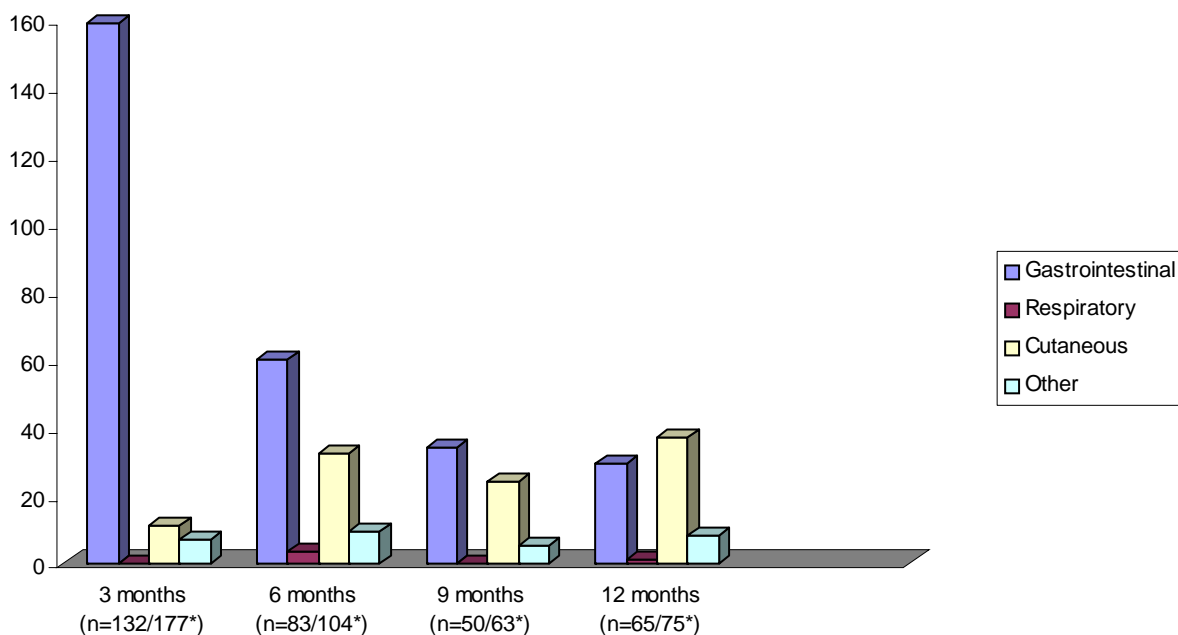
Allergen	Number sensitised over all three years (%)
HDM	28 (3.4)
Grass	25 (3.1)
Cat	36 (4.4)
Milk	7 (0.9)
Wheat	9 (1.1)
Egg	22 (2.7)
Fish	6 (0.7)
Peanut	20 (2.5)
Sesame	12 (1.5)

### 5.2.2 Parental reported food hypersensitivity

#### 5.2.2.1 Parental reported FHS during the first year of life

At 3, 6, 9 and 12 months, 927 (95.6%), 912 (94.1%), 900 (92.9%) and 900 (92.9%) follow up questionnaires were completed respectively. Symptoms of FHS were reported by 132 (14.2 %) parents at 3 months, 83 (9.1%) at 6 months, 49 (5.5%) at 9 months and 65 (7.2%) at 12 months of age. Figure 4 demonstrates the frequency of different symptoms reported in the infant's first year of life. Many parents reported more than one symptom. The foods most commonly implicated in these reported symptoms were cows' milk formulas at 3 months, cows' milk formulas, non-citrus fruits, baby rice and oats at 6 months, cows' milk or cows' milk formulas, egg and tomato at 9 months and cows' milk or cows' milk formulas, egg, tomato and fish at 12 months.

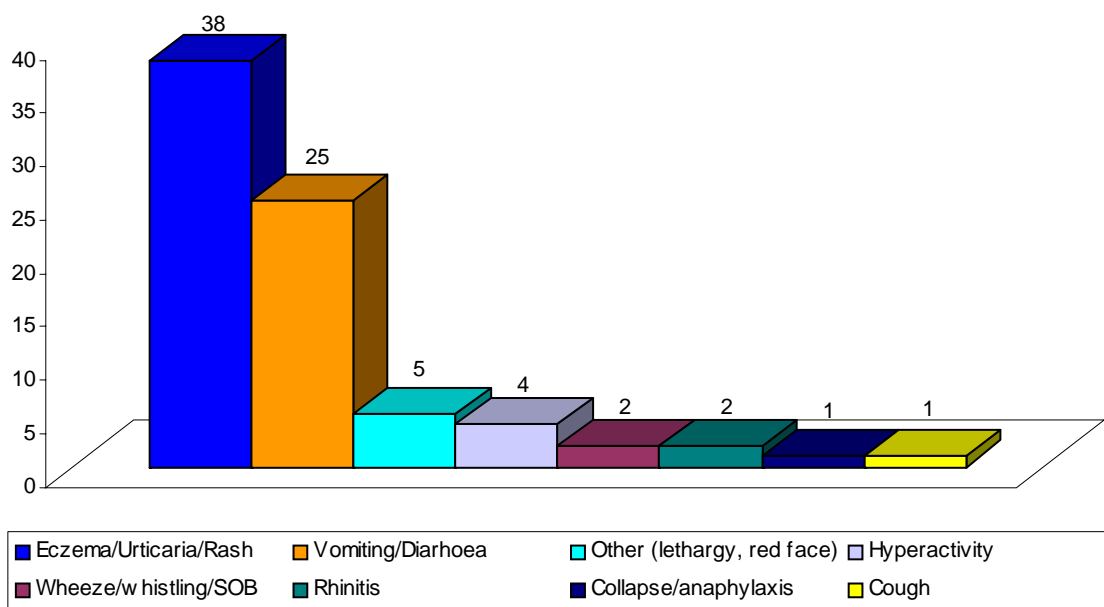
Figure 4: Reported symptoms to food at 3, 6, 9 and 12 months



5.2.2.2. Parental reported FHS at two years

Seventy two (8.4%) children reported a food related problem at two years. The symptoms most commonly reported at age two were cutaneous and gastro-intestinal (Figure 5) and the main foods attributed were milk and dairy, egg, nuts, fruit and tomato or tomato sauce.

Figure 5: Reported food related problems at two years

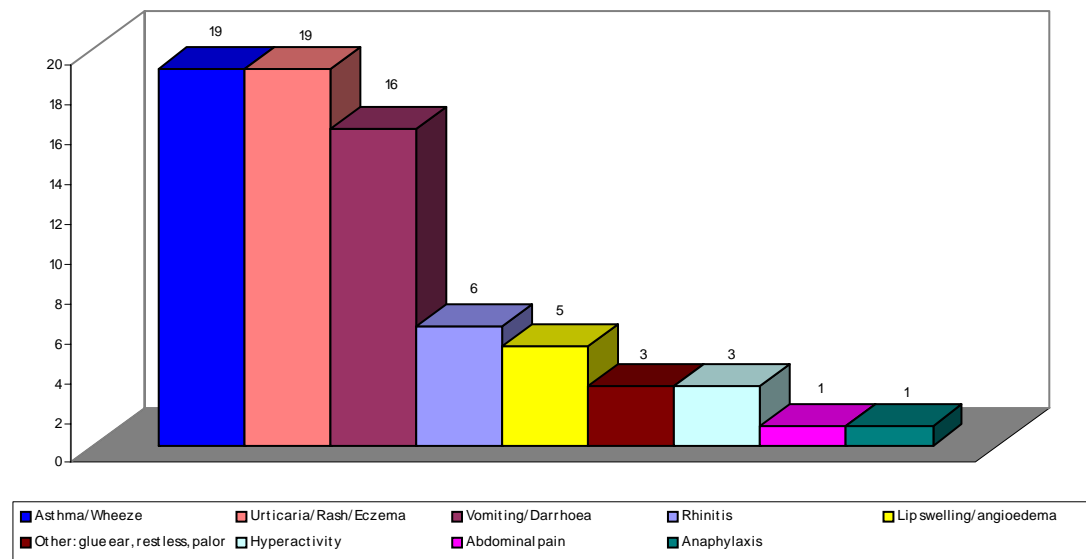




### 5.2.2.3 Parental reported FHS at three years

Seventy four (8.3%) children reported a food related problem at three. At age 3, the symptoms reported were mostly respiratory and cutaneous symptoms (Figure 6) and the foods attributed were milk and dairy, additives, fruits, egg, tomato or tomato juice and nuts.

Figure 6: Reported food related symptoms at three years



### 5.2.2.4 Cumulative incidence of reported FHS over the three years

Over the course of the 3 years 942 (97.2%) children were seen at either one, two or three years, with 807 (83.3%) children seen at one, two and three years. Of the 942, 315 (33.4%) children reported a food related problem and of the 807 children, 272 (33.7%) reported a food related problem.

### 5.2.3 Objectively diagnosed FHS

#### 5.2.3.1 Objectively diagnosed FHS at one year

##### Prevalence of food hypersensitivity assessed by food challenges between 6-9 months of age

Parents who reported adverse reactions to food at three and six months follow-up were contacted by the research dietitian and invited for a medical examination and food challenges. A total of 202 mothers reported a problem with food at either 3 or 6 months, with 13 reporting a problem at both 3 and 6 months. A total of 175 infants were

excluded from undergoing challenges as they had subsequently tolerated a food or were eating other foods from the same food group. Twenty seven infants were invited for open food challenges. Two mothers declined the food challenges due to lack of interest (n=1) and social issues (n=1). The first infant had a positive SPT to milk at 6 months and the infant's eczema improved with milk avoidance. The other infant had a negative SPT to milk but their eczema improved on milk avoidance. This infant subsequently became sensitised to milk, egg and peanut.

In total, 25 infants underwent a total of 30 open food challenges to milk, egg, wheat and citrus fruit, between the ages of six and nine months. Twelve infants had a positive OFC (11 milk and 1 wheat). These 12 infants were invited to undergo DBPCFC and challenges were performed in 9 infants. One mother declined as she did not want her infant to undergo another challenge (6mm SPT to egg). One infant only reacted on skin contact with milk (confirmed in OFC) and consumed milk without any reaction. The other infant had multiple food allergies and other allergic symptoms and their consultant allergist requested no further interventions (SPT: potato = 7 mm; egg = 8 mm; fish = 4 mm; peanut = 3 mm). Hence a total of 9 infants underwent DBPCFC and 4 were positive to milk.

The incidence of FHS at 9 months is 1.2% (12/969, CI: 0.6 to 2.2) based on OFC and 0.4% (4/969, CI: 0.1 to 1.1) based on DBPCFC. If infants with a clear history (n=2) who declined challenges are included with those who were positive on OFC, then the incidence of FHS is 1.5% (14/969, CI: 0.79 to 2.4). If infants with a positive open food challenge who declined further challenges (n=3) and infants with clear history who declined all challenges (n=2) are included with those who were positive on DBPCFC, then the incidence of FHS will be 0.9% (9/969, CI: 0.4 to 1.8).

#### Prevalence of food hypersensitivity assessed by food challenges between 9-12 months of age

Between 9 and 12 months a similar approach for food challenges was followed. In addition to obtaining information on reported adverse reactions to food at 12 months, SPT was performed on all the infants. Ninety seven mothers reported a problem to foods at either 9 or 12 months with 17 mothers reporting problems at both times. Fifty six infants were excluded from challenges for similar reasons outlined above. A total of 41 infants were invited for an OFC. An additional 8 infants, identified by means of a positive SPT without prior consumption of the food, were also invited for food challenges. Four mothers declined. One infant had a negative SPT to egg but their

eczema improved on egg avoidance. Another developed a rash with egg but was SPT negative. Two infants had positive SPT (4mm) but no history of exposure to egg.

Forty five infants underwent a total of 58 food challenges to a variety of foods (milk, egg, wheat, citrus, strawberry, tomato, fish, corn, salicylates and soya). Twenty five of these infants had 31 positive OFC to milk (n=12), egg (13), wheat (3), tomato (1), corn (1), salicylates (1) with six infants having a positive challenge to more than one food. Between them these 25 infants underwent 17 one-day open food challenges and 12 one-week open food challenges with some having both one-day and one-week challenges. These 25 infants were invited to undergo DBPCFC and challenges were performed in 15 infants. The reasons for not performing DBPCFC were: moved to the mainland (SPT egg = 5 mm); lack of interest (milk SPT = 1mm; egg SPT = 3mm); parents only agreed to a repeat OFC (one infant with two positive milk OFC and another with two positive wheat OFC; two other infants had a second OFC that was negative to either milk or tomato); medical reasons (two infants with severe reactions and one infant with celiac disease); lack of time (egg SPT negative). Of these 15 infants, 12 infants had a positive DBPCFC. Six infants had a positive milk DBPCFC (1 one-day and 5 one-week), 8 infants had a positive egg challenge (all one day) and 1 infant had a positive one-week wheat challenge. Three infants had positive DBPCFC to milk and egg.

By the age of 12 months, the incidence of FHS is 2.6% (25/969, 1.7 to 3.8 CI 95%) based on OFC and 1.2% (12/969, 0.6 to 2.2 CI 95%) based on DBPCFC. If infants with a clear history who did not undergo challenges (n=3) are included with those with a positive OFC, then the incidence of FHS will be 2.9% (28/969, 1.9 to 4.2 CI 95%). If infants with a positive open food challenge who declined further challenges (n=9) and infants with clear history who did not take part in the challenges (n=3) are included with those with a positive DBPCFC, then the incidence of FHS will be 2.5% (24/969, 1.6 to 3.7 CI 95%).

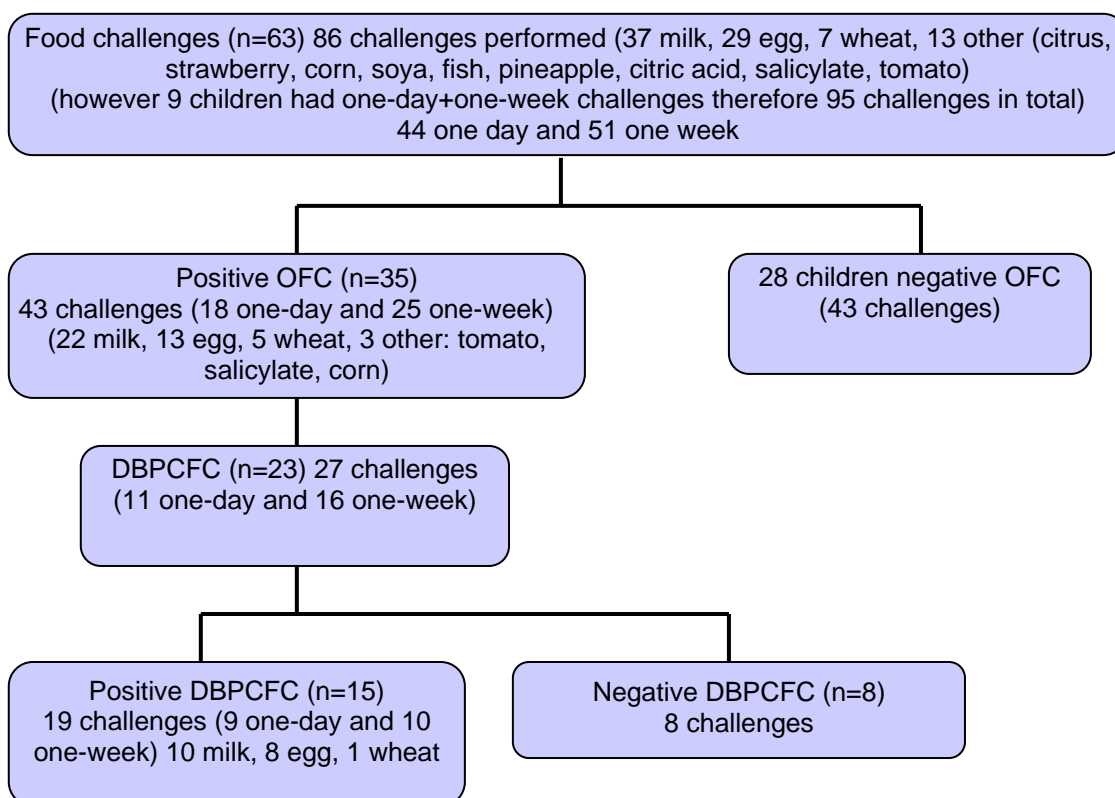
#### Cumulative incidence of FHS at one year of age

FHS was confirmed in 3.6% (35/969, 2.5 to 5 CI 95%) infants using OFC and 1.5% (15/969, 0.87 to 2.5 CI 95%) using DBPCFC during the first year of life (Figure 7). If infants with a clear history who did not undergo challenges (n=4) are included then the cumulative incidence of FHS will be 4 % (39/969, 2.9 to 5.5 CI 95%). The prevalence was lower as two infants had outgrown their FHS on repeat challenge 3.8% (37/969 CI: 2.7 – 5.2). If infants with a positive open food challenge who declined further

challenges (n=12) and infants with clear history who did not take part in the challenges (n=4) are included with those with a positive DBPCFC (n=15), then the cumulative incidence of FHS will be 3.2% (31/969, CI: 2.2 – 4.5), but the prevalence at 1 year of age will be 3.0% (29/969, CI: 2.0 – 4.3) as two infants outgrew their FHS.

Figure 7 summarises the food challenges in the one year old cohort

**Figure 7: Summary of food challenges in the one year old cohort**



The cumulative incidence of reported parental perceived food hypersensitivity was 25.8% (250/969, 23 to 29 CI 95%) by 12 months of age. Of these only 13.2% (33/250) and 8.4% (21/250) were diagnosed with FHS by means of OFC and history and DBPCFC and history respectively.

#### 5.2.3.2 Objectively diagnosed FHS at two years

Seventy two children reported a food related problem and 25 children were identified for food challenges. Another 15 children were identified from either a positive SPT without ever knowingly eating the food (2), had a previous positive food challenge (12), or phoned shortly after the 2 year questionnaire was completed to report a problem with a food (1). Of these 40 children only 23 underwent food challenges (2 of these children underwent DBPCFC only). Seventeen children/parents declined food challenges for the following reasons: Six children previously had positive challenges (at one year), but managed to successfully introduce the food at home. Nine children previously had positive challenges (at age one followed by development of symptoms on accidental exposure +/- an increase in SPT or a positive SPT to the food). These foods included milk (4), egg (6), wheat (1), salicylates (1), as more than one food was

involved in 3 children. One child had a negative SPT to milk but symptoms of severe eczema improved on food avoidance. One child had a positive SPT to egg (4.75mm), with a previous reaction on ingestion, but refused any food challenges.

Therefore, in total, 23 children underwent 26 food challenges, but only 21 children underwent a total of 24 open food challenges (12 one-day and 12 one-week) to milk, egg, wheat and citrus fruit as 2 children underwent only DBPCFC. Nine children had 10 positive OFC (milk [5], egg [4], and wheat [1]). Of these 4 were one-day challenges (egg) and 6 one-week challenges (milk 5 and wheat 1).

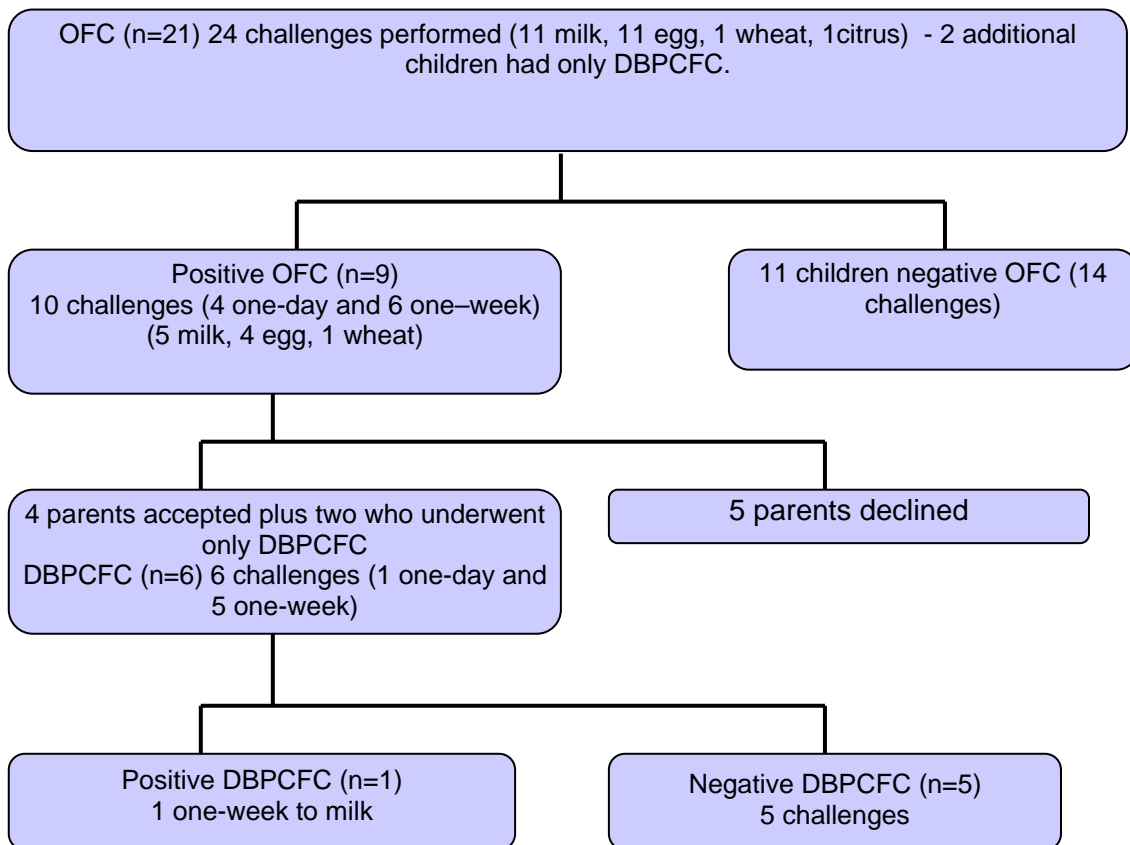
These 9 children were invited to undergo DBPCFC plus 2 children that previously had positive food challenges and who did not want to go through the process of OFC followed by DBPCFC; they just wanted the DBPCFC. Five children/parents declined DBPCFC for the following reasons: two children previously had positive OFC to egg and the parents regarded that as sufficient evidence. One child did not undergo a DBPCFC due to 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 challenge). One mother declined the DBPCFC due to the severity of the eczema upon OFC to milk. This child is also sensitised to egg and her eczema improved on exclusion of egg, but the mother also declined an egg challenge.

This led to 6 (6 challenges) children undergoing DBPCFC (1 one-day to egg and 5 one-week to milk) of which only 1 one-week challenge to milk was positive.

Only one child had a one-day DBPCFC and this was negative.

Figure 8 summarises the food challenges in the two year cohort.

**Figure 8: Summary of food challenges in the 2-year old cohort**



The prevalence of FHS at 2 years is 1.1% (9/858, CI: 0.5 – 2.0) based on OFC and 0.1% (1/858, CI: 0.0 – 0.7) based on DBPCFC. If the following children are included: nine children with previously positive challenges (at age one followed by development of symptoms on accidental exposure +/- an increase in SPT or a positive SPT to the food); one child with a negative SPT to milk whose symptoms of severe eczema improved on food avoidance; one child with a positive SPT to egg (4.75mm), and a previous reaction on ingestion; and one child diagnosed with celiac disease, then the prevalence of FHS is 2.5% (21/858, CI: 1.5 – 3.7) based on OFC and a good clinical history.

If infants with a positive open food challenge who declined further challenges (n=5), nine children with previously positive challenges (at age one followed by development of symptoms on accidental exposure +/- an increase in SPT or a positive SPT to the food); one child with a negative SPT to milk whose symptoms of severe eczema improved on food avoidance; one child with a positive SPT to egg (4.75mm), and a previous reaction on ingestion; and one child diagnosed with celiac disease are

included with those who were positive on DBPCFC (n=1), then the prevalence of FHS will be 2.1% (18/858, CI: 1.3 – 3.3).

Of the 72 children who reported adverse reactions to foods, only 14 (19.4%) could be verified by means of OFC and 12 (16.7%) by DBPCFC.

#### 5.2.3.3 Objectively diagnosed FHS at three years

Seventy four children reported a food related problem and 18 children were invited for food challenges. Another 8 children were identified as they were considered to suffer from FHS at age two and 13 children were identified from either a positive SPT to a food which they had never knowingly eaten, had a positive SPT to peanut at either one, two or three years or had a very good clinical history of suspected FHS. In total therefore 39 children were invited for food challenges. Eighteen children/parents declined food challenges for the following reasons:

Two children previously had positive challenges (at one or two years) but managed to successfully introduce the food at home. Eight children previously had positive challenges (at age one followed by development of symptoms on accidental exposure +/- an increase in SPT or a positive SPT to the food). These foods included milk (4), egg (4), wheat (1) and salicylates (1), as more than one food was involved in 2 children. One child had a positive SPT to egg (4.75mm), with a previous reaction on ingestion, but refused any food challenges. In addition, seven children were symptomatic to a food or foods on exposure and had a positive SPT. These children were symptomatic to peanut (4 [SPT: 8 mm, 6 mm, 12 mm, 4 mm]), sesame (3 [SPT 5 mm, 7 mm, 4 mm]) and brazil nut (2 [15 mm, 10 mm]) as more than one food was involved in 2 children.

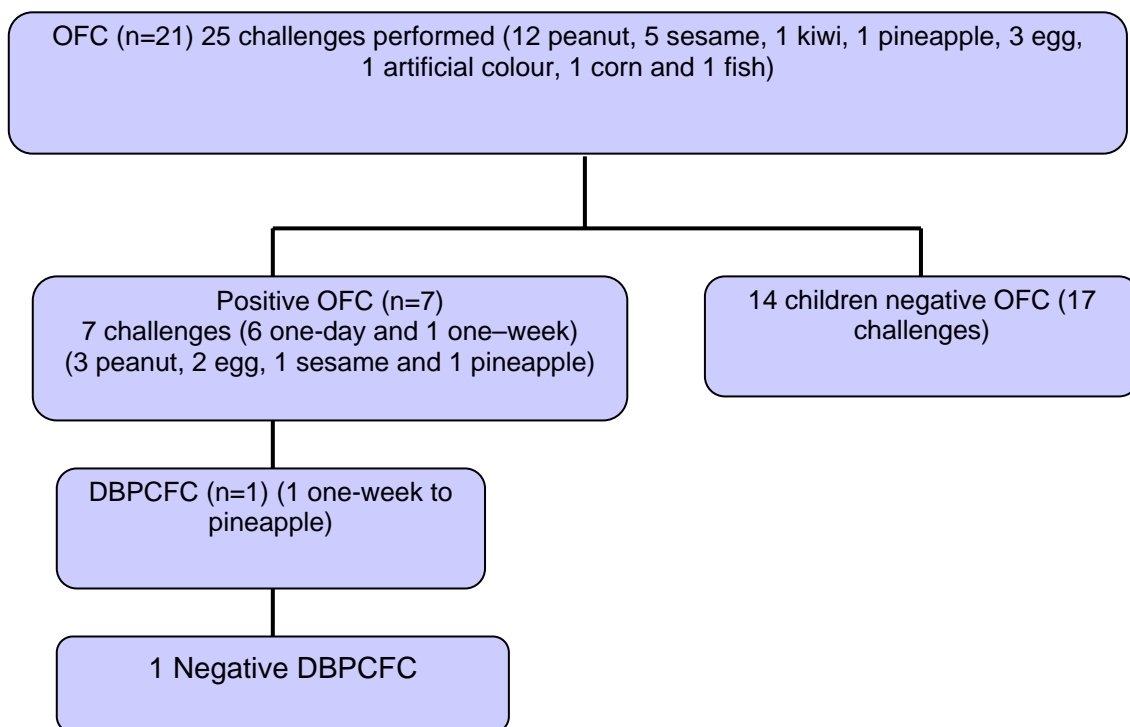
Therefore, in total, 21 children underwent 25 open food challenges (24 one-day and 1 one-week) to peanut, sesame, kiwi, pineapple, egg, colourings, corn and fish. Seven children had 7 positive OFC (peanut [2], sesame [1], egg [3], and pineapple [1]). Of these, 6 were one-day challenges (peanut and egg) and 1 one-week challenge (pineapple).

These 7 children were invited to undergo DBPCFC. Only 1 child consented; the parent's 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 due to severity of reaction on OFC (1 sesame, 1 egg and 2 peanut). Therefore, only one child had a one-day DBPCFC, to pineapple and this was negative.



Figure 9 summarises the food challenges in the three year cohort.

**Figure 9: Summary of food challenges in the three year cohort**



The prevalence of FHS at 3 years is 0.8% (7/891, CI: 0.3 – 1.6) based on OFC and none based on DBPCFC. If the following children are included:

Eight children with previously positive challenges (at age one followed by development of symptoms on accidental exposure +/- an increase in SPT or a positive SPT to the food); one child with a positive SPT to egg (4.75mm), and a previous reaction on ingestion; seven children with a positive SPT to a food and symptomatic on exposure, seven children with positive OFC; three children with negative OFC, who are allergic to other foods and one child diagnosed with celiac disease then the prevalence of FHS is 3.0% (27/891, CI: 2.0 – 4.4) based on OFC.

These 27 children were diagnosed with FHS to 40 foods, these include: milk (4), egg (9), wheat (2), salicylates (1), celiac disease (1), pineapple (1), peanut (11), Brazil nut (2), Hazel nut (1), Almond (2), Cashew nut (1), sesame (5).

If children with a previously positive challenge (at age one followed by development of symptoms on accidental exposure +/- an increase in SPT or a positive SPT to the food) (n=8); one child with a positive SPT to egg (4.75mm), and a previous reaction on ingestion; seven children with a positive SPT to a food and symptomatic on exposure,

six children with positive OFC who declined DBPCFC; three children with negative OFC, who are allergic to other foods and one child diagnosed with celiac disease then the prevalence of FHS is 2.9% (26/891, CI: 1.9 – 4.3) based on DBPCFC.

Of the 74 children who reported adverse reactions to foods, only 15 (20.2 %) could be verified by means of OFC or 14 (18.9%) by a DBPCFC.

#### 5.2.3.4 The cumulative incidence of FHS by three years of age

Using OFC and a good clinical history as the endpoint, the cumulative incidence of FHS was 6.0% (58/969, CI: 4.6 – 7.7) children. Based on DBPCFC and a good clinical history, it was 5.0% (48/969, CI: 3.7 – 6.5). Of the 807 children seen at one, two and three years, 272 (33.7%) reported a food related problem at either one, two or three years. Amongst those who reported a food related problem, 16.1% (44/272, CI: 12.1 – 21.1) were diagnosed with FHS by means of an OFC and history and 12.9% (35/272, CI: 9.1 – 17.4) by means of a DBPCFC and history.

Milk and egg were the most common food allergies encountered in the first three years of life. We found that 76% of children outgrew their milk allergy by three years and 50% their egg allergy. FHS to single foods are summarised in table 4.

**Table 4: FHS to single foods**

<b>FHS based on DBPCFC and history</b>	<b>Total over 3 years (n) (<i>IgE mediated</i>)</b>	<b>FHS at one year (n)</b>	<b>FHS at two years (n)</b>	<b>FHS at three years (n)</b>
Milk	17 (2)	16	8	4
Egg	18 (13)	15	13	9
Wheat	3 (0)	3	3	2
Peanut	11 (11)	NA	NA	11
Sesame	5 (5)	NA	NA	5
Brazil nut	2 (2)	NA	NA	2
Corn	1 (1)	1	1	0
Fish	1 (1)	1	1	0
Tomato	1 (0)	1	0	0
Salicylate	1 (0)	1	1	1

#### 5.2.3.5 Clinical Characteristics of those diagnosed with FHS based on OFC

Looking at the factors such as one or more family member with a reported history of allergic disease ( $p = 0.53$ ), maternal reported history of allergic disease ( $p=0.95$ ), one or more family member with a reported history of FHS ( $p=0.28$ ), maternal history of FHS ( $p=0.217$ ), one or more sibling with FHS ( $0.107$ ), first born ( $p=0.272$ ) and breast fed at 3 months ( $p=0.221$ ), we did not find any of these factors a significant predictor for development of FHS.

5.3 Objective to establish the temporal changes of both the incidence and prevalence data using the existing 1989 Island birth cohort as a comparator

The information on the two cohorts of children is summarised in table 5.

**Table 5: Sensitisation to food and aero-allergens in the 1989 and FAIR cohorts**

<u>Allergen</u>	<u>Group A</u> <u>1989 cohort</u> <u>(n=977)</u>	<u>Group B</u> <u>FAIR cohort (born</u> <u>2001)</u> <u>(n=642)</u>	<u>Changes in</u> <u>sensitisation</u>
	N (%)	N (%)	
Any food allergen (sesame not included)	18 (1.8)	27 (4.2)	P=0.0079
Wheat-grass cross-reactors removed (sesame not included)	18 (1.8)	20 (3.1)	P=0.1301
Milk	11 (1.1)	3 (0.5)	P = 0.1831
Egg	7 (0.7)	9 (1.4)	P = 0.2024
Wheat	1** (0.1)	8* (1.2)	P = 0.0035
Peanut	10 (1.0)	13 (2.0)	P = 0.1312
Cod	5 (0.5)	3 (0.5)	P = 1.000
Sesame	Not done	9 (1.0)	-
Any aero-allergen	145 (14.8)	70 (10.9)	P = 0.0246
HDM	105 (10.7)	43 (6.7)	P = 0.0061
Cat	51 (5.2)	21 (3.3)	P = 0.0653
Grass	69 (7.1)	26 (4.0)	P = 0.0126

\* 8 sensitised to wheat, but all cross-reacting with grass

\*\* 1 sensitised to wheat, but cross-reacting with grass

Of the 1536 children enrolled in an earlier cohort study on the Isle of Wight (children born in 1989), 1281 were seen and 977 (63.6%) were SPTed at the age of four years (1993). Comparing the 1993 data with the FAIR birth cohort at three years (2004) we found the following: Sensitisation to predefined food allergens increased significantly from 1.8% in 1993 (Group A) to 4.2% in 2004 (Group B) ( $p = 0.008$ ). When wheat-grass cross-reactors were excluded, this increase was no longer significant ( $p = 0.31$ ).

In contrast, sensitisation to aeroallergens showed a significant decrease from 14.8% to 10.9% ( $p = 0.006$ ). Notable decreases were seen in HDM ( $p = 0.006$ ), and grass ( $p = 0.013$ ). Amongst these children we therefore found a significant reduction in prevalence of sensitisation to aeroallergens.

In terms of clinical allergy, we could only compare the rates of peanut allergy between the two cohorts as we did not have any clinical data about other food allergies in the 1989 cohort: 0.5% (6/1281) of children were diagnosed with peanut allergy in 1993 and 1.1% (10/891) in 2004. The differences were non-significant ( $p=0.1$ ) It is however, important to note that peanut allergy in the children born in 1989 at the age of four years was defined as a positive SPT plus a clear history as no food challenges were performed in this cohort.

Additionally we were able to compare our data with that from a study performed in the USA more than 20 years ago. Of the 501 children enrolled into that study, 37 (7.4%) were diagnosed with FHS by means of OFC or DBPCFC. In the FAIR study, of the 969 children enrolled into the study, 6.0% (58/969, CI: 4.6 – 71.7) children were diagnosed with FHS based on OFC and history and 5.0% (48/969, CI: 3.7 – 6.5) children (62 foods) based on DBPCFC and history. The difference in prevalence was non-significant ( $p=0.30$ ).

## **6) THE SCHOOL COHORTS**

### **6.1 Study approach**

#### **6.1.1 Recruitment of the school cohorts**

The target populations included all 6 (date of birth 1 September 1997 – 31 August 1998), 11 (date of birth 1 September 1991 – 31 August 1992) and 15 (date of birth 1 September 1987 – 31 August 1988) year olds who were resident on the Isle of Wight at the time of the study. 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 of 50 primary schools (47 state and 3 independent schools), 8 high schools (5 state and 3 independent schools), 19 middle schools (16 state and 3 independent schools) and 2 schools for pupils with special needs. In order to ensure confidentiality and data protection the schools posted the study information, consent form, a self-administered questionnaire and a prepaid envelope to the parents/guardians of all eligible pupils (Appendices 31-33). They were asked to send their information and consent forms directly to the Allergy Centre. After approximately two weeks reminders were sent to the non-responders via the schools.

The reported prevalence of adverse reactions to foods and rates of foods avoided were established using a questionnaire that was completed by the parent and child. If they stated that the child had a current adverse reaction to any food they were asked to describe the symptoms that they experienced. The FAIR study team visited the schools where skin prick tests were performed on all who had consented. The presence of parents was accommodated in the primary schools.

Skin prick tests and food challenges were performed as discussed under 5.1.2 and 5.1.3.

### **6.2 Results**

#### **6.2.1 Characteristics of the study participants**

##### **6.2.1.1 Six year old cohort**

The target population for the study was all (n=1440) six-year-olds who were resident on the Isle of Wight at the time of the study.

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.

#### 6.2.1.2 Eleven year old cohort

The target eligible population comprised 1636 eleven-year-olds. A total of 775/1636 (47.4% [m=388]) eleven-year-olds were recruited into the study.

#### 6.2.1.3 Fifteen year old cohort

The target eligible population comprised 1508 fifteen-year-olds. A total of 757/1508 (50.2% [m=379]) fifteen-year-olds were recruited into the study.

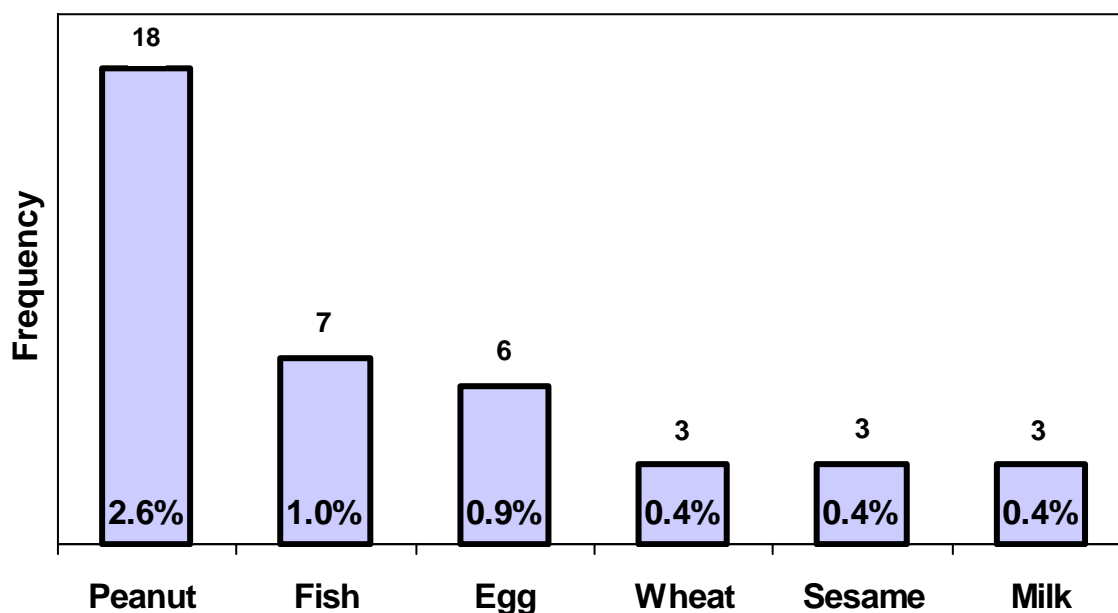
### 6.2.2 Rates of Sensitisation

#### 6.2.2.1 Six-year-old cohort

A total of 700 six-year-old children (87.8% of respondents) consented to be skin prick tested. The rate of sensitization to any allergen tested was 17.8% (125/700, CI 15.9-20.1), with 16.9% (118/700, CI: 14.2 – 19.9) 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.

The rate of sensitization to any of the predefined food allergen panel was 7.7% (54/700, CI: 5.9 – 10.). 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 (63). Only three six-year-olds 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 Figure 10.

**Figure 10: Frequency of sensitization to the predefined food panel in 700 six-year-old children**



\* Wheat - Not including grass cross-reactors

In addition, 12 six-year-olds were tested to one or more other food allergens based on their histories (almond [6], banana [1], cocoa [1], green bean [1], red/green/yellow/orange pepper [4], strawberry [1], tomato [1], walnut [6], brazil nut [6], green pea [1], hazel nut [5], cashew [5], pecan [5]). Of these, four children were sensitised (one to banana, one to green bean and green pea, one to almond and one to hazelnut).

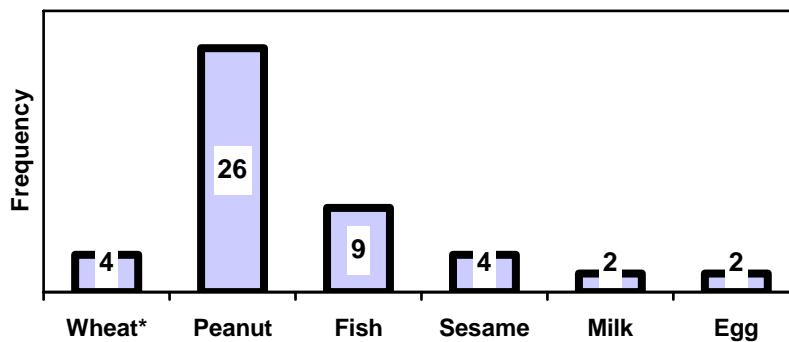
#### 6.2.2.2 Eleven-year-old cohort

A total of 699 children were skin prick tested. The rate of sensitisation to any of the predefined allergens tested was 26% (181/699, CI: 22.7 – 29.3). The rate of sensitisation to the predefined aero-allergens (HDM, Cat and Grass) was 25.5% (178/699, CI: 22.3 – 29.0; 116 children were sensitised to HDM, 120 to grass and 58 to cat). Eight SPT to other aeroallergens were carried out in 3 children based on indicated history (tree mix [1], dog [2], beech [1], alternaria [1], cladosporium [1], horse [1], silver birch [1]. One child was sensitised to dog (also sensitised to peanut) and another to silver birch and tree mix.



The rate of sensitisation to any of the predefined food allergens was 13.7% (96/699, CI: 11.3 – 16.5). However, large numbers were sensitised to both grass and wheat. Cross reactivity between grass and wheat allergen is well established in subjects with grass pollen allergy (63). If subjects with a history of grass pollen allergy who were sensitised to both grass and wheat (whilst asymptomatic to wheat) are removed, the true rates of sensitisation to any of the pre-defined food allergens will be 5.1% (36/699). 2 children were sensitised to egg, 26 to peanut, 2 to milk, 9 to fish, 4 to wheat, and 4 to sesame (Figure 11.)

**Figure 11: Eleven-year-old cohort n=699**



\* Wheat – not including grass cross-reactors

Where history indicated, the children were skin prick tested to other foods. Overall 18 children were skin prick tested to other foods (almond (7), apple (1), brazil nut (4), banana (1), carrot (1), cashew nut (5), cherry (1), cod (1), cocoa (2), pineapple fresh (1), pineapple tinned (1), green bean (1), hazel nut (7), mackerel (1), lobster (1), lychee fresh (1), lychee tinned (1), kiwi (1), mussels (1), orange (1), pecan (5), prawn (1), salmon (1), soya (2), strawberry (2), tomato (4), tuna (1), walnut (4), yeast (1)). Six of the children already sensitised to some of the predefined food allergens were sensitised to brazil nut (2), almond (2), cashew nut (1), pecan nut (1) and soya (1). Additionally three children were sensitised to prawn (1), mussels (1), lobster (1), green beans (1) and brazil nut (1) only.

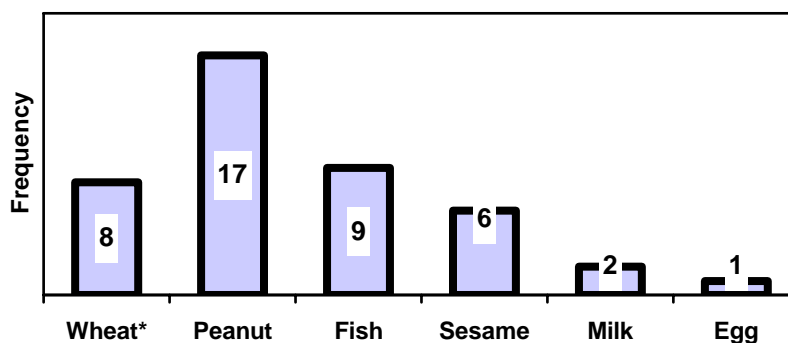
#### 6.2.2.3 Fifteen-year-old cohort

A total of 649 children were skin prick tested. The rate of sensitisation to any of the predefined allergens tested was 28.2% (183/649, CI: 24.8 – 31.8). The rate of sensitisation to the predefined aero-allergens was 27.0% (175/649, CI: 23.6 – 30.6; 116 children were sensitised to HDM, 101 to grass and 55 to cat). Seven SPT to other

aeroallergens were carried out in 7 children based on indicated history (dog [2], tree [2], latex [1], silver birch [1] and rabbit [1]). One child was sensitised to dog.

The rate of sensitisation to any of the predefined food allergens was 13.4% (87/649, CI: 10.9 – 16.3). However, large numbers were sensitised to both grass and wheat. Cross reactivity between grass and wheat allergen is well established in subjects with grass pollen allergy (63). If subjects with a history of grass pollen allergy who were sensitised to both grass and wheat (whilst asymptomatic to wheat) are removed, the true rates of sensitisation to any of the pre-defined food allergens will be 4.9% (32/649, CI: 3.4 – 6.9). 1 child was sensitised to egg, 17 to peanut, 2 to milk, 9 to Fish, 8 to wheat, and 6 to sesame (Figure 12).

**Figure 12: Fifteen-year-old cohort n=649**



\* Wheat – not including grass cross-reactors

Where history indicated, the children were skin prick tested to other foods. Overall 19 children were skin prick tested to other foods (almond (2), brazil nut (4), banana (1), cashew nut (4), carrot (1), cocoa (2), crab (3), onion (1), prawn (2), shellfish (1), shrimp (3), strawberry (2), tomato (3), hazel nut (6), kiwi (1), orange (1), pork (1), lobster (3), mussels (2), pecan (3), walnut (7), salmon (1), tuna (1) and raisin (1). Three children already sensitised to foods in the predefined panel were also sensitised to banana (1), brazil nut (1), pecan nut (1), shrimp (1), lobster (1), and hazel nut (1). Two additional children were sensitised to prawn (1) and hazel nut (1).

### 6.2.3 Parental reported food hypersensitivity

#### 6.2.3.1 Six-year-old cohort

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).

Wide ranges of foods or food ingredients were implicated in reported adverse reactions in the children (Table 6). The most frequent problems parents reported as being associated with consuming these foods were behavioural (hyperactivity and dislike) and gastrointestinal (abdominal pain, vomiting, diarrhoea). Other problems were wheeze, urticaria or other rashes, rhinitis, collapse or mucosal swelling.

**Table 6: Major foods/ingredients reported to cause symptoms in the six-year-old cohort**

<b>Food</b>	<b>Number (%) reporting problem</b>
Milk & Dairy	38 (40%) (29 to milk)
Peanut	15 (16%)
Egg	15 (16%)
Additives & colourings	13 (14%)
Tree nuts	11 (12%)
Wheat	10 (11%)
Strawberry	6 (6%)
Sesame	5 (5%)
Fish	2 (2%)

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

### 6.2.3.2 Eleven year old cohort

Parents of 90 eleven-year-old children reported that their child had a current problem with a food, with 33 children reporting problems with more than one food or food ingredient. Hence, the prevalence of reported adverse reactions to food amongst this cohort was 11.6% (90/775).

The foods most commonly implicated in these reported symptoms are shown in table 7.

**Table 7: Major foods/ingredients reported to cause symptoms in the 11 year cohort**

Food	Numbers reporting an adverse event	
	11-year-olds	(%)
Milk & dairy	22	24.4
Additives	26	28.9
Egg	12	13.3
Peanut	14	15.6
Tree nuts	9	10
Wheat	10	11.1
Fish	7	7.8
Shellfish	2	2.2

A variety of other foods and food ingredients were reported to cause problems including tomato, strawberry, vegetables, caffeine, yeast, pulses, meat, vinegar, bran, eccles cake, muffins, pizza, sugar/sweets, fatty foods, Wheetos, rice.

The problems associated with consuming these foods as reported by the cases included asthma, wheeze, cough, rash, angioedema, headache, nausea, abdominal

pain, dislike, hyperactivity and other behavioural problems with behavioural (hyperactivity and dislike) and gastrointestinal (abdominal pain, nausea, vomiting, diarrhoea) being the most common.

#### 6.2.3.3 Fifteen year old cohort

Parents of 94 fifteen-year-old children reported that their child had a current problem with a food, with 27 children reporting problems with more than one food or food ingredient. Hence, the prevalence of reported adverse reactions to food amongst this cohort was 12.4% (94/757). Only 76/94 fifteen-year-olds who reported a current problem were avoiding one or more foods, these did not necessarily include the food that they reported an adverse reaction to.

The foods most commonly implicated in these reported symptoms are shown in Table 8.

**Table 8: Major foods/ingredients reported to cause symptoms in the 15 year cohort**

Food	Numbers reporting an adverse event	
	15-year-olds	(%)
Milk & dairy	26	27.7
Additives	14	14.9
Egg	23	24.5
Peanut	19	20.2
Tree nuts	17	18.1
Wheat	9	9.6
Fish	14	14.9
Shellfish	5	5.3

Other foods reported to cause problems included tomato, citrus fruit/non-citrus fruit, meat, vegetables, soya, pulses, vinegar, caffeine, yeast/yeast extracts etc.

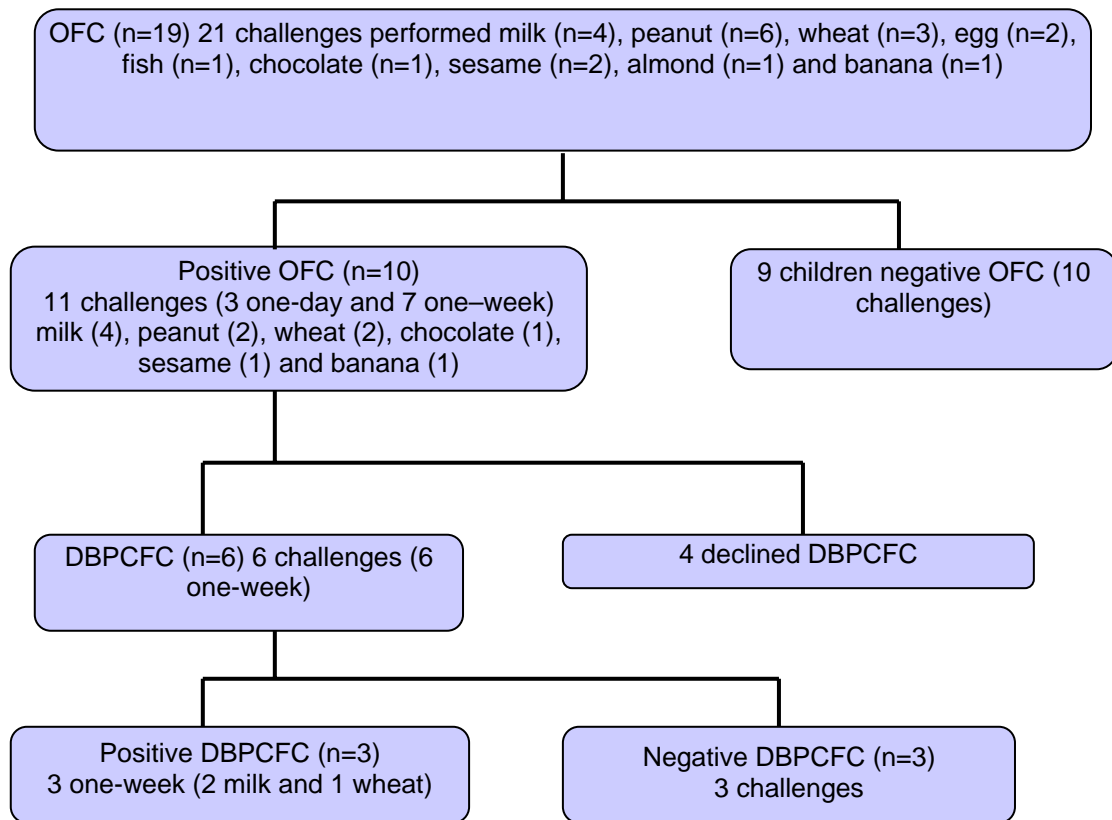
As with the eleven-year-olds, the problems associated with consuming these foods as reported by the cases included asthma, wheeze, cough, rash, angioedema, headache, nausea, abdominal pain, dislike, hyperactivity and other behavioural problems with behavioural (hyperactivity and dislike) and gastrointestinal (abdominal pain, nausea, vomiting, diarrhoea) being the most common.

#### 6.2.4 Objectively assessed FHS

##### 6.2.4.1 Six year old cohort

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 that 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 3 children were identified by means of their SPT result. Of the 31 children invited for food challenges, 12 declined food challenges due to 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 (4), peanut (2), wheat (2), chocolate (1), sesame (1) and banana (1). One child had a positive 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 4 declined, either for personal reasons or severity of reaction on open challenge. The remaining 6 children underwent DBPCFC and 3 had a positive reaction to milk (n=2) and wheat (n=1) (Figure 13).

**Figure 13: Summary of food challenges in the six-year-old cohort**



To calculate the rate of food hypersensitivity with a focus on open food challenge we included the following children: Those 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 1 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 6 children did not consent to undergo food challenges. If we apply the same rate of positive challenge rate to this group as observed with the 19 who did undergo OFC (i.e. 10/19, 53%) amongst them there will be 3 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 food hypersensitivity with a focus on double blind placebo controlled food challenges we included the following children. Three children with a positive DBPCFC + 5 (prior hospital diagnosis) + 2 (applying a 50% rate to the 4 who declined to undergo DBPCFC) + 1 (history of inadvertent reaction with positive skin test) 11/798=1.4% (95% CI 0.7-2.5).

However, we do know that 6 declined challenges altogether. To compensate for this we estimated that 3 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 3 would have undergone DBPCFCs, it is likely that 2 (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).

Of the 94 parents who reported a food related problem at six years only 20/94 (21.3%) were diagnosed with FHS by means of OFC and 13/94 (13.8%) by means of DBPCFC.

#### 6.2.4.2 Eleven-year-old cohort

Of the 90 eleven-year-olds who reported a problem with a food or foods, 60 eleven-year-olds were excluded from food challenges for a variety of reasons such as had problems with a fizzy drink as an infant; this fizzy drink is not available any more (1), dislikes a particular food such as crabsticks, rice, a glass of milk, baked beans etc. but eats it without any reaction (8), vomited after episodes of over eating only (2), Inconsistent history e.g. eats cheese but cannot eat cauliflower cheese; eats cod fish cakes but cannot eat cod; or reported a problem with hyperactivity to additives (40), high-fibre diet a problem, not wheat (1), had reaction to food once, but has eaten it since then without a problem (3), afraid of eating peanuts (3) and parents reported a problem during infancy, but food is well-tolerated at this stage (2).

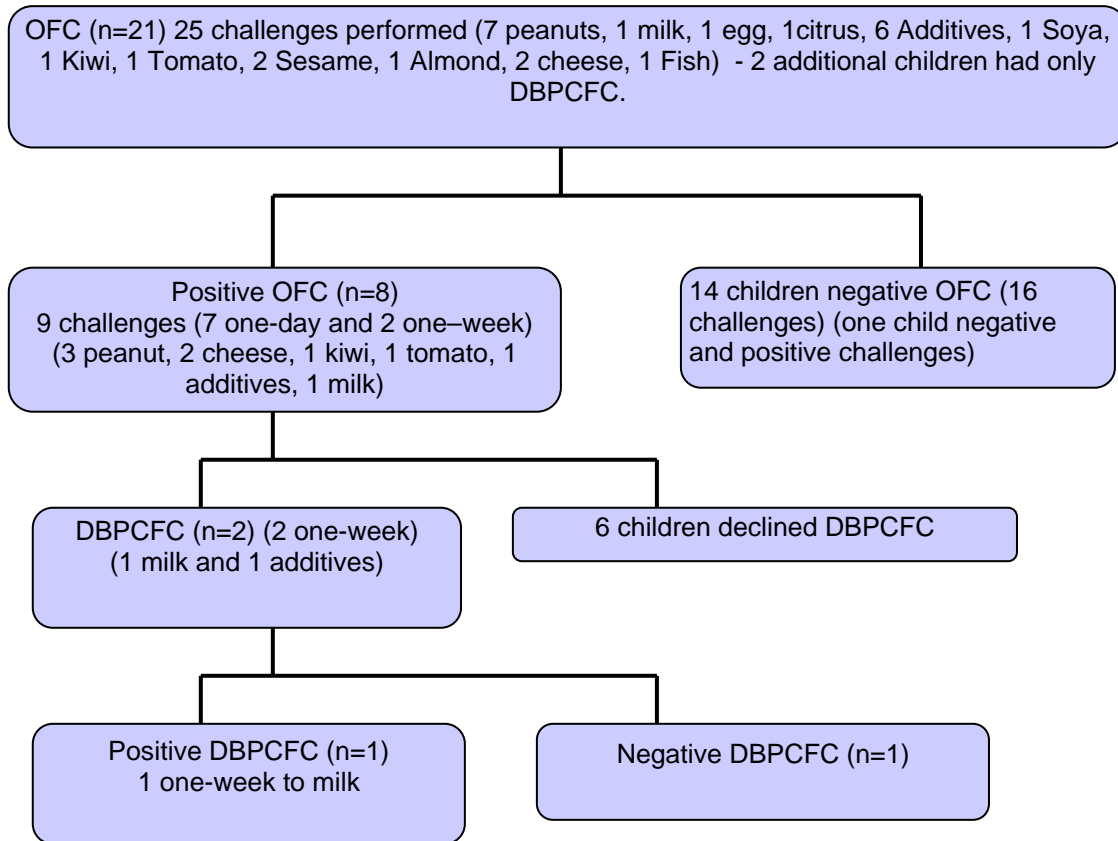
Therefore, 30 children were eligible for food challenges and were invited for challenge. A number of children did not undergo a challenge for various reasons such as physician's diagnosis of food hypersensitivity (n=6); positive SPT to a food that they previously reacted to and did not wish to undergo a challenge (n=1); declined food challenge (n=2). Hence, 21 eleven-year-olds underwent a total of 25 challenges, as some children underwent challenges to more than one food. Twenty one eleven-year-olds underwent open challenges to 10 different foods/ingredients (peanut, almond, soya, sesame, fish, cheese, kiwi, tomato, milk and additives) and 8 (38%) children had a positive challenge (7 one-day and 2 one-week, 1 child underwent two challenges).

All children who had a positive OFC were invited to undergo DBPCFC. Only 2 (2/8) children in the eleven-year-old cohort underwent DBPCFC, with parental refusal being the main reason for not undergoing DBPCFC. Of the 2 eleven-year-olds who underwent DBPCFCs (both 1 week challenges), one child had a positive challenge to milk.



Figure 14 summarises the food challenges in the eleven year cohort.

**Figure 14: Summary of food challenges in the eleven year cohort**



If one accepts the OFC as the primary endpoint, the prevalence of food hypersensitivity at eleven years of age is 8/775 (1.0%). It must be noted that a number of children did not undergo food challenges and many of these had convincing histories with a positive SPT or specific IgE test. Hence it would be justifiable to base the prevalence of FHS on a range of outcomes. Amongst the eleven-year-olds the prevalence of FHS based on a combination of a positive OFC (n=8), a clear history of previous reactions in the presence of a positive SPT or raised specific IgE (n=1) or a previous doctor's diagnosis (n=9), is 18/775 (2.3%, 95% CI 1.3 – 3.6).

If the DBPCFCs are taken as the endpoint, the prevalence of FHS, based on those who underwent these challenges is 1/775 (0.1%).

Amongst the eleven-year-olds, when the diagnosis of FHS was based on a combination of a positive DBPCFC (n=1), a clear history of previous reactions in the

presence of a positive SPT or specific IgE (n=1) or a doctor's diagnosis (n=9), the prevalence of FHS was 11/775 (1.4%, CI: 0.7 – 2.5).

Of the 90 parents who reported a food related problem at 11 years only 18/90 (20%) were diagnosed with FHS by means of OFC and 11/90 (12.2%) by means of DBPCFC.

#### 6.2.4.3 Fifteen year old cohort

Of the 94 fifteen-year-olds who reported a problem with a food or foods, 58 fifteen-year-old children were excluded from food challenges for a variety of reasons such as dislikes a particular food but eats it without any reaction (17), inconsistent history (31), high-fibre diet a problem, not wheat (1), had reaction to food once, but has eaten it since then without a problem (2), afraid of eating peanuts (5), parents reported problems during infancy, but food is well tolerated at this stage (2).

Thirty six children were eligible for food challenges and were invited for challenge. Two children did not improve on the elimination diet, which resulted in 34 children eligible for food challenges. A number of children who were eligible for a food challenge did not undergo a challenge for various reasons such as physician's diagnosis of food hypersensitivity (n= 6); positive SPT to a food that they previously reacted to and did not wish to undergo a challenge (n= 2); declined food challenge (n= 12). 14 children underwent 17 open food challenges, as some children underwent challenges to more than one food.

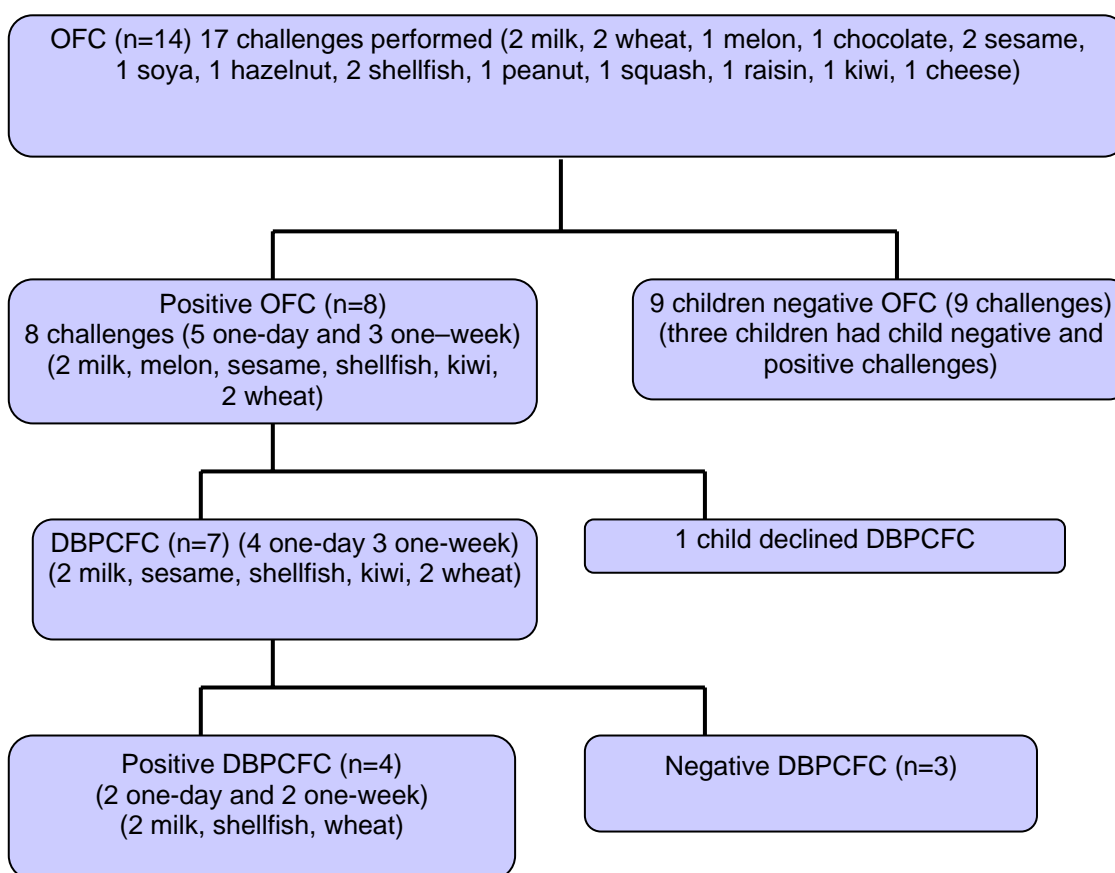
Fourteen fifteen-year-old children underwent open challenges to eleven foods/ingredients (milk, wheat, melon, chocolate, soya, hazel nut, raisin, kiwi, sesame, additives and shellfish) and 8 (53%) had a positive challenge (5 one-day and 3 one-week).

All children who had a positive OFC were invited to undergo DBPCFC. Seven (7/8) children underwent DBPCFC, with difficulty in performing DBPCFC for OAS in the fifteen-year-old cohort being the main reason.

4/7 of the fifteen-year-old children had positive DBPCFC (2 one day [milk, shrimp] and 2 one week [milk, wheat]).

Figure 15 summarises the food challenges in the 15 year old cohort.

**Figure 15: Summary of food challenges in the 15 year old cohort.**



If one accepts the OFC as the primary endpoint, the prevalence of food hypersensitivity at fifteen years of age was 8/757 (1.0%). It must be noted that a number of children did not undergo food challenges and many of these had convincing histories with a positive SPT or specific IgE test. Hence it would be justifiable to base the prevalence of FHS on a range of outcomes. Amongst the fifteen-year-olds the prevalence of FHS based on a combination of a positive OFC (n=8), a clear history of previous reactions in the presence of a positive SPT or raised specific IgE (n=3) or a doctor's diagnosis (n=6) is 17/757 (2.3%, 95% C.I. 1.3 – 3.6).

If the DBPCFCs are taken as the endpoint, the prevalence of FHS, based on those who underwent these challenges is 4/757 (0.5%) in the fifteen-year-old cohort.

For the fifteen-year-olds, when the diagnosis of FHS was based on a combination of a positive DBPCFC (n=4), a clear history of previous reactions in the presence of a

positive SPT or specific IgE (n=3) or a previous doctor's diagnosis (n=9), the prevalence of FHS in the fifteen-year-old cohort was 16/757 (2.1%, CI: 1.2 – 3.4).

Of the 94 fifteen year olds who reported a food related problem, 17 (18.1%) children were diagnosed with FHS based on OFC and history and 16 (17.0%) based on DBPCFC and history.

## **7. Discussion**

### 7.1 THE BIRTH COHORT

This is the first study conducted in the UK that investigates the rates of parentally reported FHS and clinically diagnosed FHS during the first three years of life.

The target population consisted of 1063 pregnant women with delivery dates between 1<sup>st</sup> September 2001 and 31<sup>st</sup> August 2002. A total of 969 pregnant women were recruited for the study (91% of the target population). This study had a participation rate ranging between 95.6% at three months and 88.5% at two years enabling us to be very confident of the completeness of these data. Over the course of the 3 years 942 (97.2%) children were seen at either one, two or three years, with 807 (83.3%) children seen at one, two and three years.

At one, two and three years, the rate of sensitisation to any food allergen was 1.9%, 3.8% and 4.5%. Over the course of the three years 5.3% (43/814, CI: 3.9 – 7.1) children had a positive SPT to any food in the predefined panel. No SPT was performed in the study by Bock et al. and two recent studies in children used prick to prick testing using the real food (24;64) rather than SPT with commercial allergens and we can therefore not compare our data with theirs.

In our population, the reported rate of perceived adverse reactions to food is 33.7% by three years of age. Two previous studies have looked at parentally reported adverse reactions to food. One reported the rate of parentally perceived adverse reactions to foods was 35% by two years of age (65) while Bock's study suggested it was 28% by three years of age (1).

Based on OFC and a good clinical history, the prevalence of FHS was 3.8% at one year, 2.5% at two years and 3.0% at three years. Osterballe et al. established the prevalence of FHS as confirmed by OFC was 2.3% in Danish children at three years (24). Based on DBPCFC and a good clinical history, the prevalence of FHS was 3.0% at one year, 2.1% at two years and 2.9% at three years. In a recent German study (3), 4.2% of children (0–17 years) were found to suffer from FHS as assessed by DBPCFC.

Cumulatively, by 3 years of age, 6.0% children were diagnosed with FHS based on OFC and history and 5.0% children based on DBPCFC and history. Bock et al. (1) diagnosed 7.6% of infants with FHS by three years of age. This was achieved using

either OFC or DBPCFC. Overall the foods implicated in this study (1) were milk, egg, soy, peanut, chocolate, corn, rice and wheat. These are very similar foods to those identified in our study.

Four studies have examined the incidence of cows' milk hypersensitivity during the first year of life (1;13;27;29). Our findings on prevalence of cows' milk hypersensitivity at one year (2.8% based on OFC and 1.0% based on DBPCFC) are similar to those reported by these four studies (1;13;26;27). One Canadian study (29) suggested that 7.5% Canadian infants had milk allergy in the first year of life. This study only used OFC, perhaps explaining these higher rates. One further study looked at egg and milk allergy at 2.5 year of age (26). At the age of 2 ½ years the point prevalence of milk allergy was 1.6% (26). In our study, 0.9% (8/858) suffered from milk allergy at age two and 0.4% (4/891) at age three based on DBPCFC.

Egg allergy has been reported to be 1.6% at 2.5 years of age (33). The point prevalence of egg allergy in our study was 2.2 % (13/858) children at age two and 1% (9/891) at the age of three years based on DBPCFC.

In the study by Bock et al, (1) only a quarter of infants with apparent adverse reactions had evidence of FHS. In our population, only 16.1% of children who were seen at one, two and three years and reported a food related problem were diagnosed with FHS by means of an OFC and history and 12.9% by means of a DBPCFC and history. This emphasises the need for a comprehensive evaluation of infants with adverse reactions to food to ensure that infants are not needlessly avoiding potentially important food groups in their diet.

In conclusion, we have established that almost 40% of parents report adverse reactions to foods in their infants during the first three years of life. Of these only 16% were confirmed as FHS by OFC. Our data describe the magnitude of the problem of FHS in the first three years of life and highlight the foods most frequently associated with FHS. They also emphasise the need for accurate diagnosis to prevent infants being on an unnecessary restricted diet which may be associated with inadequate nutrition at this important period of growth and development.

## 7.2 TEMPORAL CHANGES IN THE PREVALENCE AND INCIDENCE OF FHS

It is often claimed that the prevalence of FHS, just as other types of allergic disease, is escalating. This project provided us with the ideal opportunity of comparing our sensitisation data with children born 12 years earlier on the Isle of Wight. The results indicated that there was no increase in sensitisation to food allergens. There was however a significant reduction in prevalence of sensitisation to aeroallergens. There was also no significant difference (0.5% vs. 1.1%) in the number of children born in 1989 (age four years) suffering from peanut allergy compared to children born in 2001 (age 3 years).

Sensitisation to aero-allergens is on the decrease according to the data from these two cohorts. It is difficult for us to explain this finding as it is well-known that respiratory diseases are on the increase. We saw notable decreases in sensitisation to HDM and grass – it could be that the increase in respiratory disease is unrelated to sensitisation of these two allergens. FHS and sensitisation to foods do not appear to have increased based on our findings. This could be simply because there is no genuine increase in rates of FHS and food sensitisation and there is a fairly stable population level. Indeed aero-allergen sensitisation may be different to food sensitisation due to differences in routes of exposure, doses of exposure etc. However these are all unknown entities that need further research. Another explanation could be that this cohort is different from other cohorts studied but we do not feel this is the case as the source of population were the same and we kept all the procedural issues as constant as we could. It is important to remember that all these children were suffering from “atopic” allergy as they all had a positive SPT to peanuts.

Most importantly, our data is the first that can be directly compared to a study performed more than 20 years ago in the USA. The results indicated the prevalence of FHS did not increase over this period ( $p=0.30$ ). We were not able to compare those children with IgE mediated FHS in our study to those with IgE mediated FHS in Bock's study (1) as the sensitisation status of the children the Bock study (1) is not known.

## 7.3 THE SCHOOL COHORTS

This study is the first population based study establishing reported food problems and sensitisation amongst six, eleven- and fifteen-year-old children.

The rates of sensitization to the predefined panel of food allergens amongst these three cohorts were 3.6%, 5.1% and 4.9%. It is difficult to compare our sensitisation rates with other studies. Firstly there are no other population-based studies that have specifically SPTed six, 11 and 15 year olds. There are a few studies which have looked at sensitisation data amongst children of varying ages only if they had reported a problem (64) and they used prick-to-prick technique with free foods.

In our study there appeared to be a large proportion of cross-reactivity between wheat and grass on skin prick testing (29/42, six year olds 72/80 fifteen-year-olds and 76/80 eleven-year-olds who were sensitised to wheat were also sensitised to grass and were tolerating wheat and wheat containing products in their diets). In Baltimore, of 145 children with food hypersensitivity to cereal grains, grass and wheat, only 21% had symptomatic reactivity on food challenge (63). These findings are reflected in our study with only a small proportion of those sensitised to wheat reporting clinical reactivity to wheat.

A total of 94 (11.8%) six-year-olds reported a problem with a food or food ingredient, 11.6% eleven- and 12.4% fifteen-year-olds. In the Netherlands, in a cohort of 1039 children aged 5-6 years, the reported rate of food hypersensitivity was 11.4%

Based on open food challenge and/or suggestive history and positive skin tests, the prevalence of food hypersensitivity was 2.6% in the six-year-old cohort. 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). These corresponding figures were 2.3% and 1.4% for the eleven year olds and 2.3% and 2.1% for the fifteen year olds.

The foods reported by the children to cause adverse reactions are in line with other publications (14-16) suggesting that peanut, tree nut and shellfish allergy is often reported in older children and young adults.

There are no population-based studies in these age groups to compare our data with, but our figures are lower than in adult populations (2.4%) (4) and slightly higher than a previous study in adults and children (1.4-1.8%) (22). In a German study 4.2% of children (0-17years) were diagnosed with FHS. Rance et al [4] conducted a questionnaire-based survey in Toulouse (France) schools to determine the prevalence of food allergies among schoolchildren. Based on these questionnaires, the point prevalence was 6.8% for the children aged 6-10 years



Seven out of 700 six year olds (1%), 8/775 (1%) eleven-year-old children and 6 out of 757 (0.8%) fifteen-year-old children were peanut allergic in this study, which is similar to rates (1.5%) in a group of three to four-year-olds in the same geographical region (36).

Discrepancy in self-reported food-induced symptoms and physician diagnosed food hypersensitivity has been reported by others to be ten-fold in children and adolescents (64). In our study, a much smaller proportion were diagnosed to have food hypersensitivity on the basis of food challenges and inclusion of those with a physician's diagnosis or clinical reaction or inadvertent exposure coupled with sensitization. We confirmed FHS in only 21.3% six year olds, 20% eleven year olds and 18% of the fifteen-year-olds who reported a food problem despite the fact that we had mimicked the history in terms of dose needed and duration of exposure. This also compares to 35% in a study performed by Bock et al (1) in infants (0-3 years) and 10% in the population based study by Zuberbier et al (3).

In conclusion, reported food problems are common in six, eleven- and fifteen-year-old children but the rate of sensitisation to food allergens is low. Based on OFC where possible, 2.6% of six year olds and 2.3% of eleven-year-old and fifteen-year-old children in these cohorts suffered from food hypersensitivity, which is lower than previous estimates based on the figures in infants and toddlers (1).

One possible limitation of the study is the low uptake of food challenges, particularly the DBPCFC. Over the course of the first three years, 39, 21 and 27 (n=87) children were diagnosed by means of OFC and a good history; of these 87 children, 57% were diagnosed by means of a challenge. In addition, 15 children were diagnosed with DBPCFC at one year, one child at two years and none at three years; 21% of children diagnosed with FHS based on a DBPCFC and good clinical history therefore underwent DBPCFC. This gives an average of 39% children in the birth cohort undergoing food challenges. In the three school cohorts, 20, 18 and 17 (n=55) children were diagnosed by means of OFC and a good clinical history; of these 55 children, 47% were diagnosed by means of food challenges. In addition, 3 six year old children were diagnosed with DBPCFC as well as 1 eleven year old and 4 fifteen year old children, therefore 20% of children diagnosed with FHS based on a DBPCFC and a good clinical history underwent DBPCFC. This gives an average of 35% in the school cohorts undergoing food challenges. However, this compares well with the most cited

previous study where only 44% (16/37) of the infants with positive food challenges underwent DBPCFC (1). Additionally, the majority of children not undergoing a DBPCFC in our study were excluded because of severity of reaction on open challenge or a SPT diameter above the 95% positive predictive levels (66).

The reason for performing OFC first, was to eliminate those with no symptoms of FHS using a cost-effective way (50% of those children in all the cohorts who underwent OFC had a negative challenge outcome). We did not foresee the large number of children who eventually declined DBPCFCs (40% of children with positive OFC declined DBPCFC). The original study proposal included the use of OFC followed by DBPCFC as there is no consensus in the literature regarding the use of food challenges in children. In general the DBPCFC is the accepted gold standard in objectively diagnosing FHS (51;67;68). However, some clinicians consider it far from a perfect test as it can be labour intensive and more unsafe to perform than the OFC, particularly in children (69;70). There is a consensus amongst many clinicians suggesting that OFCs are acceptable in children under the age of three and the DBPCFC should be used in older children (71-73). However, there is no evidence to support this.

We have prepared a manuscript based on the food challenges in the one, two, six, 11 and 15 year old children. The results of this paper showed that the positive predictive values for one-day and one-week OFCs were 73% (95% CI: 39% – 94%) and 57% (95% CI: 39% – 74%) respectively. There was no evidence to indicate that the younger children were more likely to have a positive OFC confirmed by a DBPCFC compared to older children (Fisher's Exact  $p = 0.53$ ). OFC may be suitable for diagnosing immediate objective symptoms, whereas DBPCFC may be needed for the diagnosis of delayed and mainly subjective symptoms. Therefore, based on this information, we would choose to do only OFC in those children with objective symptoms and only DBPCFC in those children with subjective symptoms

Another weakness of the school cohort study is the low response rate of around 50% in all the cohorts. 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 were a major issue, we would expect a high rate of atopy in the responders. Approximately 18% of the cohorts 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 (74).

Furthermore, these estimates of FHS 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.

In the birth cohort, no challenges were performed in the infants sensitised to peanut or sesame at one and two years (peanut=14 and sesame=5). It was decided that infants should not be exposed to these allergens under three years of age (75). This may have resulted in us underestimating the rate of food hypersensitivity in infancy. Also it is possible that some infants were sensitised to foods that were not in our allergen panel. This is unlikely though to have significantly affected the rate of clinical allergy as infants were also tested to other foods to which they had had an adverse reaction.

Finally, in this study, we were able to estimate the prevalence and incidence of FHS in a birth cohort and three cohorts of school children. We were also in the unique position of comparing sensitisation rates to food and aero-allergens in children born 12 years apart on the Isle of Wight. Our birth cohort data provided the information that could be compared for the first time to that of a study performed in the USA more than 20 years ago.

The implications and significance of our data are as follows:

The key findings from this study indicate that, reported adverse reactions to foods are common groups in all ages, but rates of diagnosed FHS are low. Looking the rates of FHS in each age group, the FHS rate ranged between 1.4% based on DBPCFC and a good clinical history at age 11 years and 3.0% based on DBPCFC and a good clinical history at one year. Additionally, considering the birth cohort, we have found that sensitisation to foods and diagnosed FHS have not increased over the last two decades. In the light of the discrepancy between reported and diagnosed FHS, the major implication of this study is the need for accurate diagnosis to prevent children being on unnecessary restricted diets. This may be associated with inadequate nutrition at this important period of growth and development.

Furthermore, the data from this study suggests that OFCs may be useful when dealing with objective symptoms, but DBPCFCs are needed for diagnosis of subjective symptoms. The age of the patient should not play a role when deciding about which challenge to use. This is a positive finding as DBPCFCs, which are costly and tedious, may not be required for diagnosis of immediate type allergies. In our study, all the children who had a positive one-day OFC which was confirmed by a positive one-day DBPCFC presented with objective symptoms. In contrast 90% (18/20) of the children with a positive one-week OFC which was confirmed by a positive one-week DBPCFC presented with subjective symptoms. It seems therefore that immediate symptoms tend to be more objective (e.g. rash, hives, projectile vomiting) and the delayed symptoms more subjective (eczema, abdominal pain, vomiting after 2 days). Less dietitian, nursing and physician time will therefore be required. However, it seems that DBPCFC will be needed for the diagnosis of delayed symptoms, which will have a huge implication on planning of the food challenges and food preparation.

In summary, in the light of the discrepancy between reported and diagnosed FHS, the major implication of this study is the need for accurate diagnosis to prevent children being on unnecessary restricted diets. This may be associated with inadequate nutrition at this important period of growth and development. This has an important implication as there are a limited number of Allergy Specialists and Allergy Centres available in the UK. Community dietitians and GPs are often left with having to make a clinical diagnosis of FHS without the possibility of performing SPT or food challenges. They very often also do not know how to interpret specific IgE levels. This study therefore highlights the need for more allergy trained health professionals in order to rule out FHS in about 20% of the UK population who claim to suffer from FHS as well as managing FHS in about 1.5 - 3.8% of the UK population who are truly clinically allergic.

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