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Food Hypersensitivity amongst children on the Isle of Wight – An in depth dietary investigation

by

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ABSTRACT

FACULTY OF BIOMEDICAL SCIENCES

SCHOOL OF MEDICINE

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FOOD HYPERSENSITIVITY AMONGST CHILDREN ON THE ISLE OF WIGHT – AN IN DEPTH DIETARY INVESTIGATION

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Introduction:
It is unclear at present which type of food challenge (open vs. double blind) is best suited for the diagnosis of food hypersensitivity (FHS) in children. The question as to what dietary factors could have played a role in the development of FHS is also still unanswered.

This research aimed to assess 1) what is the best approach for the diagnosis of FHS; 2) how maternal dietary and infant feeding and weaning practices influence the development of FHS; 3) the role of a personal or family history of atopy in dietary practices.

Methods:
A birth cohort of children born during 2001 – 2002 was recruited at the ante-natal clinic and followed prospectively for two years. In addition, three sets of school cohorts were approached to participate in the study. To address the first aim, all cohorts were utilised and the use of open food challenges (OFC) and double blind placebo controlled food challenges (DBPCFC) were assessed in the diagnosis of FHS. To address the second aim the birth cohort was used. A food frequency questionnaire (FFQ) was developed and validated to obtain the information on the maternal diet. Standardised questionnaires were developed and used prospectively to assess feeding and weaning practices and their influence on the infant's FHS. To address the third aim the family history of atopy was obtained during recruitment of the birth cohort and this information was used to find out if a personal or family history of atopy affect maternal eating and feeding and weaning practices of the infant.

Results:
We found that the positive predictive value of the one-day OFC challenges was higher than the one-week OFC. The data therefore suggest that OFC may be suitable for diagnosing immediate (objective) symptoms, whereas a DBPCFC may be needed for the diagnosis of delayed (subjective) symptoms.
Fruit and vegetable intake during pregnancy, food avoidance during lactation and weaning age of the infant affected the development of FHS.
A family history of atopy positively affected exclusive breast feeding at three months and delayed introduction of peanuts into the infant's diet by six months.

Conclusion:
OFC are the most appropriate method for the diagnosis of immediate type symptoms of FHS and the DBPCFC for delayed type symptoms. This study showed some associations between certain dietary characteristics and the development of FHS in the infants. A family history of atopy may also have an effect on dietary, feeding and weaning practices. However, very few children were diagnosed with FHS and these findings need to be further investigated in longer studies.

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Publications

i) Book chapters

1. Venter C. 2003. Immunological reactions involved in food allergy. In: Year in Allergy 2003. Arshad SH and Holgate ST, pp. 107 – 120. Oxford: Clinical Publishings Ltd.

2. Venter C. 2003. Diagnostic methods. In: Year in Allergy 2003. Arshad SH and Holgate ST 2003, pp. 121- 144. Oxford: Clinical Publishings Ltd.

3. Venter C. 2003. Allergens in food and cross-reactions. In: Year in Allergy 2003. Arshad SH and Holgate ST 2003, pp. 145 - 162. Oxford: Clinical Publishings Ltd.

4. Venter C. 2003. Peanut/Nut allergies. In: Year in Allergy 2003. Arshad SH and Holgate ST 2003, pp. 163 - 178 . Oxford: Clinical Publishings Ltd.

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12. Venter C. Food exclusion. In: Manual of Dietetic Practice 4th edn. Thomas B and Bishop J. (planned publication 2007).

ii) Peer reviewed articles

1. Pereira B, Venter C, Grundy J, Clayton CB, Arshad SH, Dean T. Prevalence of sensitisation to food allergens, reported adverse reaction to foods, food avoidance and food hypersensitivity amongst teenagers. Journal of Allergy and Clinical Immunology, 2005, 116:884

2. Turke J, Venter C, Dean T. Maternal experiences of peanut avoidance during pregnancy/lactation: An in-depth qualitative study. Pediatr Allergy Immunol 2005; 16 (6): 512-518

3. Venter C, Pereira B, Grundy J, Clayton CB, Roberts G, Higgins B, Dean T. Incidence of parentally reported and clinically diagnosed food hypersensitivity in the first year of life. Journal of Allergy and Clinical Immunology. 2006; 117 (5):1118 - 24.

4. Venter C, Pereira B, Grundy J, Clayton C, Arshad H, Dean T. Prevalence of sensitisation, reported and objectively assessed food hypersensitivity amongst 6-year-old children – A population based study. Pediatric Allergy and Immunology. 2006; 17 (5): 356 – 363.

5. Venter C, Higgins B, Grundy J, Clayton B, Gant C, Dean T. Reliability and Validity of a Maternal Food Frequency Questionnaire designed to estimate consumption of common food allergens. Journal of Human Nutrition and Dietetics. 2006;19 (2):129 - 38.

iii) Invited articles

1. Venter C, Dean T. Prevalence of Food Hypersensitivity. Food Science and Technology 2005; 19(2):31-34.

International Presentations

i) American Academy of Allergy, Asthma and Immunology 2004:

1. Factors associated with avoidance of peanuts and/or other nuts during pregnancy and lactation.*
2. Characteristics of infants born from atopic vs non-atopic mothers during the first 6 months of the infants life.*
3. Sensitisation rates to food and aeroallergens amongst 1 year olds in UK – A population based study.
4. Sensitisation rates to food allergens and prevalence of reported and objectively assessed food allergies amongst 15 year olds in UK.

ii) European Academy of Allergology and Clinical Immunology 2004:

1. Maternal experience of peanut avoidance during pregnancy/breastfeeding.*

iii) World Allergy Organisation Congress 2005:

1. Prevalence of sensitisation to food allergens, reported adverse reaction to foods and food hypersensitivity (FHS) amongst a birth cohort at one year of age.*
2. Prevalence of sensitisation to food allergens, reported adverse reaction to foods, food avoidance and food hypersensitivity (FHS) amongst 15 year old children in the United Kingdom– A population based cohort study.*
3. Feeding and Weaning practices of mothers with a reported maternal or family history of atopy.*
4. Prevalence of reported adverse reaction to foods, food avoidance and sensitisation to food allergens amongst 2-year-old children on the Isle of Wight.
5. Prevalence of reported adverse reaction to foods, food avoidance, sensitisation to food allergens and food allergy amongst 6-year-old children on the Isle of Wight.
6. Prevalence of reported adverse reaction to foods, food avoidance, sensitisation to food allergens and food allergy amongst 11-year-old children on the Isle of Wight.
7. Peanut avoidance during pregnancy and reported compliance with UK Governmental advice on peanut consumption.

* presented by C. Venter as first author

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List of abbreviations

AEG	Allergic eosinophilic gastroenteritis
AEO	Allergic eosinophilic oesophagitis
AMED	Allied & Complementary Medicine Database
ANOVA	Analysis of Variance
APT	Atopy patch test
BDA	British Dietetic Association
BNID	British Nursing Index Database
CD	Celiac Disease
CMA	Cow's milk allergy
COT	Committee on Toxicity of Chemicals in Food,Consumer products and the environment
DBPCFC	Double blind placebo controlled food challenge
EAACI	European Academy for Allergy and Clinical Immunology
EMBASE	Excerpta Medica database
EPIC	European Prospective Investigation into Cancer and nutrition
ESPACI	European Society for Paediatric Allergology and Clinical Immunology
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
FAEIA	Food associated exercise induced anaphylaxis
FAIR	Food Allergy and Intolerance Research
FFQ	Food frequency questionnaire
FFQR1	Food frequency questionnaire completed at 30 weeks gestation for reliability study
FFQR2	Food frequency questionnaire completed at 36 weeks gestation for reliability study
FFQV1	Food frequency questionnaire completed by the author with information obtained from the food diaries for validity study
FFQV2	Food frequency questionnaire completed at 36 weeks gestation for validity study
FHS	Food hypersensitivity
FPIES	Food protein induced enterocolitis syndrome
GI	Gastro-intestinal
GINI	German infant nutrition
HDM	House dust mite
IgE	Immunoglobulin E

IgG	Immunoglobulin G
kU_A/L	kilounits of allergen per litre
MEAD	Maternal egg avoidance study
NRR	National research trials register
OAS	Oral allergy syndrome
OFC	Open Food Challenge
RAST	Radio-allergo sorbent tests
SACN	Scientific Advisory Committee on Nutrition
SBPCFC	single blind placebo controlled food challenges
SIGLE	System for Information on Grey Literature
SPT	Skin prick test
Th	T-helper
TPN	Total Parenteral Nutrition
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation
χ^2	Chi square

Chapter 1

Introduction

1.1 Introduction

This chapter aims to comprehensively review the current evidence in the area of food hypersensitivity (FHS). It is structured to start with broad issues such as definition, prevalence, diagnosis and it moves on to areas that relate directly to work undertaken in this thesis. These are the use of food challenges in the diagnosis of FHS and the role of maternal food intake, breastfeeding and weaning practices in the development of FHS.

The specific objectives of this thesis were:

1. To compare Open Food Challenges (OFCs) and Double-blind Placebo Controlled Food Challenges (DBPCFCs) in the diagnosis of FHS.
2. To validate a Food Frequency Questionnaire (FFQ) which assesses maternal dietary intake during pregnancy
3. To investigate the association of maternal dietary factors, feeding and weaning practices in the development of FHS in the infant.
4. To describe dietary experiences and feeding/weaning practices of mothers with either a familial or maternal history of allergic disease

1.1.1 Search Strategies

A search strategy was used to obtain all the available evidence in the areas covered in this thesis. The search strategy used incorporated database searches, conference proceedings and abstracts of conferences on CD-Rom.

1.1.2 Databases

The electronic databases searched were:

- Pubmed database, covering journals from 1951 to 2006
- Theses databases: www.theses.com, http://www.collectionscanada.ca/thesescanada/index-e.html and http://www.umi.com/umi/dissertations.
- Allied & Complementary Medicine Database - 1985 to 2006 (AMED)
- British Nursing Index Database - 1994 to 2006 (BNID)
- Cochrane Library (2006)
- Excerpta Medica database - 1974 to 2006 (EMBASE)
- National research trials register – 2006 (NRR) (www.nrr.nhs.uk). The National Research Register (NRR) is a database of ongoing and recently completed research projects funded by, or of interest to, the United Kingdom's National Health Service.

- Dietary Assessment Calibration/Validation register 1980 – 2006 (www.dacv.ims.nci.nih.gov)
- Edina CAB abstracts – 1973 to 2006. This database is provided by the University of Edinburgh and indexes articles in the fields of agriculture, aspects of human health, human nutrition, animal health and the management and conservation of natural resources.
- Clinical Trials database (www.clinical trials.gov) - 2006. This website is provided by the National Institute of Health in the United States of America and developed by the National Library of Medicine. It provides regularly updated information about federally and privately supported clinical research in human volunteers.
- Zetoc - 1993 to 2006. The database contains details of conference records in science, technology, medicine, engineering, business, law, finance and the humanities.
- SIGLE (System for Information on Grey Literature) - 2006. This online database contains citations to reports, conference papers, and other non-conventional literature issued informally throughout Europe on most scientific and technical subjects.

1.1.3 Conference proceedings and abstracts

Grey literature was searched by reviewing the conference proceedings and abstracts on CD-Rom for the American Academy of Allergy and Clinical Immunology (2001 – 2005), European Academy of Allergy and Clinical Immunology (2001- 2005) and World Allergy Organisation (2001, 2003 and 2005).

1.1.4 Search terminology

The electronic databases and conference proceedings were searched using both free text and MeSH terms where appropriate.

The following keywords were used:

Food hypersensitivity

Food allergy

Food intolerance

Adverse reactions to food

Other terms used in conjunction with the above included:

Definition

Prevalence

Diagnosis

Food challenges

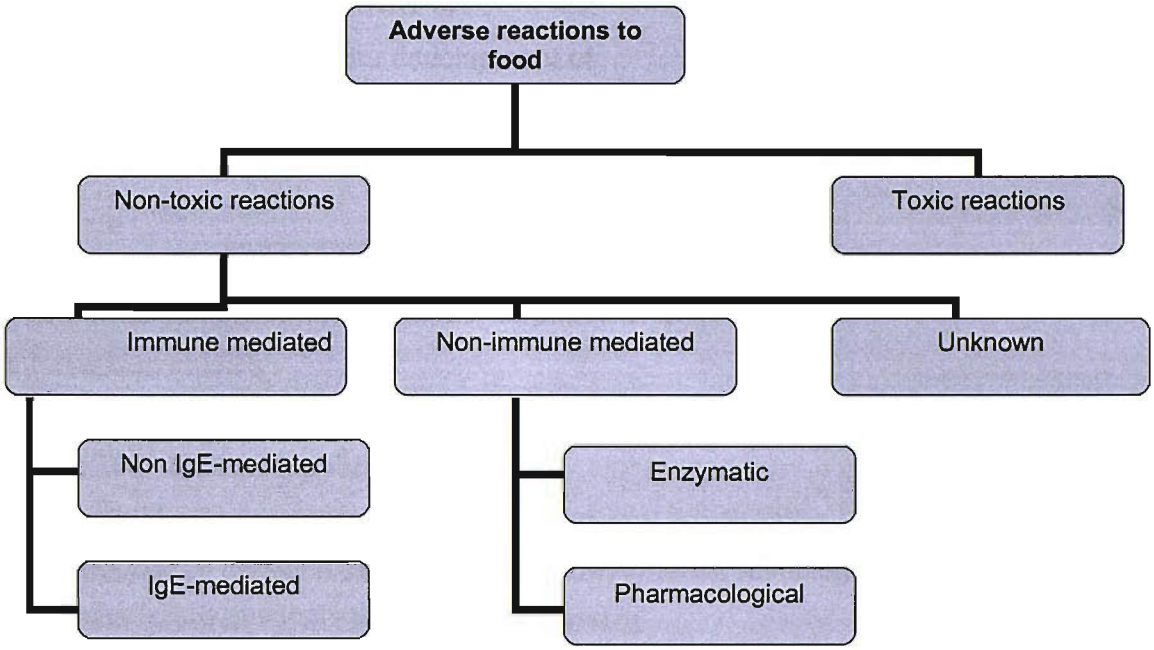
Open food challenges
Double blind placebo controlled food challenges
Oral provocation test
Factors involved in development of ...
Dietary intake and development of ...
Maternal food intake and the development of ...
Breastfeeding and food intake
Breastfeeding and the development of ...
Weaning practices
Weaning practices and the development of...
Foeto-maternal environment and development of ...
Intervention studies
Food challenges
Methods of determining dietary intake
Dietary intake during pregnancy
Food frequency questionnaires with the following terms reliability, reproducibility, validity, validation, pregnancy, allergy and atopic disease

1.2 Definition of food hypersensitivity

"Adverse food reactions" is the umbrella term referring to any untoward reaction following the ingestion of a food (or food additive). Adverse reactions to food can be divided into toxic and non-toxic reactions. Toxic reactions are dose related and can affect any individual exposed to toxic compounds, which may be naturally occurring in foods or added during food preparation e.g. scromboid fish poisoning or aflatoxins in peanuts (Committee on Toxicity of Chemicals in Food 2000).

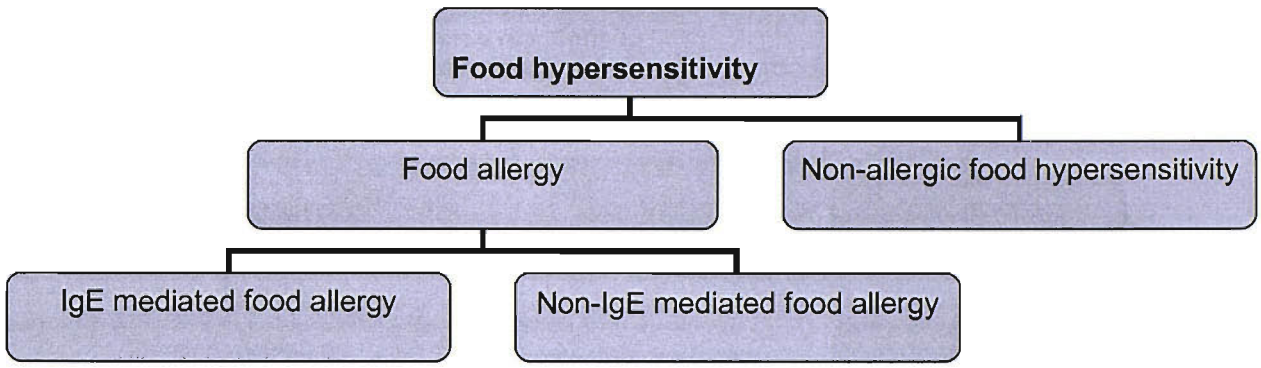
One method of classifying the non-toxic reactions is to divide them into food allergy (immune mediated) and food intolerance (non-immune mediated) (Fig. 1.1). However, in the clinical practice of allergy it is often unclear whether the problem is an allergy or intolerance due to the time delay between ingestion and symptoms and insufficient diagnostic tools (Committee on Toxicity of Chemicals in Food 2000;Ortolani et al. 1999). There is a popular practice of calling all adverse reactions 'allergies.' This is inaccurate and causes confusion to both the general public and health professionals.

Figure 1.1: Classification of adverse reactions to food based on the Committee on Toxicity of Chemicals in Food (COT) report: Consumer products and the environment (Committee on Toxicity of Chemicals in Food 2000).



A European Academy of Allergy and Clinical Immunology task force (Johansson et al. 2004) has recently suggested that any adverse reaction to food should be called food hypersensitivity (Fig. 1.2). 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 (Johansson et al. 2004).

Figure 1.2: Proposed nomenclature for food hypersensitivity.
(Johansson et al. 2004)



The term food hypersensitivity (FHS) will be used throughout this thesis according to the above European Academy for Allergy and Clinical Immunology (EAACI) classification.

1.3 Prevalence of food hypersensitivity

This section will discuss prevalence and incidence of FHS in adults and children including both studies looking at a variety of foods and studies on single foods. It is important to have accurate national data on the prevalence of FHS in order to meet the needs of the allergic community, particularly as the prevalence of food allergies varies depending on the diet and exposure to food allergens. Examples include fish allergy, which is frequently seen in Spain (Crespo et al. 1995) and peanut allergy that is common in the USA (Sicherer et al. 2001).

FHS is believed to affect 1.5% of adults and 6–8% of children (Bock 1987;Fuglsang et al. 1994;Jansen et al. 1994;Zuberbier et al. 2004) and is more common in atopic individuals (Kurukulaaratchy et al. 2003). Cow's milk, eggs, peanut and tree nuts, soy and wheat are among the most common food allergens in infants and children (Bock & Atkins 1990;Burks et al. 1998;Crespo et al.1995;Dalal et al. 2002;Eigenmann & Calza 2000;Hosking, Heine, & Hill 2000;Host & Halken 1990). Peanuts and tree nuts (Sicherer, Munoz-Furlong, & Sampson 2003) as well as fish and shellfish (Sicherer, Munoz-Furlong, & Sampson 2004b) are reported to be the most common food allergens in teenagers and adults. Oral allergy syndrome is also frequently reported in this older group (Mattila et al. 2003).

FHS is the most common cause of anaphylaxis in children in western countries, and more specifically the United Kingdom (A report of the Royal College of Physicians Working Party on the provision of allergy services in the UK 2003;Alves & Sheikh 2001). 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 (Bock, Munoz-Furlong, & Sampson 2001a;Eigenmann & Zamora 2002) and milk in the United Kingdom (UK) (Macdougall, Cant, & Colver 2002).

The few studies which have addressed the prevalence of FHS have mainly investigated adult populations (Jansen et al. 1994;Young et al. 1994) 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 (Bock 1987). Recently, one population based study utilising food challenges, has been published looking at the prevalence of food allergy in both adults and children (Zuberbier et al. 2004).

The prevalence studies conducted in adults comprise information from Dutch, UK 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% (Jansen et al.1994). 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 (European Union 2003). 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 (Young et al. 1994). 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 High 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 10 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 responses.

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 (Zuberbier et al. 2004). 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 Immunoglobulin E (IgE)-mediated and 1.1% non-IgE-mediated. Females were more frequently affected (60.6%) than men. Based on 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 the USA, 480 consecutive children born into a paediatric clinic were recruited at a routine two-week appointment. The researchers determined that 8% (cumulative incidence) of the children (0-3 years) out of the 28%, who presented with possible symptoms of food allergy, were truly food allergic as assessed by food challenges (Bock 1987). This study utilised open and/or DBPCFCs over a one-day period using a standard dose of dried, rather then 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 (Zuberbier et al. 2004), 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 single-blind or open food challenges depending on the patient's 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.

Rance et al.(Rance, Grandmottet, & Grandjean 2005) 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 cow's 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.

A recently published study (Osterballe et al. 2005) investigated the prevalence of FHS in children and adults in Denmark. They used a very interesting recruitment strategy. A newborn cohort were recruited and evaluated for FHS at 3 years of age (n=486). The siblings and parents of these children were also investigated, providing 111 children younger than one year, 301 children older than 3 years and 936 adults. The prevalence of FHS was 2.3% in the children 3 years of age, 1% in children older than 3 years of age and 3.2% in adults. Although the authors claimed that OFCs were used in the children younger than 3 years, in fact, no food challenges were performed in this group and therefore, no prevalence figure was given.

The few studies looking at FHS to cow's milk as a single food show that about 2.5% of children suffer from cow's milk allergy (Bock 1987;Eggesbo et al. 2001b;Gerrard et al. 1973;Hide & Guyer 1983;Host & Halken 1990;Schrander et al. 1993), but not all these reported reactions were confirmed by means of food challenges. Milk hypersensitivity data range from 1.1% in Spain (Eggesbo et al. 2001b), 2.1% in Denmark (Host & Halken 1990), 2.2% in the USA, (Bock 1987), 2.3% in the Netherlands (Schrander et al. 1993), 2.5% in the UK (Hide & Guyer 1983) to 7.5% in Canada (Gerrard et al.1973). 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 cow's 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 (Host 1994). 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) (Host et al. 1995;Iacono et al. 1998;Schrander et al.1993).

Population prevalence for soya allergy has not been widely studied, but it is estimated to be 0.3-0.4% and is commonly outgrown (Bock 1987). 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 (Bock & Atkins 1990).

About 0.2% (Bock 1987) -1.1% (Eggesbo et al. 2001a) 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 (Dannaeus & Inganas 1981). Deaths related to egg allergy have been reported (Bock, Munoz-Furlong, & Sampson 2001b).

Peanut is reported as the most common food causing severe IgE mediated reactions in children and adolescents in the USA and Europe (Bock, Munoz-Furlong, & Sampson 2001a;Eigenmann & Zamora 2002). It is estimated that 0.8% children in the USA (Sicherer, Munoz-Furlong, & Sampson 2003) and 1.5% children in the UK (Grundy et al. 2002) 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 (Assem et al. 1990;Ewan 1996). In a study performed by Lack and colleagues (Lack et al. 2003), 49 children out of 13971 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 (Fleischer et al. 2003). However, it has been suggested that it may recur (Busse et al. 2002). Allergy to tree nuts affects about 0.5% of the USA population (Sicherer, Munoz-Furlong, & Sampson 2003) 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 (Sicherer, Munoz-Furlong, & Sampson 2004b). 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 shell fish (Bernhisel-Broadbent, Scanlon, & Sampson 1992;Hansen et al. 1997;Sicherer, Munoz-Furlong, & Sampson 2004a) and this allergy is not generally outgrown (Solensky 2003).

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 (Dalal et al. 2002;Dalal et al. 2003;Lucas et al. 2004;Mattila et al. 2003). 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 (Kanny et al. 2001) and children (Bock 1987) 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.

1.4 Symptoms associated with food hypersensitivity

Symptoms that are most commonly associated with FHS can broadly be divided into symptoms associated with the skin, gastro-intestinal tract, respiratory system and systemic reactions. Symptoms experienced upon ingestion of a specific food may occur within minutes, hours or days of ingestion.

Ultimately, one would like to map the symptoms specifically against either immediate or delayed reactions or IgE mediated and non-IgE mediated reactions. However, this is not easy as many manifested symptoms (e.g. eczema) can occur as IgE or non-IgE mediated reactions or a mixed pattern of both. Furthermore, previous research utilising either OFCs or DBPCFCs clearly showed that some symptoms can be both immediate and delayed in nature (Hill et al. 1988). Table 1.1 highlights the reported symptoms most often associated with FHS in the literature. These symptoms were taken from papers utilising food challenges to diagnose FHS.

Table 1.1: Symptoms of FHS as reported in the literature.

Target organ	Symptoms	References
Skin	Pallor Erythema Pruritis Urticaria Angioedema Eczema Dermatitis Herpetiformis	(Bock 1987; Eggesbo et al. 2001a;Bock 1987;Isolauri & Turjanmaa 1996;Sampson & Ho 1997;Fuglsang et al. 1994;Hill et al. 1993;Niggemann et al. 1999;Medica, Zmak, & Persic 2003)
Gastro-intestinal tract	Oral Allergy Syndrome (OAS) Food protein enteropathy syndrome Gastro-oesophageal reflux Allergic eosinophilic gastroenteritis/oesophagitis Oral itch, throat itch, lip swelling Diarrhoea, nausea and vomiting Abdominal pain Enteropathy Proctocolitis Enterocolitis Coeliac disease Constipation	(Levy & Danon 2003;Ortolani et al. 1989;Hill et al. 1993; Latcham et al. 2003;Spergel et al. 2002; Hourihane et al. 1997;Bock 1987;Fuglsang et al. 1994;Hill et al. 1993;Sampson & Ho 1997;Eggesbo et al. 2001a;Anveden-Hertzberg et al. 1996; Bonamico et al. 1997;Majamaa et al. 1999a;Majamaa et al. 1999b)
Respiratory Tract	Heiner's Syndrome* Rhinorrhoea	(Fourrier 1997;Eggesbo et al. 2001a)
Multisystem	Anaphylaxis Exercise induced anaphylaxis	(Bock, Munoz-Furlong, & Sampson 2001a;Palosuo et al. 2003)
Controversial symptoms	Otitis media Hyperactivity Migraine/Abdominal migraine Enuresis	(Tikkanen et al. 2000;Bateman et al. 2004;Egger et al. 1992)
Other	Irritability Listless with other symptoms	(Hill et al.1993;Eggesbo et al. 1999)

* Food-induced pulmonary haemosiderosis (Heiner's syndrome) has been described previously as a syndrome characterised by recurrent episodes of pneumonia associated with lung infiltrates, haemosiderosis, blood in stools, anaemia and failure to thrive in young children. The offending foods reported most often are cows' milk, and also egg, and pork. Peripheral blood eosinophilia and IgG precipitating antibodies to cow's milk have been described in this syndrome, but the underlying immunological mechanisms are not clear (Host & Halken 2002).

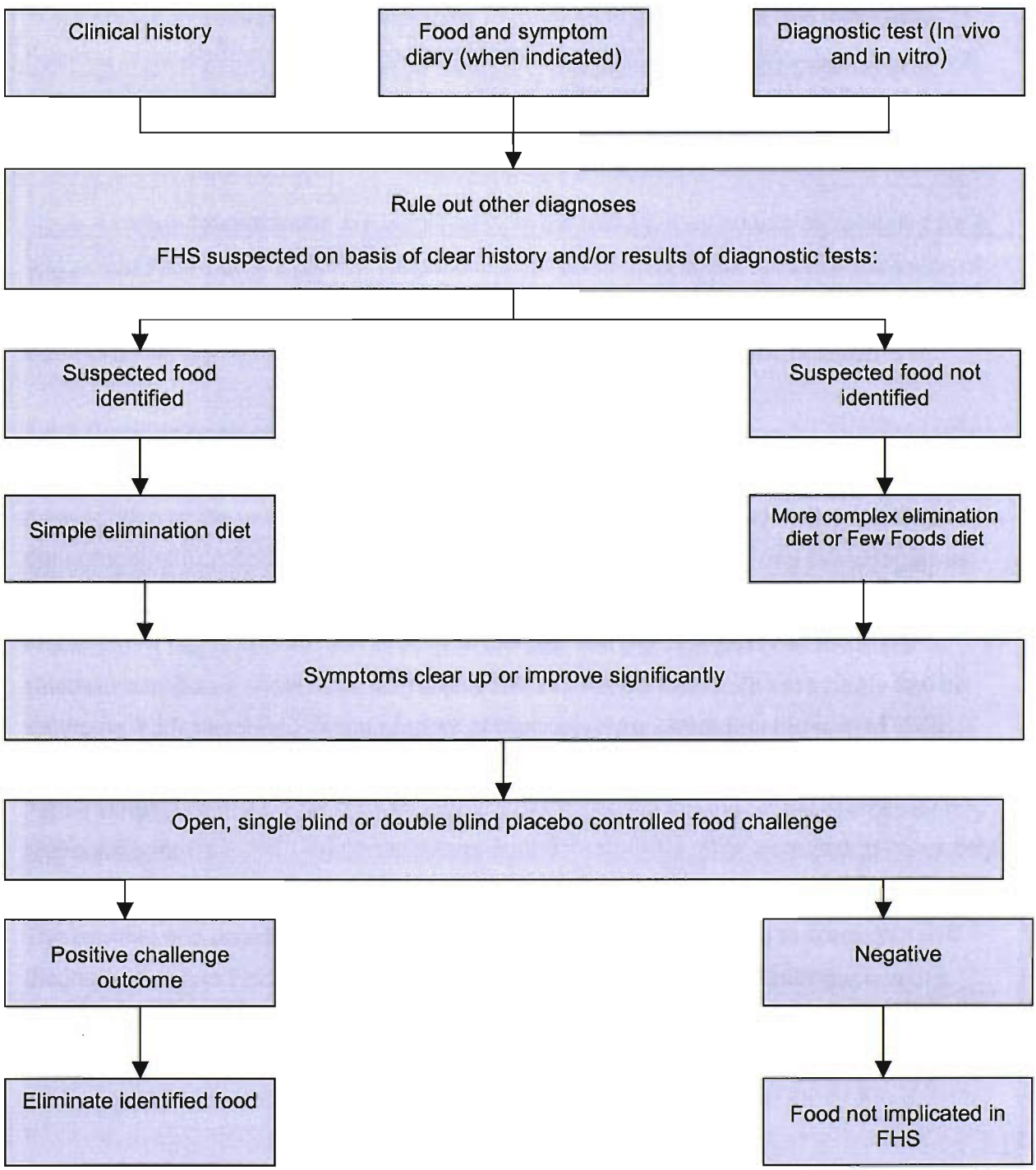
1.5 Diagnosis of food hypersensitivity

Correct diagnosis of FHS is important to ensure appropriate patient care and to accurately establish the population prevalence and incidence. Furthermore, false negative diagnoses can lead to the risk of ongoing symptoms with further (severe) reactions. False positive diagnoses on the other hand can lead to unnecessary restrictions on life style and possible disease from nutrient restriction (Christie et al. 2002;Eggesbo, Botten, & Stigum 2001;Sicherer, Noone, & Munoz-Furlong 2001). It has also been suggested that early

identification of children with FHS and atopic dermatitis may provide opportunities to prevent the development of asthma (Bender, Leung, & Leung 2003).

An algorithm of FHS diagnosis is shown in Figure 1.3. It can be noted that the diagnosis pathway starts with the clinical history alongside diagnostic tests and symptom diaries when indicated. When these diagnostic measures are suggestive of FHS an elimination diet is suggested. Upon improvement of symptoms, the patient may need to undergo an ORC test. Each of these will be discussed in detail focussing on food challenges.

Figure 1.3: Algorithm for the diagnosis of FHS (Muraro et al. 2004c)



1.5.1 Clinical history

Careful history taking and physical examination form the basis of diagnosis of FHS. Taking a history achieves two goals: 1) to make an accurate diagnosis based on the history and 2) to obtain useful information for performing a food challenge (Bock & Sampson 2003). It is clear from studies that good clinical diagnosis alone cannot correctly identify FHS as despite careful history taking, the correlation between suspected food allergy and food allergy as confirmed by DBPCFC is between 23% - 65% of patients with a positive skin prick test (SPT)/specific IgE and history (Grundy et al. 2002;Hill et al. 1988;Monti et al. 2002;Morisset et al. 2003).

The symptoms reported by the patient are paramount in making a correct diagnosis. Keeping accurate records of all ingested foods/beverages and any developed symptoms can therefore be helpful in the diagnosis of food allergy, although cause and effect can very rarely be established from diet diaries alone.

Once a certain food or foods are identified from the history, they should be excluded for a trial period based on the history. Diagnostic elimination diets could comprise exclusion of a certain food or using a substitute formula. However, in more complex cases a multiple exclusion diet or few foods diet may need to be incorporated as well.

1.5.2 Diagnostic tests

The sensitivity, specificity, positive predictive value and negative predictive value will give an indication of the usefulness of a test. Sensitivity can be expressed mathematically as the number of true positives divided by the sum of the true positives and false negatives. Specificity is a measure of the likelihood that a positive result is a true positive. A positive result from a highly specific test is likely to indicate that the individual has the disease, whereas a negative result does not reliably rule out the condition. The specificity can be mathematically described as the number of true negatives divided by the sum of the true negatives and false positives (Bateman 2000). The most desirable test is therefore both highly sensitive and specific. Unfortunately there is usually a trade off between specificity and sensitivity.

The positive and negative predictive values indicate a test's suitability to correctly diagnose or refute FHS. Positive predictive value is the proportion of individuals with a positive result who actually have the disease. The negative predictive value is the proportion of individuals with a negative result who are disease free.

At present, all in vivo and in vitro tests are compared to the current gold standard, the DBPCFC in terms of sensitivity, specificity, negative predictive value and the positive predictive value. The DBPCFC is considered to be the gold standard as it eliminates bias from both the clinician and patient.

1.5.2.1 Skin prick tests

This test measures specific IgE attached to mast cells in the skin, and is therefore used to detect IgE mediated food allergy. When performing SPT, glycerinated food extracts (1:10 or 1:20) weight per volume dilutions are placed on the skin and pricked with a lancet or needle. A positive (histamine) and negative (saline) control should always be used (Bernstein et al. 1988). The positive control gives an indication of skin reactivity and the negative control can identify patients with dermatographism. The size of the wheal caused by the food allergen should be interpreted in relation to the size of the negative control in order to make a correct diagnosis.

A positive SPT is considered to be one which has a 3 mm wheal in the presence of a negative control (Bock et al. 1977;Bock & Atkins 1990;Eigenmann & Sampson 1998). There is no lower age limit for performing a SPT. However, some researchers and clinicians may question the use of a 3 mm cut off point for infants under the age of three years. Menardo and colleagues demonstrated that wheal sizes in infants to both the positive control and allergen may be smaller and needs to be interpreted with caution, especially those younger than six months (Menardo et al. 1985). This argument is further supported by the fact that the histamine induced wheals in children increase 125% from 4 days - 2 years and 150% from 2-18 years indicating that skin reactivity may increase over time, affecting SPT wheal size (Sampson 1999).

The negative predicted value of SPT (>95%) is much higher than its positive predictive value (50%) (Isolauri & Turjanmaa 1996;Sampson & Albergo 1984). SPT could therefore be considered a good test although not a perfect test for excluding IgE-mediated food allergy, but it could only suggest IgE mediated allergy (when positive) due to the high rate of clinically insignificant positive SPTs. Foods with a high negative predictive value include egg, milk, wheat, peanut, tree nuts, fish, and shellfish and SPT with these foods could be very helpful when negative (Eigenmann & Sampson 1998).

One should, however, always remember that these tests are only applicable for IgE mediated disease and they do not prove or disprove the role of FHS in delayed type symptoms.

Recently, researchers have been suggesting the use of cut off points for the diagnosis of IgE mediated FHS based on wheal diameter, rather than using food challenges. Hill and colleagues defined food-specific SPT wheal diameters that were '100% diagnostic' for allergy to cow's milk (≥8 mm), egg (≥7 mm) and peanut (≥8 mm) in children with a median age of three years. The 95% CI for this data was calculated as 91% to 100% (Roberts & Lack 2005). In children less than two years of age, the corresponding weal diameters were ≥6 mm, ≥5 mm and ≥4 mm respectively (Hill, Heine, & Hosking 2004;Hill, Hosking, & Reyes-Benito 2001;Sporik, Hill, & Hosking 2000). It is worthwhile reflecting that, these cut off points were established against OFCs rather than the gold standard DBPCFC. Another important point to notice is that a number of children with negative SPT to egg and peanut ended up with positive responses to food challenges. This questions the high negative predictive value of SPT and suggests that a 3 mm or even 2 mm cut off point for SPT cannot completely rule out food allergy. The authors did unfortunately not mention whether these children with positive challenges and negative SPT (<3mm) presented with immediate or delayed symptoms. Delayed symptoms may be non-IgE mediated which will explain the negative SPT.

Eigenmann and colleagues determined wheal sizes for common food allergens that could accurately predict FHS with 95% confidence as compared against DBPCFC (Eigenmann & Sampson 1998). These positive cut off points were as follows: egg 4mm, milk 5mm, soy 3mm, wheat 3mm and peanut 6mm for children with a median age of 4-6 years. Positive challenges in children with negative SPT (<3 mm) were also seen in this group of patients. One should, however, take into account that the study sample was highly selective as all children suffered from atopic dermatitis, which could have influenced the results (Eigenmann & Sampson 1998). In another study with a highly selective sample of children (Verstege et al. 2005) suffering from atopic dermatitis, 95% and 99% predictive values for egg and milk were determined as 2.6 and 3.7 mm for egg and 2.7 and 3.7 mm for milk. Information regarding SPT decision points is summarised in appendix 1.1.

Using these diagnostic decision points can have an economical implication as it can greatly reduce the number of specific IgE tests and food challenges needed or even the number of patients prescribed an elimination diet for long periods of time. The decision points can therefore give a good indication of which children may not need to undergo food challenges. However, a SPT below the cut off point with a good history does not rule out an allergy and will still need to be investigated. Caution needs to be applied in extrapolating this data to other populations, as a number of factors can affect the reliability of the SPT.

The SPT result may differ with different operators and different techniques. Basomba and colleagues (Basomba et al. 1985) demonstrated that the variation coefficient could differ between 41% and 115% using three testing devices and three members of staff. In addition, quality of the extracts, including batch variability and extracts produced by different companies may affect the results of the SPT due to different concentrations of allergenic proteins (Sampson 1988a).

Another method of SPT involves the prick-to-prick testing. Prick-to-prick tests involve using fresh food or food extracts in order to perform a SPT (Ortolani et al.1989;Rosen et al. 1994;Zuberbier et al. 2004). A positive and negative control should be used just as when using commercial extracts. The main reason for using these tests are that food allergens of specifically fruit and vegetables may be destroyed during the preparation of commercial extracts, leading to false negative skin test results. Prick-to-prick tests are also useful when no commercial allergen extract is available e.g. spices.

Although prick-to-prick testing is sometimes used in the clinical setting, standardisation of this method is necessary in order to provide allergists with a universally comparable test. There is currently no evidence regarding the sensitivity, specificity, positive predictive value and negative predictive value of these tests.

In summary, SPT provide an easy method to screen for patients with an IgE-mediated sensitivity to foods. In general, allergens eliciting a wheal size of ≥ 3mm bigger than the negative control are considered positive, indicating (50% positive predictive accuracy) that the patient may have a true allergy to the food. The use of SPT in the diagnosis of IgE mediated food allergy can be optimised by using SPT sizes that are 'highly predictive' of food allergy in combination with a good clinical history. Setting these 'highly predictive' SPT sizes is however still in the developmental phase and needs to be determined for different foods, ages and population groups. A negative SPT is extremely useful (95% negative predictive value) in ruling out IgE mediated food allergy. This means that a small proportion of children may react immediately to foods to which they had a negative SPT. One main limitation of the SPT should not be ignored: SPT are not useful in the diagnosis of delayed type/non-IgE mediated food allergy or non-allergic FHS, basically due to the fact that IgE producing mast cells are not the main cells involved in the development of these symptoms.

1.5.2.2 Specific IgE tests

Specific IgE tests are performed by analysing blood samples of potentially allergic individuals. Specific IgE tests can be used in order to determine levels of circulating specific IgE to allergen in the circulation. The presence of specific IgE in the blood indicates that an individual is sensitised to an allergen, but not necessarily clinically allergic. This also applies to detection of mast cell bound IgE when performing SPT. Specific IgE tests used to be conducted by employing radio-allergo sorbent tests (RAST). Nowadays, specific IgE is measured as fluorescent enzyme-labelled IgE (CAP-RAST FEIA). This test seems to be more sensitive (89%) and specific (91%) according to the manufacturers (Pharmacia 2004), has a wider measuring range to better reflect the biological response, and shows a higher reproducibility than the older RAST test. There is no agreed level above which specific IgE measured as kilo units of allergen per litre are considered positive. Some clinicians grade specific IgE levels between levels 1- 6 and would consider level 2 and above as positive in clinical practice, although this is not evidence based. In general, the higher the level of specific IgE the more likely the child is to be allergic, but there is no clear cut-off point between being allergic or not. Specific IgE levels of >15 kilounits of allergen per litre (kU_A/L) for milk, >7 kU_A/L for egg and >14 kU_A/L for peanut corresponds with grade 3-6 (personal communication Sheffield laboratories).

Therefore, in order to establish the reliability of specific IgE tests, Sampson and colleagues compared test results with DBPCFC outcome (Sampson 2001b). High positive predictive values (95%) were determined for milk (32 kU_A/L), peanut (15 kU_A/L), egg (6 kU_A/L) and fish (20 kU_A/L). The 95% CI for the peanut cut-off point was determined as 71% - 100% (Roberts & Lack 2005). Basically, specific IgE levels above these points indicated that there is a 95% likelihood that the child will be allergic to that food. One should however take into account that this was a population with severe eczema and 90% came from atopic families, known to be associated with high IgE levels. In a follow up study, they validated the previously established diagnostic decision points (Sampson & Ho 1997) by determining their ability to correctly predict DBPCFC outcome. Using the combined data of these two studies (Sampson 2001b;Sampson & Ho 1997), high predictive (95%) cut-off points were further narrowed down to milk (15 kU_A/L), peanut (14 kU_A/L), egg (7 kU_A/L), fish (20 kU_A/L), soya (65 kU_A/L) and wheat (80 kU_A/L). Unfortunately, during this follow-up study, many parents refused a food challenge when they were informed that their child's food specific IgE concentrations were above the 95% positive decision point previously set. Therefore only limited numbers of food allergy were confirmed by DBPCFCs in this study, ranging from 2-34% for milk, egg, fish and peanut.

As the previously set diagnostic predictive value for soy and wheat were poor, most children underwent DBPCFCs to these two foods. The use of these curves is however limited at present, as they may need to be determined for each population. These curves are also more useful in indication of FHS than ruling out FHS.

A number of studies were performed investigating diagnostic decision points for egg. These studies demonstrated a cut off level to egg white that predicts a clinical allergic reaction with more than 95% certainty in patients with egg allergy: 6 kU_A/l (Sampson & Ho 1997), 0.35 kU_A/l in children under two years (Boyano-Martinez et al. 2002), 1.5 kU_A/l (including some children under two years) (Osterballe & Bindslev-Jensen 2003) and 17.5 kU_A/l (Roehr et al. 2001). Three important points were demonstrated by these studies. Cut off levels to predict challenge outcome vary between centres; cut off levels differ according to the test used and that has important implications as new methods for detecting specific IgE levels are being developed; most importantly, specific IgE levels give no indication of the dose of allergenic food the patient may react to.

The preference for using either SPT or specific IgE tests varies between clinicians and researchers. SPT is often regarded as the method of choice due to the ease of use, low cost and immediate results (Bock & Sampson 2003). However, specific IgE tests of any type are very useful in children with severe skin disease, dermatographism or when it is impossible to discontinue antihistamine.

In summary, detection of specific IgEs in the serum of patients may indicate the presence of IgE mediated allergy (as with SPT). Previously, RAST tests were used, but this is now giving way to quantitative measurement of IgE by means of the CAP-FEIA system. Diagnostic levels with a 95% predictive value have been set for milk, egg, peanut and fish by a number of investigators as summarised in Appendix 1.1. One must take into account that these tests may be useful in confirming IgE mediated food allergy, but cannot rule out food allergy due to the low negative predictive values for particularly milk and egg. Another important point is that these values are set on a curve and that in the case of a carefully taken history, a specific IgE level with 60% predictive value may be sufficient to confirm an IgE mediated food allergy. As with the diagnostic decision points set for SPT, the data needs to be assessed for different patient groups, age groups and foods. Specific IgE tests cannot be used to investigate non-IgE mediated FHS or non-allergic FHS.

1.5.2.3 Other tests

A number of tests are still in the experimental stage and not routinely used in the diagnosis of FHS. These tests include the atopy patch test (Niggemann, Reibel, & Wahn 2000;Spergel et al. 2002), intradermal testing (Fox et al. 1999), bowel wall thickening (Kino et al. 2002), basophil histamine release (Crockard & Ennis 2001), intestinal cell activity following direct application of food antigen (Bischoff et al. 1997), IgE in stools (Andre et al. 1995), Immunoglobulin G (IgG) tests (Jensen-Jarolim et al. 1992), Vegatesting (Krop et al. 1997) and Multidetection assays (Moneret-Vautrin, Kanny, & Fremont 2003).

1.5.3 Food challenges

The accepted standard in objectively diagnosing FHS is a food challenge and in particular the DBPCFC. During food challenges, the suspected food is given to the individual in a titrated fashion until a clinical reaction occurs (Niggemann 2004). Food challenges can be used to prove or disprove FHS (Bock & Atkins 1990), determine whether a FHS is outgrown (Bock 1987), determine tolerance levels (Taylor et al. 2004) or to determine cross-reactivity (Crespo et al. 1995). Food challenges can also be used in conjunction with other tests to determine risk scales, which could determine how likely a patient is to be truly suffering from FHS.

Details regarding performing food challenges in the literature can be obtained from four main sources: 1) Guidance by experts, 2) Procedure manuals, 3) Position statements, and 4) Published research literature. Table 1.2 summarises the evidence in this area under these four sources.

Table 1.2: Publications describing food challenges

Title
1. Guidance by experts
• Immunologically mediated food allergy: the importance of food challenge procedures (Sampson 1988b) • Blind food challenge testing with wide-open eyes (Bahna 1994) • Food allergy: when and how to perform oral food challenges (Sicherer 1999) • What safety measures need to be taken in oral food challenges in children? (Reibel et al. 2000) • Standardization of double-blind, placebo-controlled food challenges (Bindslev-Jensen 2001) • Diagnosis of food allergy: the oral provocation test (Muraro 2001) • Use of food-challenge tests in children (Sampson 2001a) • Role of oral food challenges in the diagnostic work-up of food allergy in AEDS (Niggemann 2004) • Masking foods for food challenge: practical aspects of masking foods for a double-blind, placebo controlled food challenge (Huijbers et al. 1994) • Double Blind Placebo Controlled Food Challenges: The dietitians perspective (Carter 1995) • Development and validation of challenge materials for double-blind, placebo-controlled food challenges in children (Vlieg-Boerstra et al. 2004) • Practical aspects of preparation of foods for DBPCFC (Noe et al. 1998)
2. Procedure manuals
• Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual (Bock et al. 1988) • Workshop on Experimental Methodology for Clinical Studies of Adverse Reactions to Foods and Food Additives (Metcalfe & Sampson 1990) • AGA technical review on the evaluation of food allergy in gastrointestinal disorders. American Gastroenterological Association (Sampson, Sicherer, & Birnbaum 2001) • A consensus protocol for the determination of the threshold doses for allergenic foods: how much is too much? (Taylor et al. 2004)
3. Position statements
• Standardization of food challenges in patients with immediate reactions to foods—position paper from the European Academy of Allergology and Clinical Immunology (Bindslev-Jensen et al. 2004)
4. Published research literature
• Distinct patterns of cow's milk allergy in infancy defined by prolonged, two stage double-blind, placebo-controlled food challenges (Canada) (Baehler et al. 1996). • Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life (USA). (Bock 1987). • Evidence of very delayed clinical reactions to cow's milk in cow's milk intolerant patients (Denmark) (Carroccio et al. 2000). • The prevalence of allergy to egg: a population based study in young children; The prevalence of CMA/CMPI in young children: the validity of parentally perceived reactions in a population-based study (Denmark) (Eggesbo et al. 2001a;Eggesbo et al. 2001b). • Natural history of cows' milk allergy in children: immunological outcome over 2 years (Australia) (Hill et al.1993). • A prospective study of cow milk allergy in Danish infants during the first 3 years of life. Clinical course in relation to clinical and immunological type of hypersensitivity reaction (Host & Halken 1990). • Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis. (Finland) (Isolauri & Turjanmaa 1996). • Outcome of double-blind, placebo-controlled food challenge tests in 107 children with atopic dermatitis.(Germany) (Niggemann et al. 1999). • Dose-response in double-blind, placebo-controlled oral food challenges in children with atopic dermatitis. (USA) (Sicherer, Morrow, & Sampson 2000). • Diagnosis of IgE-mediated food allergy among Swiss children with atopic dermatitis (Eigenmann & Calza 2000). • Prevalence of adverse reactions to food in Germany - a population study (Zuberbier et al. 2004). • The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: The German Infant Nutritional Intervention Study, a randomized double-blind trial (von Berg et al. 2003).

Food challenges can be performed as open food challenges (OFCs), single blind placebo controlled food challenges (SBPCFCs) or DBPCFCs.

Food challenges can be divided into three basic steps, planning and patient information prior to the challenge, performing the food challenge (methodology) and after care. When planning the food challenge, the clinician or dietitian involved should be clear regarding the type of challenge that will be used and the challenge procedure that will be used such as the dose and duration. The challenge setting and location should be well equipped with all safety measures in place. Patients should be well informed prior to the challenge regarding food avoidance and which medications should not be used.

During the challenge, food is given to the patient in increasing doses and the challenge should be medically supervised. Sufficient after care should be provided to the patient once the challenge is completed. The next section will focus on the different type of challenges and challenge procedures such as, history taking, elimination period, the food and dose to use as well as challenge duration.

1.5.3.1 Open food challenges

During an OFC, both the patient and the clinician performing the challenge know the ingredients of the challenge food e.g. peanut flapjack used for a peanut challenge. According to the literature presented in table 1.2, there are a number of instances where an OFC would be suitable for the diagnosis of FHS.

OFCs are very useful when the history suggests the challenge outcome may be negative. OFCs are also indicated (by opinion rather than evidence) when an immediate, objective reaction is suspected (Bock 2000;Sicherer 1999). The food proteins involved in oral allergy syndrome are extremely heat labile, which poses problems with masking the foods. It is therefore acceptable to use an OFC when dealing with oral allergy syndrome (OAS) (Bindslev-Jensen et al. 2004). As mentioned before, some clinicians dealing with FHS, claim that OFCs are acceptable when dealing with young children under the age of three as the psychological factors involved in reported FHS should be minimal (Bahna 1994;Muraro 2001). However, the power of the human mind should never be underestimated and even in young children, observations during food challenges may be misleading (Bock 1986).

Finally, OFCs could be performed prior to the DBPCFC (Bindslev-Jensen et al. 2004) as these OFCs can give useful information regarding the challenge dose needed (for the

DBPCFC), when the history regarding symptoms developed and food ingested is unclear (Bock 2000;Carter 1995).

OFCs may occasionally be performed at home rather than in the hospital providing that there is no risk of the patient developing immediate severe symptoms (Bock et al. 1988;Sicherer 1999).

1.5.3.2 Single blind placebo controlled food challenges

For single blind placebo controlled food challenges (SBPCFC), the health professionals involved should be able to administer the challenge without the patient knowing which dose is active and which is placebo. Sufficient masking of the challenge food is therefore very important. During SBPCFC, foods will be masked and just as in a DBPCFC, an active and placebo challenge will take place.

SBPCFC are particularly useful when performing food challenges in children or adults that have major concerns about ingesting the particular food (Bahna 1994;Bock 2003). Some authors also suggest the use of single blind challenges to precede the DBPCFC in research studies or when diagnosing FHS in patients with a long list of possible offending foods (Bock 2000). However, single blind challenges can be performed as DBPCFCs with almost no extra effort, and although their use is clear in clinical practice, a DBPCFC should be the method of choice in research studies (Bindslev-Jensen et al. 2004).

1.5.3.3 Double blind placebo controlled food challenges

The DBPCFC is internationally recommended as the 'gold standard' for both research and clinical diagnostic evaluations (Bock et al. 1988). The first DBPCFC was performed by Loveless in 1950 (Loveless 1950) and the principles of these first challenges were refined by May in 1973 (May 1976). One of the strengths of the DBPCFC is that neither the patient nor the investigator knows when the active or the placebo challenge is performed. It therefore rules out measurement and reporting bias from the observer and the psychological effect from the patient. There are, however, some who point out problems with this method. It is claimed that the test can be labour intensive and tedious. Some clinicians administer the challenge food in a capsule and this concentrated source of dried food could provoke serious reactions in some children (Carter 1995;Hide 1994;Hill & Hosking 1991).

There are several protocols that can be used for the administration of the DBPCFC. One approach is to have a single day for the active and a separate day for the placebo

challenge (Niggemann et al. 2004). This approach is however not always possible due to time constraints and often in practice one challenge is performed in the morning and another in the afternoon (Sicherer, Morrow, & Sampson 2000;Zeiger et al. 1999). The limitation of this approach is that slow or delayed onset symptoms could be missed or confused. Another approach is to interchange the active and placebo doses (Wensing et al. 2002). This procedure may be useful when studying subjective or vague symptoms that are reported to begin promptly after ingestion of the incriminating food.

Despite the many publications on food challenges (summarised in Table 3), no universally accepted protocols for OFCs, SBPCFCs or DBPCFCs have been agreed on.

1.5.3.4 Open food challenges vs. double blind placebo controlled food challenges

Researchers and clinicians often claim that there is a consensus regarding the use of OFCs and DBPCFCs in paediatric populations. They suggest that OFCs are acceptable in children under the age of three years and the DBPCFC should be used in older children (Bahna 1994;Bindslev-Jensen et al. 2004;Muraro 2001;Niggemann et al. 2005). When scrutinising the literature (Table 1.3) it is obvious that there is no consensus regarding this matter.

Table 1.3: Type of challenges used for cow's milk, egg, wheat, soy and peanut

Food	Symptoms studied	Method of challenge	Reference
Milk	Any	DBPCFC	(Baehler, et al. 1996)
	Eczema	DBPCFC	(Niggemann et al. 1999)
	Any	DBPCFC	(Carroccio et al. 2000)
	Eczema	DBPCFC	(Sicherer, Morrow, & Sampson 2000)
	Any	OFC	(Hill et al. 1993)
	Any	OFC and/or DBPCFC	(Bock 1987)
	Any	OFC and/or DBPCFC	(Eggesbo et al. 2001b)
	Any	OFC and/or DBPCFC	(Host & Halken 1990)
	Eczema	OFC and/or DBPCFC	(Isolauri & Turjanmaa 1996)
	Any	OFC and/or DBPCFC	(Zuberbier et al. 2004)
	Any	OFC and/or DBPCFC	(Eigenmann & Calza 2000)
Egg	Eczema	DBPCFC	(Niggemann et al. 1999)
	Eczema	DBPCFC	(Sicherer, Morrow, & Sampson 2000)
	Any	OFC	(Sporik, Hill, & Hosking 2000)
	Asthma	OFC and DBPCFC	(Yazicioglu et al. 1999)
Peanut	Eczema	DBPCFC	(Sicherer, Morrow, & Sampson 2000)
	Any	DBPCFC	(Torr et al. 2002)
	Any	OFC	(Sporik, Hill, & Hosking 2000)
	Any	OFC	(Grundy et al. 2002)
	Any	OFC	(Pucar et al. 2001)
Soy	Eczema	DBPCFC	(Niggemann et al. 1999)
	Eczema	DBPCFC	(Sicherer, Morrow, & Sampson 2000)
	Any	DBPCFC	(Zeiger et al. 1999)
Wheat	Eczema	DBPCFC	(Niggemann et al. 1999)
	Eczema	DBPCFC	(Sicherer, Morrow, & Sampson 2000)
	Any	OFC	(Majamaa et al. 1999b)

Only one study has compared the OFC with the DBPCFC. Kaila et al (Kaila & Isolauri 1997) compared OFCs with DBPCFCs in a population of children (2 - 36 months) with suspected cow's milk allergy (although a within case comparison was not made). More infants were diagnosed with cow's milk allergy after OFCs (56%) than DBPCFCs (44%). One interesting finding in this study was that the parents considered the DBPCFC a more definite test than the open challenges. In children who underwent OFCs, 20/85 parents disagreed with the challenge outcome (10 with positive and 10 with negative challenges). In contrast with this, in those children who underwent DBPCFCs only 4/71 parents disagreed with the challenge outcome (1 with a positive and 3 with negative challenges). This difference was highly significant (χ^2 8.192; p=0.004). This raises the question as to whether parents will follow avoidance advice when they are not convinced by the results of the diagnostic method.

1.5.4 Procedural issues on food challenges

For the purpose of this literature review, only papers utilising food challenges for diagnostic purposes are included. Publications looking at tolerance levels and cross-contamination are excluded.

1.5.4.1 History taking prior to the food challenge

It is important to obtain sufficient information from the patient in order to plan a food challenge. This information enables the clinician or dietitian to mimic the patient's history in terms of the possible foods causing the reactions, challenge duration, dose needed to elicit the reaction and any other factors that should be taken into account. Insufficient information or an inaccurate history may lead to dismissal of patient symptoms or false negative challenges.

Procedure manuals and text books on FHS recommend that the following information should be obtained during history taking: (Baehler et al. 1996;Bock & Sampson 2003;Muraro 2001;Sicherer 2001)

- The age of patient to determine how difficult it may be to perform the food challenge and to help in identifying the possible food causing the symptoms.
- The type of food or foods causing reported symptoms e.g. raw egg versus cooked egg.
- The age of onset of symptoms as well as the frequency and reproducibility of the reaction.
- The time of onset of symptoms.
- The clinical manifestation and duration of the symptoms.
- The quantity of food causing symptoms in order to prevent false negative food challenges.
- A thorough description of the most recent reaction is also very important in designing challenges. The details of the most recent reaction may be more helpful than those of more distant reactions.
- A list of foods that are well tolerated and that could be used as placebo or vehicle.

Sometimes, more than one food or factor is needed to elicit a positive challenge outcome e.g. more than one food eaten together (Aihara et al. 2001), exercise induced anaphylaxis (Aihara et al. 200;1Fiedler, Zuberbier, & Worm 2002) or concomitant drug intake (Sicherer 2003).

1.5.4.2 Elimination period

Once a certain food or foods are identified from the history and food diaries, they should be excluded for a trial period based on the history. The period of exclusion is determined by the symptoms and symptom pattern of the patient. There is no consistency in the literature (Table 1.4) on the period of elimination and it can vary between two and six weeks or a minimum of 24 hours for additives (Bock et al. 1988).

Table 1.4: Elimination periods used in previous research papers.

Food	Symptoms studied	Elimination period	Reference
Milk	Any	6 weeks	(Baehler et al. 1996)
	Eczema	5 days	(Niggemann et al. 1999)
	Any	4-6 weeks	(Carroccio et al. 2000)
	Eczema	1-2 weeks	(Sicherer, Morrow, & Sampson 2000)
	Any	Up to 6 wks*	(Hill et al. 1993)
	Any	4 weeks	(Host & Halken 1990)
	Eczema	4 weeks	(Isolauri & Turjanmaa 1996)
	Any	3 – 7 days	(Zuberbier et al. 2004)
	Any	3-4 weeks	(Eigenmann & Zamora 2002)
Egg	Eczema	5 days	(Niggemann et al. 1999)
	Eczema	1-2 weeks	(Sicherer, Morrow, & Sampson 2000)
	Any	Up to 6 wks*	(Sporik, Hill, & Hosking 2000)
	Asthma	1 week	(Yazicioglou et al. 1999)
Peanut	Any	Up to 6 wks*	(Sporik, Hill, & Hosking 2000)
Soy	Eczema	5 days	(Niggemann et al. 1999)
		1-2 weeks	(Sicherer, Morrow, & Sampson 2000)
Wheat	Eczema	5 days	(Niggemann et al. 1999)
		1-2 weeks	(Sicherer, Morrow, & Sampson 2000)
		3-4 weeks	(Majamaa et al. 1999b)

* depending how long it takes for the symptoms to go into remission

1.5.4.3 Challenge dose

Challenge doses used in previous research studies (Table 1.5) vary widely and will be discussed in the following section.

Table 1.5: Food challenge doses used in the diagnosis of FHS

Food	Type of Challenge	Dose	Duration	Reference
Milk	DBPCFC	1 drop, 0.5, 1, 2.5, 5, 10, 20, 30, 60, >210 ml	8 days	(Baehler et al. 1996)
	DBPCFC/OFC	Increasing increments ending with a total dose of 8g of the dried food	1 day	(Bock 1987)
	OFC	0.5, 2.5, 5, 10, 20, 30, 120 ml, 240 ml, >450ml/day	4 days	(Hill et al. 1993)
	OFC or DBPCFC	1,5,10,50, 100ml until normal intake	7 days	(Isolauri & Turjanmaa 1996)
	DBPCFC	Divide final dose (8-10g) into: 1%, 2%, 5%, 10%, 20%, 20%, 20%, 22%	1 day	(Sicherer et al. 2000)
	DBPCFC	Divide final dose (8-10g) into: 1%, 2%, 5%, 10%, 20%, 20%, 20%, 22%	1 day	(Eigenmann & Zamora 2002)
	DBPCFC	0.1, 0.3, 1.0, 3.0, 10.0, 30.0 up to 100 ml	48 hour	(Niggemann et al. 1999)
	OFC or DBPCFC	3 protocols: 1 drop doubled every 30 min till 81 ml reached or 1 ml doubled every 30 min till 180 ml reached or 5 ml doubled every 30 min till 380 ml reached	Up to 5 days	(Eggesbo et al. 2001b)
	DBPCFC	5 ml building up to the equivalent of a full feed over 3 hours	Up to 4 weeks	(Carroccio et al. 2000)
	OFC	Breastfed infants: mothers instructed to drink 0.5 l milk per day Formula fed infants: 5, 10, 20, 40 ml up to total dose of 155 ml	> 1 day	(Host & Halken 1990)
Egg	OFC	1/8,1/4,1/2,1 tsp up to 1 egg white	1 week	(Sporik, Hill, & Hosking 2000)
	DBPCFC/OFC	Increasing increments ending with a total dose of 8g of the dried food	1 day	(Bock 1987)
	DBPCFC	Divide final dose (8-10g) into: 1%, 2%, 5%, 10%, 20%, 20%, 20%, 22%	1 day	(Sicherer, Morrow, & Sampson 2000)
	OFC or DBPCFC	1 g doubled every 30 min till 16 g reached or 7.5 ml doubled every 30 min till 60 g reached	4 days	(Eggesbo et al. 2001a)
	DBPCFC and OFC	1 whole raw egg	4 days	(Yazicioglu et al. 1999)
Soya	DBPCFC	Divide final dose (8-10g) into: 1%, 2%, 5%, 10%, 20%, 20%, 20%, 22%	1 day	(Sicherer, Morrow, & Sampson 2000)
	DBPCFC/OFC	Increasing increments ending with a total dose of 8g of the dried food	1 day	(Bock 1987)
Wheat	DBPCFC	Divide final dose (8-10g) into: 1%, 2%, 5%, 10%, 20%, 20%, 20%, 22%	1 day	(Sicherer, Morrow, & Sampson 2000)
	DBPCFC	10 g wheat protein masked in 100 ml casein: 0.1, 0.3, 1.0, 3.0, 10.0, 30.0 up to 100 ml every 30 min	48 hours	(Niggemann et al. 1999)
	DBPCFC/OFC	Increasing increments ending with a total dose of 8g of the dried food	1 day	(Bock 1987)
Variety of foods	OFC or DBPCFC	No information provided	1 day	(Zuberbier et al.2004)
	OFC or DBPCFC	Started with small dose until 8 g of food tolerated as a single dose	1 day	(Bock 1987)

Starting dose

The quantity and timing of the challenge doses are determined by the patient's history, reason for performing food challenge e.g. diagnostic or threshold studies and available data from the literature (Bindslev-Jensen et al. 2004). There is however, no recommended "starting dose" that should be used for all patients/challenges. For example the starting dose for milk challenges have varied in the past between 1 drop (Baehler et al. 1996;Eggesbo et al. 2001b;Hill et al. 1993), less than indicated by the history (Bock 1987), 1 ml (Isolauri & Turjanmaa 1996) 5 ml (Carroccio et al. 2000;Host & Halken 1990), or 100 mg (Sicherer, Morrow, & Sampson 2000).

Clearly, the starting dose also will differ according to the reason for performing the food challenge e.g. diagnosis, determining tolerance or determining a threshold level. For egg, starting doses varied between 1/8 of lightly boiled egg (Sporik, Hill, & Hosking 2000), 100 mg of raw egg (Niggemann et al. 1999), 100 mg of dried egg white (Sicherer, Morrow, & Sampson 2000), or 1 g egg in muffin/flapjack (Eggesbo et al. 2001a). The soya challenges have started with one drop (Zeiger et al. 1999), 0.1 ml (Niggemann et al.1999) and 100 mg (Sicherer, Morrow, & Sampson 2000) in three studies and similar dosages for wheat were used in the studies by Sicherer (Sicherer, Morrow, & Sampson 2000) and Niggemann (Niggemann et al. 1999). For peanut, the starting doses used were 1/32 of a flapjack (1/4 of a peanut) (Grundy et al. 2002), 100 mg (Sicherer, Morrow, & Sampson 2000), 10 – 50 mg (Pucar et al. 2001), 500 mg (Torr et al. 2002), 1/8 teaspoon peanut butter (Sporik, Hill, & Hosking 2000).

Some clinicians prefer to start the challenge, with a labial rub of the lip. The development of symptoms is considered a positive test and a negative labial rub can be followed by the oral challenge doses (Rance & Dutau 1999).

Dose increments

For immediate type symptoms it has been suggested that the dose may be doubled at each interval, guided by the patient's history. A time-span of 15 – 30 minutes can be allowed between each dose (Bock 1987;Eggesbo et al. 2001b;Niggemann et al. 1999;Sicherer, Morrow, & Sampson 2000). The dose can also be increased logarithmically (Bindslev-Jensen et al. 2004). The most important consideration in deciding the timing of the dose increments should be that the timing between each dose should be sufficient to allow symptoms to develop.

For the diagnosis of slow-onset or delayed symptoms, usually just one dose of food per day is recommended (Baehler et al. 1996;Carroccio et al. 2000;Isolauri & Turjanmaa 1996), although some studies used a gradual increase of the dosages after day one of the challenge (Eggesbo et al. 2001b;Hill et al. 1993;Sporik, Hill, & Hosking 2000).

Total versus final dose

Great confusion exists regarding whether the total dose or final dose should be used when dealing with immediate type symptoms. One of the main problems with extrapolating data from previous research is the difficulty in deciding what the "final", "total" or "top" dose is as the challenge protocols vary widely.

Some researchers use a *total* of 8-10g of the dried food for challenge purposes (Sampson 2001b;Sicherer, Morrow, & Sampson 2000) whereas others (Bock 1987;Bock & Atkins 1990;Eigenmann & Calza 2000;Isolauri & Turjanmaa 1996;May 1976;Niggemann et al. 1999) used 8g as the *final* dose, thus giving about 18g dried food in total.

According to the publication "Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: A Manual", (Bock et al.1988) the challenge should continue until 8 -10g of the dried food is ingested as a *single* dose, thus providing a total dose of 15 – 20g.

In another document "Workshop on Experimental Methodology for Clinical Studies of Adverse Reactions to Foods and Food Additives"(Metcalfe & Sampson 1990) the authors state, "When 8 -10 gm of dried food has been administered without the production of symptoms, the challenge may be considered negative".

The latest position paper by EAACI recommends that the top dose should be "the normal daily intake in a serving of the food in question, adjusted for the age of the patient" (Bindslev-Jensen et al. 2004). In the UK, information regarding normal portion sizes for specific age groups can be obtained from the National Dietary and Nutritional Surveys performed in 1995 and 2000 (Gregory et al. 1995;Gregory et al. 2000).

When using real food as opposed to dried food, it is recommended that 60 – 100 g of wet food should be used for challenge purposes.

In principle, the food challenge should provide a sufficient amount of the allergenic food to rule out food allergy. In some cases however, subsequent reactions may still be

experienced at home, even after consumption of a normal portion of food on the challenge day (Caffarelli & Petroccione 2001).

Apart from the amount reported by the history, there are no specific recommendations regarding the dose used when performing food challenges to diagnose delayed symptoms such as eczema or constipation, (Bock et al. 1988). This raises practical issues where the patient is a very vague historian. Another difficult area is with infants suffering from eczema. It is not clear in most cases whether the eczema is caused by a single dose of a food or the total daily consumption of a food. Table 1.6 summarises the final dose use in previous publications.

Table 1.6: Final dose used in food challenges

	Milk	Egg	Wheat	Soya	Peanut
Immediate Symptoms	2.2 g (Sicherer, Morrow, & Sampson 2000)	2.2g dried egg white (Sicherer, Morrow, & Sampson 2000)	NA	2.2 g of dried soya milk (Sicherer, Morrow, & Sampson 2000)	From 2.2 g (Sicherer, Morrow, & Sampson 2000),
	100 ml (Niggemann, et al. 1999)	16 – 60 g egg (Eggesbo et al. 2001a)	NA	100 ml of soya milk (Niggemann et al. 1999)	8-10 g (Kagan et al. 2003)
	Full feed (Carroccio et al. 2000)	30ml raw egg (Niggemann et al. 1999)	NA	10 g soya milk powder (Zeiger et al. 1999)	15 g (Torr et al. 2002)
	8 g dried food (Bock & Atkins 1990)	8 g dried food (Bock & Atkins 1990)	8 g dried food (Bock & Atkins 1990)	8 g dried food (Bock & Atkins 1990)	8 g dried food (Bock & Atkins 1990)
	60 ml (Baehler et al. 1996)	1 white egg followed by 1 egg yolk (Sporik, Hill, & Hosking 2000)	NA	NA	7 teaspoons (Sporik, Hill, & Hosking 2000).
	155 ml (Host & Halken 1990)	NA	NA	NA	NA
Delayed symptoms	child's usual intake (Baehler et al. 1996;Hill et al. 1993;Host & Halken 1990;Isolauri & Turjanmaa 1996)	gave the children 45 ml of raw egg (Niggemann et al. 1999),	10g wheat flour (Majamaa et al. 1999a).	NA	NA
	Normal daily intake (Host & Halken 1990)	1 cooked egg white; 1 cooked egg yolk (Hill et al. 1993)	NA	NA	NA
	100 ml/day (Niggemann, et al. 1999)	NA	NA	NA	NA
	child's usual intake or at least 200 -210 ml/day (Baehler et al. 1996;Isolauri & Turjanmaa 1996)	NA	NA	NA	NA
	360 ml (Eggesbo et al. 2001b)	NA	NA	NA	NA
	120 ml (Hill, et al. 1993)	NA	NA	NA	NA

In summary, it is unclear whether we should we be looking at the total or final dose and how much food should be used. The only data available regarding the false negative rate of food challenges was reported by Sicherer (Sicherer, Morrow, & Sampson 2000) and Caffarelli (Caffarelli & Petroccione 2001). In the study by Sicherer et al, (Sicherer, Morrow, & Sampson 2000), the percentages of children with eczema reacting after the final dose of the DBPCFC (total dose of 8g dried food) were egg 11%, milk 12%, soy 19%, wheat 12.5%, peanut 8.7%, and fish 25%. However, Sampson (Bock & Sampson 2003) claims this figure to be 1% based on symptoms of both allergic and non-allergic FHS.

Caffarelli and colleagues mention in a letter to the Lancet (Caffarelli & Petroccione 2001) that they have experienced "false negative food challenges" after conducting food challenges. Apparently, five children (out of 193) developed symptoms when the same food was eaten at home the day after the challenge even though the last three doses were equal to an average daily intake. In the absence of IgE-mediated mechanisms, this could be explained, but all these children had a positive SPT and experienced immediate type symptoms when given the food at home.

1.5.4.4 Challenge duration

There is relatively little research on how long a challenge should be. It has been suggested that when dealing with immediate type symptoms, a positive reaction should be obtained within two hours (Bock 1987;Sicherer, Morrow, & Sampson 2000). A longer challenge period (1 – 4 weeks) is recommended when looking for delayed reactions (Baehler et al. 1996;Isolauri & Turjanmaa 1996;Majamaa et al. 1999a).

In the majority of cases, especially when dealing with objective symptoms, one active and one placebo challenge should be sufficient, due to the small number of patients reacting to the placebo (Hourihane et al. 1997;Jansen et al. 1994;Niggemann et al. 1999;Zuberbier et al. 2004). However, in cases where patients present with subjective symptoms, three active and placebo dosages or three plus two may be used (Briggs et al. 2001;Gellerstedt et al. 2004;Niggemann 2004).

The timing between two challenges should allow for symptoms to develop and/or subside as well as taking the disease pattern into account. Guidance in papers and procedure manuals recommends a waiting time of 3-4 hours, allowing therefore more than two hours, when dealing with immediate symptoms and at least one week when dealing with delayed symptoms (Bindslev-Jensen et al. 2004;Bock et al.1988;Muraro 2001).

1.5.4.5 Challenge food used

In open challenges, dried, cooked, or raw food as indicated by the history, should be used (Bindslev-Jensen et al. 2004). Lidman and colleagues established that 7% of children had a reaction to raw or less well cooked egg, following a negative challenge to cooked egg (Lidman et al. 2004). In DBPCFC, many researchers use dried food for the challenge (Sicherer, Morrow, & Sampson 2000). However, as with OFCs, real food, or the food as indicated by the history, would be a preferred option in order to mimic the history as close as possible (Carter 1995;Vlieg-Boerstra et al. 2004).

Any vehicle used for masking the food for a blind challenge, must enable the clinician to perform a truly blind challenge, masking the smell, flavour and texture of the food. Blinding procedure should be well-planned e.g. fat content of the vehicle can influence the challenge outcome (Grimshaw et al. 2003). The vehicle must also allow for enough challenge food to be used. An imaginative dietitian may be able to offer ingenious methods for challenges, especially where dose is an issue (Bock et al. 1988).

A variety of foods can be used for blinding such as ice-cream, rice-pudding, applesauce, milk shakes, mashed potatoes, tapioca, soup, chocolate pudding, carob, fruit juice/puree etc. Foods with strong taste and colour, are particularly useful for blinding and include foods such as black currant juice, beetroot juice, cocoa or peppermint oil (Carter 1995;Vlieg-Boerstra, Bijleveld et al. 2004;Noe et al. 1998).

Many commercial products such as egg free, milk free, wheat free cakes, biscuits or pastas can be used as placebo. It can be very difficult to find a suitable placebo and/or vehicle when dealing with children with multiple food allergies, i.e. finding a food that is well tolerated and accepted by the child (Carter 1995).

According to the EAACI position statement (Bindslev-Jensen et al. 2004) and other authors (Vlieg-Boerstra et al. 2004) the "active and placebo challenges should be identical regarding taste, appearance, smell, viscosity, texture, structure and volume". Blindness should also be assessed by standard procedures using for example the duo-test/paired comparison test and triangle test (Lawless 1998;Meilgaard et al. 1999). The triangle test belongs to the overall difference tests. The objective of the triangle test is to discover whether a perceivable difference exists between two samples, no matter which attribute differs between samples. The paired comparison test belongs to the attribute difference tests. The objective of this test is to determine in which way a particular sensory characteristic, which in our study was the taste of the allergenic food, differs between two samples. For the paired comparison test, more food tasters are needed because of random correct responses of 0.5, compared with the triangle test, in which this chance is 0.33. Although this seems to be a reasonable standard in adults and older children, one does query such stringent standards in the very young child.

Also, apart from one study (Zuberbier et al. 2004), the majority of research papers do not mention whether the DBPCFCs have been tested for blindness (Baehler et al. 1996;Bock 1987;Sicherer, Morrow, & Sampson 2000).

Cooking, canning or roasting (Ballmer-Weber et al. 2002;Cooke & Sampson 1997;Dreborg & Foucard 1983;Franck et al. 2002;Maleki et al. 2000;Simonato et al. 2001) can have different effects on the allergenicity of food proteins. Any form of processing used for preparing the challenge food could therefore potentially influence the challenge outcome. Based on this information, it is recommended that a negative challenge, either an OFC or DBPCFC, should always be followed up by consumption of a normal portion of the food, prepared according to the history (Bock et al. 1988;Metcalfe & Sampson 1990). This eliminates many of the issues raised about cooking, digestion etc, that may have an effect on the allergenicity of the challenge food.

Capsules are sometimes used as the challenge vehicle when using dried food to perform a challenge, but this is not the preferred option, especially for patients suffering from OAS (Bindslev-Jensen et al. 2004;Ortolani et al. 1999). In addition, capsules are not suitable for young children who cannot or will not swallow them (Carter 1995). They are also not suitable for home challenges as capsules can be opened (Bock et al. 1988).

In summary, when performing food challenges, challenge food should be used in such a way that it mimics the history as close as possible. Sufficient blinding of the challenge food is necessary when performing DBPCFCs, but the way of assessing the blindness has not been addressed by any position papers. When blinding food, great care should be taken not to alter the allergenicity of the food protein by means of any food processing used.

1.5.4.6 Interpretation of food challenges

The final and most important part of the challenge is the interpretation of the symptoms during the challenge (Gellerstedt et al. 2004). This is not always easy as there are some confounding effects.

Diseases such as eczema and chronic urticaria go into remission from time to time. It is possible that the results of a DBPCFC could be falsely negative when the disease is in remission or falsely positive when the disease is active. Allergic reactions to inhalant allergens can also affect the challenge outcome (Carter 1995;Reekers et al. 1999).

During OFCs, symptoms affecting the skin, gastro-intestinal and respiratory tract are monitored on a symptom record chart. Challenges are considered positive when the patient experiences symptoms in line with the history during the food challenge or when symptoms related to FHS are experienced during the food challenge and verified by the

supervising clinician. Challenges are considered negative when no symptoms are experienced during the food challenge; symptoms are experienced during the placebo phase of the food challenge, or when symptoms are reported during the food challenge that cannot be verified by the supervising clinician. When symptoms are experienced during both the active and placebo phase of a food challenge, the challenge needs to be repeated. Symptoms experienced during food challenges should be recorded on a symptom score chart in hospital or symptom diaries at home. There are no clear guidelines regarding at what point a challenge should be considered positive. The clinician should therefore make the final decision based on clinical discretion and the safety of the patient. Information regarding food challenge procedures can be obtained from guidance papers, experts, procedure manuals, position statements and published research literature.

In conclusion, when performing food challenges, one should be clear regarding which method of challenging would suit the purpose of the challenge most. At present, there are not clear guidelines regarding elimination period, starting dose, dose increments, final/total dose, challenge duration or challenge food used. This will therefore be decided based on the history and available tests by either the clinician or dietitian planning the food challenge. When blinding challenge food, one should ensure that the suspected food is sufficiently blinded without altering the allergenicity of the food proteins. The most important factor of the food challenge is the clinical assessment and evaluation of the challenge outcome and standardised assessment forms should be used.

1.6 Factors involved in the development of allergic disease

Allergic diseases, such as asthma, rhinitis, eczema and food allergies are increasing in both the developed (Austin et al. 1999) and developing (Dennis et al. 2004) world. There is, however, still a need for well-designed, large-scale, prospective epidemiologic studies designed to define precisely the magnitude of the worldwide problem created by allergic disorders. A number of key factors such as genotype, exposure to allergens and development of the immune response are involved in the development of allergic disease. It is reported that infants born to families with a history of atopy are more at risk of developing allergic diseases than those born to non-atopic families (Kurukulaaratchy et al. 2003) with genetic influences most definitely playing a role (Van Eerdewegh et al. 2002). The well-known figures from Kjellman (Kjellman 1977) suggest that the risk for a child to develop an allergy is as follows:

Both parents with identical allergy 72%
Both parents with non-identical allergy 43%
One parent with allergy 20%
One sibling with allergy 32%
Neither parent allergic 12%

Lifestyle factors such as socio-economic status (Golding & Peters 1987), sib-ship position (Strachan, Taylor, & Carpenter 1996), early childhood infections (Kuyucu et al. 2004), maternal or parental smoking (Kuyucu et al. 2004;Lau et al. 2002), day care attendance (Kuyucu et al. 2004) and growing up in anthroposophic families or on a farm (von Mutius 2004) are thought to be of relevance for the development of allergic conditions.

The role of maternal diet during pregnancy and breastfeeding, feeding and weaning practices of mothers in the development of allergic disease are still unanswered despite numerous attempts to resolve this issue. Dietary factors involved in the development of food allergy are of particular interest to the investigations undertaken for this thesis. These are discussed in more detail.

1.6.1 Maternal food intake during pregnancy

1.6.1.1 Observational studies of maternal food intake during pregnancy and its association with the development of food hypersensitivity in infants

Observational studies looking at maternal intake during pregnancy have focussed mainly on oil and fat consumption (Ushiyama et al. 2002), vitamin and mineral intake (Stazi et al.

2002) and peanut consumption (Hourihane et al. 2003) in the development of allergic disease in the infant.

In a study by Ushiyama et al, (Ushiyama et al. 2002) the vegetable oil and fat intake of 2,642 pregnant women was determined by a FFQ. The authors found that a high intake of energy and lipids, mainly omega-6 fatty acids as found in vegetable oil, during pregnancy are positively related to the development of allergic diseases such as eczema, food allergy and asthma in infants. These diets are rich in linoleic acid, a precursor of arachidonic acid which promotes prostaglandin E_2 production. This in turn, promotes Interleukin$_4$ production as the main cytokine involved in IgE production which can also skew T-helper (Th) cell population towards the Th2-phenotype. A Th2-phenotype is associated with asthma and allergy (Naito et al. 1996).

In an Italian study (Stazi et al. 2002) of 201 children aged three months to five years, low maternal intake of fruit (less than three portions per week) was associated with a positive SPT to six allergens, of which milk was the only food allergen, and eczema. However, recall bias regarding maternal intake five years post delivery could have influenced the data.

Hourihane et al (Hourihane, Dean, & Warner 1996) found that in utero exposure to peanut or maternal peanut intake during breastfeeding can trigger sensitisation, in particular where there is a family history of atopy. Based on this study, the Committee on Toxicity if Chemicals and Food (COT) issued precautionary advice in 1998 that 'pregnant or breastfeeding women who are themselves atopic, or where another first-degree relative of the child is atopic, may wish to avoid eating peanuts and peanut products during pregnancy and breastfeeding' (Committee on Toxicity of Chemicals in Food: Department of Health 1998). It is unclear at present how this message has been interpreted and implemented by health care professionals and pregnant and lactating women. Interestingly, Van Odijk and colleagues found that some pregnant women in Sweden avoided peanuts during pregnancy, even though this is not recommended in Sweden. Avoidance of peanut was unrelated to atopic status (van Odijk et al. 2004).

In contrast with the above study by Hourihane et al, (Hourihane, Dean, & Warner 1996) Lack and colleagues (Lack et al. 2003) determined that in utero sensitisation of the foetus to peanuts did not seem to be a factor in the development of peanut allergy, as there was no peanut-specific immunoglobulin E identified in cord blood samples from the children with positive peanut challenges. There was also no significant difference in maternal

peanut intake during pregnancy between the groups of children with and without peanut allergy. Unfortunately, the authors do not make it clear how old the children were at the time that the mothers were questioned regarding peanut intake during pregnancy and the result may therefore be subject to recall bias. The questionnaires used to determine this information is not discussed and it is not clear whether these questionnaires were validated. In this study, the authors also found an association between infant soya milk consumption and development of peanut allergy. However, children who have food allergies are more likely than children who do not have such allergies to have been given soy formula because of atopic dermatitis, gastroesophageal reflux, or immediate hypersensitivity to a food. The authors' results may therefore reflect a general association between food allergy and exposure to soy protein, rather than a specific association with peanut allergy.

In summary, is it very difficult to make any major conclusions regarding food intake during pregnancy and development of FHS from the above studies as three (Hourihane, Dean, & Warner 1996;Lack et al. 2003;Stazi et al. 2002) of the four studies are potentially confounded by recall bias. This question will be addressed under objective two.

1.6.1.2 Intervention studies of maternal food intake during pregnancy and its association with the development of allergic disease in infants

There are only a few studies that have investigated the manipulation of maternal diet during pregnancy. These studies have mainly looked at maternal food allergen intake and supplementation of diet with probiotics or omega-3 fatty acids. Only some of these studies looked at reduction in FHS *per se*, the objective of this thesis. However, all studies looking at reduction of allergic disease have been included in the following section to ensure a comprehensive discussion.

Falth-Magnusson et al (Falth-Magnusson & Kjellman 1992) looked at the effect of dietary manipulation during late pregnancy on the development of allergic disease in the offspring. There were 209 pregnant women from high risk families who were recruited into this randomised trial. One group of pregnant women continued on their normal diet and the second group were asked to completely avoid cow's milk and egg from 28 weeks of pregnancy until delivery. One hundred and ninety eight children (95%) were evaluated at the age of five years. Compared to the control group, no difference was found in eczema, allergic rhinoconjunctivitis, and asthma between the groups. However, persistent food allergy to egg was significantly more common in children of the mothers who avoided milk and egg. Dietary manipulation during pregnancy as instructed by this research team did

therefore not reduce allergic disease in young children. Unfortunately, the research team did not give any indication of the degree of adherence to the trial diet or difference in level of cow's milk and egg intake between the control and intervention group.

In the second study performed two years later by Lilja et al (Lilja et al. 1988) 165 pregnant women with respiratory disease and an allergy to pollen and/or animal dander were randomly allocated to four diets ranging from a diet free from egg and cows' milk to a diet containing intake of one egg and one litre of milk daily during the third trimester of pregnancy. These dietary changes showed no significant difference in terms of maternal or cord blood IgE to ovalbumin, ovomucoid and betalatoglobulin. Maternal IgG antibody concentrations to ovalbumin, ovomucoid and betalactoglobulin were influenced by the diet, but no effect on cord blood IgG was seen. Although this study clearly indicated that the dietary measurements had no effect on IgE production, no long term follow-up was performed to look at the clinical development of atopic disease in these infants. IgG measurements did however provide some evidence regarding adherence to the dietary instructions, although this was not the reason why IgG was measured.

These two studies suggest that maternal dietary intervention does not impact on development of atopy. Nevertheless, one may argue that these two groups intervened too late in pregnancy to have an effect and that dietary interventions during pregnancy should start much earlier. Central to all these studies is 1) how confident the researchers are in being convinced that mothers have avoided certain foods and 2) to what extent the food avoidance has been assessed.

The maternal egg avoidance study (MEAD) (Vance et al. 2004) conducted in UK is a more recent randomised controlled trial. Pregnant women from high-risk families were recruited at 16 weeks of pregnancy and randomised into one group continuing with their normal diet and one group avoiding egg. This research team found that egg intake from week 20 of pregnancy was reflected in the IgG levels to egg in the pregnant women. The authors did not however specify whether an IgG sub class or total IgG was measured. The infants (age six months) of those mothers with low and high serum IgG levels i.e. low and high egg intake, were less likely to be atopic than those with mid range IgG levels, i.e. moderate egg intake. Atopy was defined by atopic dermatitis and/or positive SPT (>2mm). This could have major implications on the results as 2mm is not generally accepted as a cut off point for a positive SPT, although this could perhaps be accepted in children of this young age as discussed under 1.5.2.1. One also needs to follow these infants for longer as outcomes may differ greatly by 1, 2 and 3 years. Credibility was added to the study

results as maternal intake was monitored by both IgG levels and food diaries analysed by the research dietitian.

The findings of the MEAD study (Vance, Grimshaw, Briggs, Lewis, Mullee, Thornton, & Warner 2004) which contradict the results from Falth-Magnusson (Falth-Magnusson & Kjellman 1992) and Lilja (Lilja et al. 1988) could be explained by an earlier intervention and because the research confirmed that mothers' were following the dietary intervention.

Other dietary avenues for reducing allergic disease included supplementation of the maternal and infant's diet with probiotics or omega-3 fatty acids.

Kalliomäki and colleagues (Kalliomaki et al. 2001) supplemented a group of high risk mothers with a gram-positive probiotic, *Lactobacillus rhamnosus* (*Lactobacillus GG*) during the last four weeks of pregnancy and the infants first six months of life. The prevalence of eczema was reduced by 50% in the intervention group when compared to a control group. The results of this study should be read with caution however as no significant difference in the number of children with positive SPT was noted in either group (10 in the probiotic group versus nine in the placebo group). One would therefore conclude that the prevalence of eczema, not necessarily atopic eczema was reduced. Unfortunately 25% of the study participants dropped out, which could also have led to selection bias and no indication of scoring of the eczema was given.

In a recent study from Australia, 98 atopic, pregnant women received fish oil as 3.7 g omega-3 poly-unsaturated fatty acids per day or placebo from 20 weeks gestation until delivery (Dunstan et al. 2003). Of these, 83 women completed the study. Although not designed to look at the clinical effect of fish oil supplementation, infants in the fish oil group were three times less likely to have a positive SPT to egg at one year of age. The hypothesis of the study, fits well with the findings of the study by Ushiyama et al (Ushiyama et al. 2002) as described under 1.6.1.1. One way of reducing the arachidonic content of inflammatory cells is to provide omega-3 fatty acids, which may in turn prevent production of Th2 cytokines such as Interleukin$_{13}$ as found by this group. However, this is preliminary data that needs confirming in a larger study focusing on clinical endpoints.

The data obtained from these intervention studies do not give undisputable evidence to incorporate any of these measures into clinical practice. At best they may have only transiently reduced in FHS and eczema for which the exact immunological mechanisms is unclear and different nomenclature is used across the world e.g. atopic eczema, atopic

eczema/dermatitis syndrome, atopic dermatitis etc. These intervention studies are also guilty of methodological problems such as a lack of exploring adherence to the dietary intervention, an insufficient follow-up period, insufficient power or use of debatable criteria (e.g. SPT size) for measuring reduction in the prevalence of allergic disease.

1.6.1.3 Determining maternal food intake

In order to establish the role of maternal dietary intake in the development of FHS it is crucial to use a validated and reliable measure of food intake.

A variety of dietary intake measures could be used such as 24-hour recall and 1 - 7 day food diaries. The FFQ, which evaluates a person's usual intake over a certain period, i.e. during pregnancy, is a relatively easy way of assessing nutritional intake in large scale epidemiological studies (Kipnis et al. 2002). FFQs are not as detailed or accurate as food diaries, but a validated questionnaire can give important information regarding frequency of food intake. In general, the FFQ determines how often and in what amounts each food on a list is consumed.

The FFQ is ideally suited for large population based studies to assess habitual dietary intake (Kassam-Khamis, Judd, & Thomas 2000;Kipnis et al. 2002;Ocke et al. 1997a). A number of studies found the FFQ a useful tool in determining food intake during pregnancy (Olsen et al. 2001;Robinson et al. 1996;Suitor, Gardner, & Willett 1989).

Two research groups (Lagiou et al. 2004b;Moore et al. 2004) have used a FFQ to obtain information on food intake during pregnancy and its relationship to the size of the infant at birth. FFQs have also been used to assess which foods mainly contribute to nutrient intake in pregnancy (Siega-Riz, Bodnar, & Savitz 2002) and overall quality of diet (Bodnar & Siega-Riz 2002). It is well known that food intake during pregnancy may differ from trimester to trimester. FFQ can provide useful information regarding pregnancy related changes in diet (Brown et al. 1996), micronutrient intake during pregnancy (French, Barr, & Levy-Milne 2003;Hashim & Norliza 2004;Lagiou et al. 2004a;Otto et al. 2001;Rogers & Emmett 1998) and the relationship between the pregnancy diet and disease development in the infant (Fronczak et al. 2003).

A literature search was performed and 95 papers looking at the dietary intake during pregnancy were found. There are no validated FFQs investigating intake of the major allergenic foods in pregnancy. This thesis addresses this gap under objective two where a detailed discussion regarding the FFQ design and validation will be discussed.

1.6.2 Breastfeeding and maternal diet in the development of allergic disease

In 2001, the World Health Organisation (WHO) (Department of Health 2001) recommended exclusive breastfeeding for the first six months of an infant's life, rather than just four months. In addition, the Scientific Advisory Committee on Nutrition (Scientific Advisory Committee on Nutrition 2004b) stated that there was sufficient evidence to suggest that exclusive breastfeeding for six months is nutritionally adequate. The UK, represented by the Chief Medical Officer, supported this recommendation at the World Health Assembly.

The WHO's recommendation for exclusive breastfeeding is based on the information that breast milk strengthens the immune systems of the infant due to the hormones, growth factors and colony stimulating factors and nutrients present in breast milk (Oddy 2002). In addition to this, breast milk promotes gastrointestinal mucosal maturation, decreases the incidence of infection and has immunomodulatory and anti-inflammatory functions (Field 2005). Although the human gut is anatomically and physiologically mature at birth in the full term infant, immaturities in digestion, absorption and protective function exist at birth. This may predispose the infant during the first six months of life to age-related gastrointestinal disease. Exclusive breastfeeding provides both passive and active support of the infant's gut function during the first six months of life and should therefore be recommended as such (Goldman et al. 2001). It is clear from the above that for the general health status of the infant, exclusive breastfeeding should be recommended for six months. It is unclear at present whether this is applicable for allergy prevention per se.

1.6.2.1 Observational studies of breastfeeding and its association with the development of allergic disease in infants

The effect of breastfeeding on allergy prevention is still very controversial, due to a number of studies with contradicting results. One major problem is that we have to rely on observational studies rather than randomly controlled trials as infants could never ethically be randomised into a breastfeeding and formula feeding group.

Observational studies investigating the effect of breastfeeding on allergic disease have been performed in both unselected and selected populations and can be divided into those concluding that 1) breastfeeding protects against allergic disease; 2) breastfeeding does not protect against allergic diseases.

The following studies were all performed in an unselected population and show a protective effect of breastfeeding. Saarinen and colleagues (Saarinen et al. 1999)

demonstrated in a birth cohort of 6,029 infants that exclusive breastfeeding for more than six months reduced the rate of food allergy significantly. However 2.1% of breastfed infants developed food allergy proven by challenge, compared to 2.4% of infants receiving cow's milk formula. In a Swedish study looking at a birth cohort of 4,089 infants, exclusive breastfeeding for four months resulted in less asthma, rhinitis and eczema, but had no effect on reported food allergy at the age of two years (Kull et al. 2002). One major advantage of this study is that 80% of mothers exclusively breast fed their infants for four months, which provides a large study sample. A disadvantage of the study is however that they only looked at reported problems of food allergy rather than diagnosed FHS. However 20% of parents reported food related problems and it is known that less than a third of these children will truly be suffering from FHS (Bock 1987). Oddy et al (Oddy, Peat, & de Klerk 2002) followed 2,602 children from 18 weeks of age and established that a breastfeeding duration of four months or longer significantly decreased the children's risk of asthma at six years. Mothers were asked to keep diaries regarding feeding practices. However, one should take into account the breastfeeding in this study was defined as no introduction of cow's milk only. Therefore, some of the infants in the breastfeeding group might already have been on solid food by four months. Interestingly, maternal asthma did not alter the protective effect of breastfeeding, but the authors did not investigate other factors such as maternal eczema etc.

Similar results were seen in prospective studies performed in high-risk children.
In a group of 184 infants with a family history of atopy the incidence of eczema fell when exclusive breastfeeding was continued for longer than 12 weeks (Pratt 1984). Saarinen and colleagues (Saarinen & Kajosaari 1995) followed a group of high risk infants for 17 years (n=150). Those children breastfed for longer than six months showed a lower incidence of eczema (age 1-3 years), asthma (age 17 years) and food allergy (age 1-3 years) than those fed for a shorter period of time.

Hence a total of five studies indicate that breastfeeding for at least 12 weeks prevented some symptoms of allergic disease. Only two studies (Saarinen et al. 1999;Saarinen & Kajosaari 1995) found that breastfeeding prevented food allergy and only one of these studies (Saarinen et al. 1999) diagnosed food allergy by means of food challenges.

There are, however, also a number of studies in unselected cohorts which have shown that breastfeeding increases the risk of allergic symptoms, (Bergmann et al. 2002;Pratt 1984;Sears et al. 2002;Wright et al. 2001) but none of these looked at the effect of breastfeeding on FHS.

In a study from the USA (Wright et al. 2001), 1246 infants were recruited at birth and followed-up for six years. Information regarding infant feeding practices was obtained throughout the first year of life. Only 359 (29%) mothers managed to exclusively breastfeed for ≥ 4 months. The authors determined that at the age of six years, after adjusting for confounders, children with asthmatic mothers but not asthmatic fathers were significantly more likely to have asthma if they had been exclusively breast fed (OR 8.7, 95% CI 3.4 to 22.2). No other familial facts such as maternal eczema etc. have been investigated. This is in contrast with the results of Oddy et al (Oddy, Peat, & de Klerk 2002) who found that maternal asthma did not alter the protective effect of breastfeeding.

The study by Sears et al (Sears et al. 2002) involved a large prospective birth cohort study (n=1037) recruited at age 3 years. These children were followed up at regular intervals up to the age of 26 years. Respiratory questionnaires were completed at each follow up and pulmonary function, bronchial challenge and SPT were introduced at later follow-ups. Although considered a prospective study, the method of infant feeding was recorded retrospectively at three years. Children who were breastfed were more likely to be atopic at all ages (13 - 21 years) than those who were formula fed. Also more children who were breastfed reported current asthma at 9 and 26 years than those who were not. This study once again raises questions regarding the protective effect of breastfeeding against allergy. However, the main weaknesses of the study revolve around the information obtained regarding feeding practices as the data was collected retrospectively, although it was verified against nursing notes. It is unclear from the results how many of the breastfeeding mothers (n=533) were exclusively breastfeeding, although the authors mentioned that it was only a small number. Also, children were significantly more likely to be breastfed than formula-fed if they were born to parents of higher socioeconomic status. One could speculate that antigen exposure may be lower or at least different in this group. Furthermore, children born into a higher socioeconomic class probably have better access to health-care facilities, resulting in their being prescribed more antibiotics. Antibiotic use can influence gut flora, which may have an effect on the development of allergic diseases. In summary, the higher incidence of asthma in the breastfed group in this population could be associated with lower antigen exposure and increased antibiotic consumption in the higher socioeconomic class and needs to be addressed.

There were 1314 children recruited into the German MAS study and followed prospectively up to the age of seven years (Bergmann et al. 2002). The risk of developing eczema in the infant increased with each additional month of breastfeeding (OR = 1.03 and 95% CI=1.00-1.06), particularly in those with a parental history of eczema. This was a

well-conducted study and statistical correction for the confounding variables was employed.

The above three studies all question the protective effect of breastfeeding. Three possible explanations are: firstly, that the lower omega-3 fatty acid levels of the serum and breast milk of atopic mothers vs. non-atopic mothers may play a role in the development of asthma and eczema of the infant (Yu, Duchen, & Bjorksten 1998). Secondly, the reduced levels of soluble CD14 and omega-3 fatty acids in breast milk could also favour the development of atopy in the infant (Jones et al. 2002). Unfortunately, none of the studies investigating the role of breastfeeding has determined the breast milk composition of the mothers as well. Thirdly, it has been suggested that perhaps those with the highest degree of atopic heredity will tend to be breastfeeding for the longest period. This implies that when we are looking at the effect of breastfeeding on allergy prevention, the breastfeeding group may naturally include more of those highest at risk as they are the group that breastfeed for a longer period. However, no difference in breastfeeding duration was found between atopic and non-atopic families in a number of studies (Kull et al. 2002;van Odijk et al. 2004;Wilson et al. 1998).

However, in contrast, a study by Siltanen and colleagues (Siltanen et al. 2003) looked at 4,674 unselected infants. The authors divided the infants into four groups: atopic heredity and breast fed for >3 months; non-atopic heredity and breast fed for >3 months; atopic heredity and cow's milk from birth; non-atopic heredity and cow's milk from birth. At four years the group with atopic heredity and breastfed for >3 months showed less aero-allergen sensitisation and allergic disease than the non-atopic group breastfed for >3 months. One should however take into account that the atopic breastfeeders smoked less and had less furry pets. The authors tried to exclude these confounders in their statistical analysis.

It is clear from the above studies that breastfeeding may not protect against all types of allergic disease in all infants and that the effect of breastfeeding on allergy prevention in both the high risk and unselected groups is still very controversial. Only one study (Saarinen et al. 1999) looked at the effect of breastfeeding on the prevalence of FHS and found a protective effect providing the infant was breastfed for more than six months. Apart from the different results regarding prevention of allergic disease, it is also well-reported that up to a third of infants will develop cow's milk allergy during exclusive breastfeeding, probably to the cow's milk protein in breast milk (Jarvinen & Suomalainen 2001). Therefore, whether breastfeeding protects against allergic disease and FHS per se

still needs further research. Two systematic reviews (Gdalevich et al. 2001;Mimouni et al. 2002) reached the conclusion that exclusive breastfeeding does seem to have some protective effect on the development of allergic disease and that this effect is greater when there is a family history of atopic disease. We may therefore in future find that in a subgroup of mothers, breastfeeding may be more effective in preventing allergies, based on the mothers own atopic status and the composition of the breast milk (Jones et al. 2002;Yu, Duchen, & Bjorksten 1998) as the most important determining factors.

1.6.2.2 Intervention studies of breastfeeding and its association with the development of allergic disease in infants

The main aim of the intervention studies discussed in this section was to determine whether dietary manipulation during breastfeeding can reduce or prevent allergic disease. No intervention studies in unselected populations have been performed as yet, primarily because a very large population will be needed to show a significant effect of the intervention.

A number of randomised controlled trials in high-risk infants have investigated the effect of different dietary allergy prevention programs during breastfeeding or pregnancy and breastfeeding.

In a study by Chandra et al (Chandra, Puri, & Hamed 1989), 48 lactating mothers with dual hereditary of atopic disease were instructed to avoid milk, egg, fish, peanuts and soya for the full duration of breastfeeding. Eczema was seen less often and was milder in the infants (age18 months) whose mothers were on the intervention diet than those in the control group (49 mothers).

In the Isle of Wight intervention study (n= 120), a group of lactating mothers (n=58) with dual hereditary of atopic disease, avoided milk, egg, fish and all nuts during the full duration of breastfeeding. This group also avoided house dust mite. Less allergic disorders (14% vs. 40%) were seen in these infants at 12 months and significantly less wheeze and nocturnal cough at eight years. However, 10% (n=6) of infants in the control group showed positive SPT to food and aeroallergens compared to only 3% (n=2) in the intervention group (Arshad et al. 1992;Arshad, Bateman, & Matthews 2003). This study employed both dietary and environmental intervention measures, which make it difficult to interpret the data as the results could have been influenced by the dietary modification and/or HDM reduction.

A Japanese study compared the development of allergic disease in three groups of infants. Infants in group 1 were exclusively breast fed or a given a whey hydrolysate. The lactating mothers of these infants were given the same whey hydrolysate as their only source of protein. Infants in group 2 were breast fed, with the lactating mothers consuming cow's milk. In the third group, infants were given cow's milk formula. The infants in group 1 showed a lower incidence of atopic dermatitis and cow's milk allergy than the infants in the other two groups (Fukushima et al. 1997).

Hattevig and colleagues (Hattevig, Sigurs, & Kjellman 1999), followed high risk children up to age 10 years. Their mothers (n=65) avoided egg, milk and fish for the first three months during breastfeeding. The infants from the intervention group showed less eczema at six months than the control group (n=50), but there was no difference in the number of positive SPT to egg, cow's milk or fish at nine months and no difference in atopic manifestations at age 10 years. Children were included into this study if the mother, father and a sibling reported a past or present history of asthma, eczema or allergic rhinitis.

Based on the above studies described here, a recent review paper by the EAACI concludes that there is no evidence for maternal dietary intervention during pregnancy or lactation in the prevention of allergic disease (Muraro et al. 2004b). However, three major problems arise when comparing these studies. The inclusion criteria and intervention varied and none of these studies reported measuring dietary compliance. This could have significantly influenced the study outcomes.

1.6.2.3 Infant weaning practices

The recommended weaning age is six months of age taking into account the individual needs of the mother and infant (Scientific Advisory Committee on Nutrition 2004a). However, more specific recommendations have been suggested for high-risk infants. The joint guidelines of the European Society for Paediatric Allergology and Clinical Immunology (ESPACI) and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommend that solid food introduction should be delayed until the infant is five months of age (Host et al. 1999). The American Academy of Paediatrics' advice is more detailed, suggesting that solids should be delayed until six months of age, cow's milk until one year, egg until two years, and peanuts, tree nuts, and fish until three years (Zeiger 2003). This advice was mainly based on two studies described under 1.6.2.3.1. A review paper by EAACI recommends that solid food should be avoided for preferably six months, but ideally four months (Muraro et al. 2004b). In addition to this, COT report (UK) recommends that peanuts should not be given to

children from high risk families until the age of three years (Committee on Toxicity of Chemicals in Food: Department of Health 1998). It is clear from the above that weaning of high risk infants, in particular delayed introduction of the high risk foods, is controversial with guidelines from experts varying (Host et al. 1999;Muraro et al. 2004b;Zeiger 2003).

In an attempt to clear up the confusion for dietitians, The British Dietetic Association (UK) (Food Allergy and Intolerance Interest group: BDA 2004) made the following practical recommendations regarding weaning for allergy prevention in high risk infants:

- From the age of six months, those foods more likely to precipitate food allergies may be introduced, singly and with caution.
- By the age of 12 months, all the major high-risk foods should have been introduced, apart from peanuts which, in accordance with Government guidelines, should not be introduced until the age of three years.
- There is no research evidence to support delayed weaning (>6 months).

1.6.2.3.1 Observational studies of weaning and its association with the development of allergic disease in the infant

Observational studies looking at the role of weaning in allergy prevention can be divided into three groups: 1) introduction of solids before 3-4 months increases the risk of allergic disease; 2) delaying introduction of solids beyond 3.5 - 6 months increases the risk of allergic disease; 3) early feeding practices have no effect on allergic symptoms. It must be acknowledged that a number of other factors, such as duration of breastfeeding, type of infant formula used and type of solids introduced could act as confounding factors.

In a study by Kajosaari et al (Kajosaari & Saarinen 1983) in the early 1980's, 135 infants from atopic parents were exclusively breastfed for six months without any cow's milk based supplements. Of these infants, 70 were exclusively breastfed (no solids) during the first six months, and 65 were started on solid foods at the age of three months. The diet of all the infants was similar from 6 - 12 months of age. At the age of one year, the infants in the breastfed group showed less eczema and food allergy than those who received solids at three months of age (Kajosaari & Saarinen 1983). However, no difference was seen at the five year follow up (Kajosaari 1991).

Fergusson and colleagues (Fergusson, Horwood, & Shannon 1990) found more eczema at 2–4 years of age in a group of infants fed four or more solid foods before age four months compared with infants receiving no solid foods before four months of age. This difference was maintained until 10 years of age. In addition, a prospective study of 674

infants by Wilson et al (Wilson et al. 1998) showed that early solid feeding (<15 weeks) was associated with an increased probability of wheeze during childhood: 21.0% of children (age 7 years) who had solids before 15 weeks presented with wheeze compared to 9.7% in those who had solids after 15 weeks.

Morgan et al (Morgan et al. 2004) followed 257 otherwise well unselected preterm infants from three maternity units, until one year of age. The introduction of four or more solid foods before 17 weeks postterm was associated with a higher risk of eczema in infants unrelated to their family history of allergic disease. They unfortunately did not specify the degree of prematurity of the infants, which could influence the results as increasing prematurity is known to be associated with a decreased risk of atopy (Siltanen et al. 2001). This could be due to a higher risk of developing infections and altered gut microbial flora in more preterm infants, with higher risks of sepsis and necrotising enterocolitis.

In summary, the above studies were conducted in three unselected groups of infants (Fergusson et al. 2004;Wilson et al. 1998) and one group of high risk children (Kajosaari 1991). All the studies were prospectively conducted and the research teams concluded that introduction of solids before 3-4 months of age increased the risk of developing allergic disease.

However, this was directly contradicted by Saarinen et al studying an unselected cohort of 6,209 children and Zutavern et al studying 642 high risk children prospectively. Saarinen et al (Saarinen & Savilahti 2000) found that delaying introduction of solids from 3.4 - 4 months can increase the infant's likelihood of developing IgE mediated food allergy as confirmed by food challenges. This was further emphasised in a study of 642 high risk children followed from birth to 5½ years (Zutavern et al. 2004). The results from this study suggested that the prevalence of doctor's diagnosed eczema and a history of food allergy were increased at age one year in infants fed solids after six months of age compared with those infants with solids introduced at three months, but no difference was seen at the five year follow up. In addition, Schoetzau and colleagues (Schoetzau et al. 2002) determined that providing weaning does not take place before four months, the age of first introduction of solid food and the variety of solid foods (expressed as number of food groups), showed no effect on eczema incidence or sensitisation to milk and egg allergens. These infants were recruited for an intervention study looking at the effect of cow's milk formula, extensively hydrolysed formula and partially hydrolysed formula in the prevention of allergic disease. The groups of children studied (weaning before four months vs.

weaning after four months) were therefore not exactly similar in terms of the formulas they have received, which could have confounded the results.

Finally, Gustafsson et al (Gustafsson, Sjoberg, & Foucard 2000) looked at 100 high risk infants with eczema and showed that early feeding patterns, time of weaning, and introduction of solid foods did not influence the risk of development of allergic symptoms. However, one must take into account that this information was obtained retrospectively rather than prospectively as the children were recruited between the ages of 4–35 months, which could lead to reporting bias. Weaning patterns were determined by obtaining information on: breastfeeding for at least six months, introduction of cow's milk formula before four months, introduction of egg before 12 months and introduction of fish before seven months of age. Food allergy was diagnosed on the basis of a positive RAST or SPT and clinical symptoms rather than a food challenge. These authors also did not look at actual time of introduction of solids.

In summary, from these observational studies we can learn that weaning before the age of three months and beyond the age of six months may increase the risk of allergic disease. Whether weaning at three or four months as opposed to six months poses a higher risk for developing allergic disease was unanswered until very recently. Zutavern and colleagues (Zutavern et al. 2006) answered this much discussed topic in a prospective study in 2612 infants. These authors found that introduction of solid foods after 4 months decreased the odds ratio for atopic dermatitis. Delaying solid food introduction beyond 6 months, did not provide any additional benefits.

Once again, the question can be asked whether a family history of allergic disease had any effect on weaning practices and whether this could have influenced the research data. Only two studies reported on this, with conflicting results. In a retrospective study, Van Odijk and colleagues found no difference between timing of introduction of solids or introduction of highly allergic foods in the atopic and non-atopic families (van Odijk et al. 2004). There were 467 children recruited into this study with the primary aim of looking at feeding practices in Swedish children in the first year of life and investigating feeding and weaning practices of atopic and non-atopic families as a secondary aim. In contrast, Schoetzau and colleagues (Schoetzau et al. 2002) found that mothers of infants with a familial risk of eczema had delayed solid food feeding beyond the first six months more frequently than mothers of subjects without a familial history. As mentioned, these infants were initially recruited for the GINI study and mothers received strict advice regarding weaning practices, which could have influenced the findings of this paper.

1.6.2.3.2 Weaning practices as part of another intervention in the development of allergic disease

Following on from the dietary intervention studies performed during lactation as discussed in 1.6.2.2, mothers enrolled into these studies were also given dietary advice regarding weaning of their infants. Comparing these different study protocols in terms of the weaning advice given, showed no consistency and a lack of evidence.

A number of randomised controlled trials in high-risk infants have investigated the effect of different dietary allergy prevention programmes during breastfeeding or pregnancy and breastfeeding.

Zeiger et al (Zeiger et al. 1989) randomised 288 pregnant women (prophylactic group n=103 and control group on normal diet n=185) into a dietary intervention trial which included: no cow's milk, soy, wheat or corn in the infant's diet before 12 months, no egg before 24 months and no peanut or fish before 36 months. Interestingly, by the age of three years, fewer children in the intervention group had been exposed to peanut and fish than the control group. However more than 96% of children had ingested egg in some form and all the children in both groups had been exposed to milk, wheat, rice, corn, soya, beef, legumes and citrus by the age of three years. In the Isle of Wight dietary intervention study performed during lactation only (Arshad et al. 1992), mothers did not feed the infants any solid foods for six months and then introduced milk, egg, fish, and all nuts, soya, wheat, and orange in a staggered approach up to the age of 12 months. Cow's milk was introduced after six months of age and egg after nine months of age into the infant's diet in the study by Hattevig et al (Hattevig, Sigurs, & Kjellman 1999)

In the GINI study, comparing the effect of a partially hydrolysed formula with an extensively hydrolysed formula on allergy prevention, no solid foods were allowed during the strict intervention period (six months) and mothers were thereafter instructed to add not more than one new food per week but to avoid milk and dairy products, hen's egg, soy products, fish, nuts, tomatoes, and citrus fruits during the first year (von Berg et al. 2003). Oldaeus et al (Oldaeus et al. 1997) performed a similar study in 155 high risk infants recommending no cows' milk during the first nine months and no egg and fish up to 12 months.

No conclusions can be drawn from the above weaning data as the advice given in the studies differed greatly. It also formed part of either another intervention such as food allergen avoidance during lactation and/or pregnancy (Arshad et al. 1992;Hattevig, Sigurs,

& Kjellman 1999;Zeiger et al. 1989) or compared different formulas for allergy prevention (Oldaeus et al. 1997;von Berg et al. 2003). Also, none of these studies asked mothers to keep food diaries and no data is reported regarding the actual age of solid food introduction, apart from the study conducted by Zieger et al (Zeiger et al.1989).

1.6.2.3.3 Studies of weaning practices in the development of allergic disease

Studying the age of introduction of a particular food and the subsequent development of FHS seems to point towards earlier introduction of solids causing sensitisation, although only a few studies, some with small numbers, have been published in this area.

In a retrospective South African study by Frank et al (Frank et al. 1999) the mean age of peanut introduction into the diet of the peanut allergy sufferers (n=25) was 12.5 months and for the control group (n=18) 17.3 months.

It seems that introduction of cow's milk in the infants diet within the first few days is associated with development of cow's milk allergy (Host, Husby, & Osterballe 1988;Saarinen, Juntunen-Backman, Jarvenpaa, Kuitunen, Lope, Renlund, Siivola, & Savilahti 1999). These findings have been confirmed by a prospective, randomised, double-blind study by Saarinen et al (Saarinen et al. 1999). They showed that in non-selected neonates given cow's milk formula, hydrolysed formula, or breast milk during the first few days after birth, the incidence of cow's milk allergy during the first year almost doubled from 1.6% with hydrolysed formula or breast milk to 2.6% with the cow's milk formula. The cow's milk allergy was diagnosed by means of food challenges.

A research group in Slovenia demonstrated that avoidance of egg up to one year of age prevented the development of eczema in infants at the age of 18 months. Specific IgE levels to egg were the highest in the group where egg was introduced at six months (Kocijancic LB 2004).

These studies investigated the role of age of introduction in the development of eczema or FHS to specific food. Data are available on only peanut and milk in terms of age of introduction and development of FHS. Although it seems that earlier introduction increases sensitisation and FHS, one must take into account that the study by Frank et al (Frank et al. 1999) is guilty of recall bias. This is an area with huge opportunity for further research.

Finally, it is clear from the above data on weaning and allergy prevention, that we need more studies looking into this very confusing area. On the one hand it seems that solid food introduction before 3-4 months, may increase the risk of allergic disease, which has been confirmed with early introduction of cow's milk and development of cow's milk allergy. However on the other hand, delaying introduction of solids beyond six months may increase the prevalence of allergic symptoms or have no further beneficial effects. This does not support the data that delayed introduction of egg (beyond one year) and peanut (beyond 17 months) may reduce the risk of FHS to these particular foods.

1.7 Summary

FHS is an adverse reaction upon ingestion of food which can either be immune or non-immune mediated. FHS is commonly reported in children, but there is a large discrepancy between reported and diagnosed FHS. It is crucial that a correct diagnosis of FHS should be made for either research or clinical purposes. A good clinical history forms the basis of the patient assessment. Diagnostic tests such as specific IgE measurements and SPT can provide a good indication of whether a patient truly is allergic by means of using diagnostic decision points. These tests can also indicate if a food challenge is needed. At present, the "gold standard" for the diagnosis of food allergy is the DBPCFC. Information regarding food challenges can be obtained from various sources, but guidelines regarding procedural issues most often vary greatly. In particular, there does not really seem to be a consensus regarding the use of OFCs vs. DBPCFCs in diagnosing FHS and very little guidelines for performing food challenges when dealing with delayed type symptoms. This poses practical problems when performing food challenges for either research or clinical purposes.

Once diagnosed, the question often arises as to why FHS develops and how it could have been prevented. A number of factors such as family history of atopy, socioeconomic status and sib-ship position have been identified in the development of allergic disease, but very little is known about risk factors for developing FHS. Some factors such as maternal diet and feeding/weaning practices have been investigated. Observational studies looking at food intake during pregnancy are often guilty of recall bias and intervention studies during pregnancy have failed to accurately record adherence to the dietary intervention or lack an adequate follow-up period, valid diagnostic criteria or sufficient power. In order to establish the role of maternal dietary intake in the development of FHS, a variety of dietary intake measures could be used such as a FFQ. It is crucial any dietary assessment tool should be reliable and valid.

Only one observational study has looked at the effect of breastfeeding on the development of FHS diagnosed by food challenges and found that exclusive breastfeeding for more than six months can reduce the prevalence of FHS (Saarinen et al. 1999). In addition to this, there is at present no evidence for manipulating the maternal diet during breastfeeding based on the available data.

The WHO recommends that solid foods should not be introduced into the infant's diet before the age of six months based on data looking at the general health status of infants. For the purpose of allergy prevention, observational studies looking at weaning age and development of allergic disease, determined that weaning after the age of three months reduces the risk of allergic disease. It does seem however that delaying weaning past six months may increase the risk of allergic disease or have no further beneficial effect. Very little can be learned from existing intervention studies involving specific weaning advice for allergy prevention as the weaning advice given in all these studies formed part of another intervention such as maternal dietary manipulation or the use of either extensively or partially hydrolysed formulas. Age of introduction of specific foods and the subsequent development of FHS to that particular food, needs more research.

Finding answers to questions about the effect of factors such as maternal diet during pregnancy and lactation, feeding practices, weaning age and timing of introduction of the major allergenic foods on the development of accurately diagnosed FHS may act as an important incentive for future prevention studies.

To conclude, in this introductory chapter, relevant information surrounding the objectives of this thesis was obtained and discussed. The chapter therefore started with a discussion on the prevalence and diagnosis of FHS. This is followed by a discussion on factors that may lead to the development of allergic disease, focusing on FHS.

The first objective of this thesis focused on diagnostic procedures for FHS, particularly the use OFCs vs. DBPCFCs. In order to meet this objective a birth cohort of children born during 2001 – 2002 was recruited at the ante-natal clinic and followed prospectively for two years. In addition, three sets of school cohorts were approached to participate in the study. To identifty those that may be suffering from FHS, information on reported symptoms of FHS was obtained and the children underwent SPTs to determine their sensitisation status to six major food allergens (milk, egg, wheat, fish, peanut and sesame). Based on this information, children underwent food challenges. To compare the use of OFCs and DBPCFCs, all children with a positive OFC were invited to undergo a

DBPCFC. Information on symptoms experienced during food challenges vs. reported symptoms, dose and timing of reactions, ease/difficulties in performing food challenges, parental acceptance of food challenge outcome were of particular importance in comparing OFCs and DBPCFCs.

Once diagnosed with FHS, we set out to determine the role of dietary factors in the development of FHS in the birth cohort. In order to determine maternal dietary intake of particularly the highly allergenic foods during pregnancy, a FFQ was developed and validated (objective 2). Standardised questionnaires were developed and used prospectively to assess feeding and weaning practices during the infant's first two years of life. The information obtained from the FFQs and the questionnaires was compared with sensitisation status and diagnosed FHS in order to find any associations (objective 3).

Finally, the family history of atopy was obtained during recruitment of the birth cohort and this information was used to find out if a personal or family history of atopy affect maternal eating and feeding and weaning practices of the infant (objective 4). This was done as it is often claimed that a history of allergic disease may influence maternal dietary practices from pregnancy through weaning.

Chapter 2

Comparison of Open Food Challenges and Double Blind Placebo Controlled Food Challenges in the Diagnosis of Food Hypersensitivity

2.1 Introduction

Food challenges, in particular the DBPCFC, are the accepted gold standard in objectively diagnosing FHS (Bock et al. 1988;Pastorello et al. 1991;Sampson & Ho 1997). Although the DBPCFC is considered as the gold standard, it is far from a perfect test and some clinicians consider it to be labour intensive and it could be less safe to perform than the OFC, particularly in children (Hide 1994;Hill & Hosking 1991). Furthermore, no clear guidelines regarding procedural issues for either DBPCFCs or OFCs exist. Clearly certain issues such as selection of appropriate cases, history, elimination period, use of medication, challenge protocol e.g. dose, duration and blinding and information post challenge need to be considered. A major issue in the diagnosis of FHS is when to use OFCs as opposed to DBPCFCs. Researchers/clinicians often claim that there is a consensus regarding the use OFCs and DBPCFCs in paediatric populations. They suggest that OFCs are acceptable in children under the age of three and the DBPCFC should be used in older children (Bahna 1994;Muraro 2001). However, there is no evidence to support this. Even with older children, there is no consistency in published literature regarding when to use the OFCs vs. DBPCFCs and a number of research studies have used either OFCs, DBPCFCs or a combination of both (Baehler et al.1996;Bock 1987;Hill, Hosking, & Reyes-Benito 2001;Isolauri & Turjanmaa 1996;Sicherer, Morrow, & Sampson 2000).

Only one previous study (Kaila & Isolauri 1997) has compared OFCs with DBPCFCs in children. This study investigated parental acceptance of food challenge outcome and found that parents were more likely to accept the outcome of a DBPCFC than an OFC. This raises the question as to whether parents will follow avoidance or reintroduction advice when they are not convinced by the results of the diagnostic method.

The aim of this objective was therefore to compare OFCs and DBPCFCs in the diagnosis of FHS.

2.2 Plan of investigation

2.2.1 Research Design

A population based cohort approach underpins this study. The work conducted for this thesis is based on a five year project, the Food Allergy and Intolerance Research (FAIR) study, funded by the Food Standards Agency.

The aim of the FAIR study was to establish the prevalence and incidence of FHS, as well as providing evidence for temporal changes of incidence and prevalence of FHS.

Approval for the study was obtained from the Isle of Wight, Portsmouth and South East Hampshire Local Research Ethics Cornmittee (Reference 09/01) (see page 299 for ethical approval letter). The FAIR study included all babies born between 1 September 2001 and 31 August 2002 who were followed up to three years of age as well as three whole population cohorts comprising of all the 6, 11 and 15 year olds resident on the Isle of Wight.

As with all large scale epidemiological studies there are a number of researchers who contribute to a study of this nature. The role and contribution of each team member including the author were as follows:

i) Research nurses

- Recruitment of birth cohort
- Data collection at three, six, and nine months by means of a questionnaire
- Skin prick test (SPT) of both the birth and school cohorts
- Assist research fellow in completion of one, two and three year old questionnaire
- Assist with the food challenges
- Assist with day to day running of the project

ii) Research fellow

- Design of one, two and three year questionnaire for the follow-up of the birth cohort
- Medical examination of the birth cohort at one, two and three years plus completion of the follow-up questionnaire
- Identify patients for possible food challenges from the questionnaires and SPT results for both the birth and school cohorts
- Medical supervision of food challenges and school visits

iii) Research dietitian (Author)

- Development of recruitment questionnaire
- Contribute to recruitment of birth cohort
- Design three, six and nine months follow-up questionnaire for the birth cohort
- Design of food related questions for both the birth cohort yearly follow-ups and the school cohorts
- Contribute to data collection for the birth cohort by gathering information with telephone administered questionnaires at three, six and nine month

- Identify patients for possible food challenges from the questionnaires and SPT results for both the birth and school cohorts
- Consult the families of all children identified for food challenges regarding dietary considerations
- Design diet sheets for elimination diets (Appendix 2.1)
- Guide children and parents on elimination of offending foods/ingredients
- Design challenge protocols/procedures
- Supervision of dietary aspects and organisation of food challenges
- Oversee food challenges at home for the diagnosis of delayed symptoms
- Design and complete all datasheets to transfer challenge data on to SPSS (type of symptoms, time of onset of reaction, final and total dose etc.)
- Design recipes for DBPCFCs in conjunction with the two chefs
- Provide follow-up and after care

2.2.2 Recruitment of the birth cohort

All pregnant mothers with an estimated delivery time 1 September 2001– 31 August 2002 were approached (Appendix 2.2) at antenatal clinics to participate in this study. Following consent (Appendix 2.3), 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 2.4).

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 2.5-2.7). Most questions were based on the ISAAC questionnaires (von Mutius 1996).

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 and two years of age, all the children were reviewed at clinic for a medical examination guided by a detailed questionnaire (Appendices 2.8 and 2.9). The

questionnaire covered symptoms of atopy, feeding and weaning practices, immunisation history and environmental factors.

2.2.3 Recruitment of the school cohorts

The target populations included all 6, 11 and 15 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 52 Primary Schools (47 state and 3 independent schools), 19 Middle schools (16 state and 3 independent schools) 8 High Schools (5 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 2.10 -2.12). 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 food 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.

2.2.4 Skin prick tests

Children in both 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 2.13). 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 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.

2.2.5 Food challenges

Two members of the research team (the author as 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 (Sampson, Hill, & Hourihane 2003).

Prior to the food challenges, children and parents were advised by the research dietitian (author) 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 (Bock et al. 1988). Following consent (Appendix 2.14) 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 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) (Bock, Sampson, Atkins, Zeiger, Lehrer, Sachs, Bush, & Metcalfe 1988) (Appendices 2.15 -2.17) and delayed (one-week challenge protocols) (Baehler et al. 1996;Isolauri & Turjanmaa 1996;Majamaa et al. 1999a;Majamaa et al. 1999b) (Appendices 2.18 – 2.19) symptoms. One-day challenge protocols were based on the consumption of a total of 8-10g of dried food (Sampson 2001a), 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 (Holland et al. 2000).

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 (Sampson 1998). 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 (Gregory et al. 1995;Gregory et al. 2000).

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 (Gregory et al. 1995;Gregory et al. 2000)
- Portion sizes indicated by the Clinical Paediatric and Dietetics (Watling 2001)

- Portion sizes calculated from the Food Portion Size Handbook (MAFF 1993)
- 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 DBPCFCs due to the severity of the reaction upon open challenge. We aimed to perform the DBPCFCs within six weeks of the open challenge to exclude the possibility of children in the birth cohort outgrowing their FHS. Foods used for the DBPCFCs 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 DBPCFCs as for the open challenge was used, except if the patient reacted to the first dose used during the OFCs. In this case, in some instances we started with half the dose to which the patient reacted (Appendices 2.20- 2.21). The dose given for delayed symptoms was the same as that used during the 1- week OFC (Appendices 2.22 – 2.23).

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 author on to food challenge outcome forms for data entry and analysis (Appendices 2.24 – 2.33). Parents were phoned one month after the challenge by the author to enquire whether they have introduced the food into the child's diet in case of a negative challenge.

2.3 Results

Initially the baseline characteristics, reported rate of food related problems and food avoidance and sensitisation data of the 5 cohorts, pooled into one cohort will be described. This will set the background for the main results of this chapter, the outcome of the food challenges.

2.3.1 Baseline characteristics of cohorts

The study population:

A) The birth cohort defined as those who where born between 1 September 2001 to 31 August 2002. The target population consisted of 1063 pregnant women with delivery dates during this time. A total of 969 pregnant women were recruited for the study. At three, six, nine and twelve months, 927, 913, 900 and 900 follow-up questionnaires were completed respectively,

B) The same birth cohort (A) at the age of two years (n= 858).

C) A cohort of 6 year old children resident on the Isle of Wight (n=798)

D) A cohort of 11 year old children resident on the Isle of Wight (n=775)

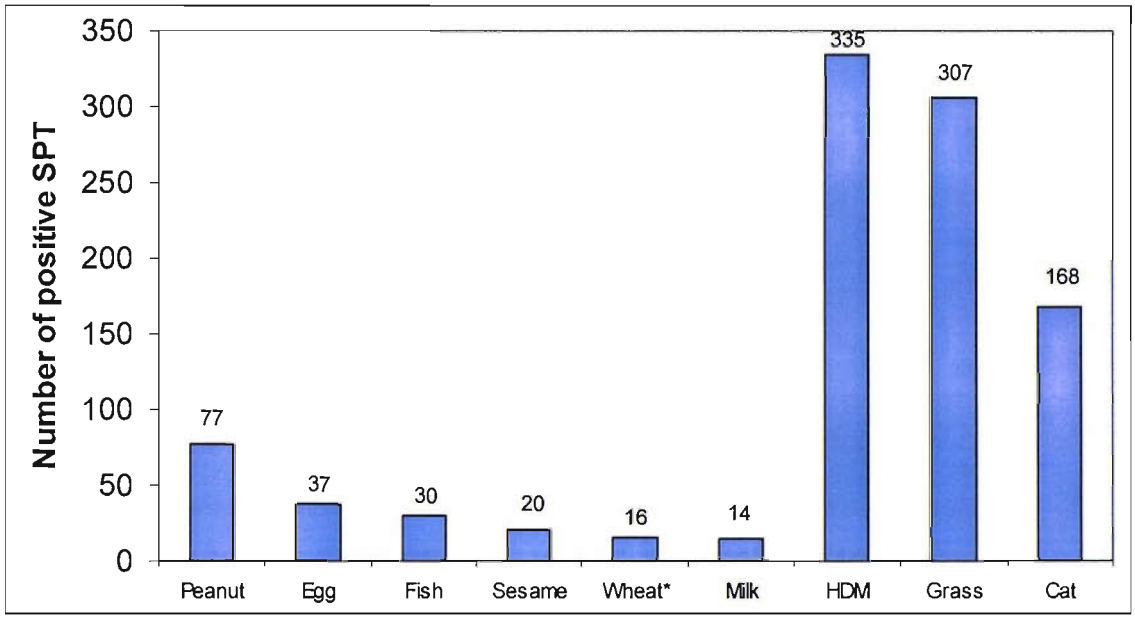
E) A cohort of 15 year old children resident on the Isle of Wight (757)

These five cohorts were pooled into one cohort to address the objective, which this chapter focuses on. Therefore in total, 6616 families were invited to participate and 4088 took part in the study.

2.3.2 Sensitisation rates

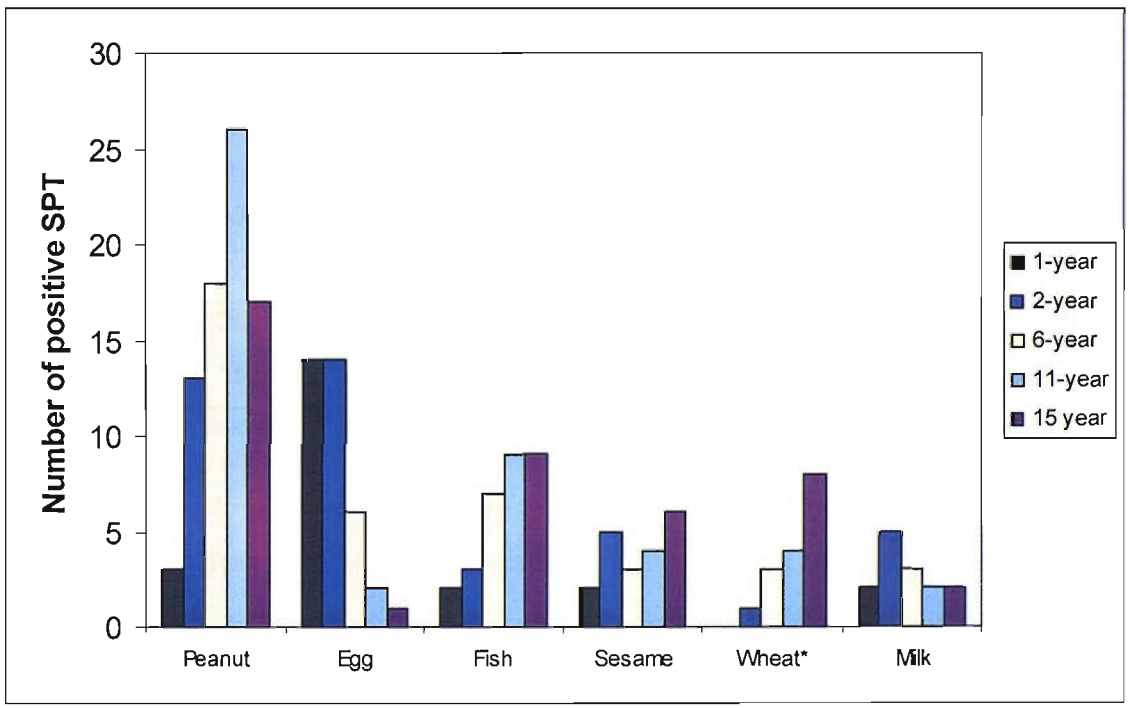
A total of 3469 infants/children underwent SPTs. Lack of parental consent was the main reason for some children not being tested. Children were SPTed to the predefined food (milk, egg, wheat, cod fish, peanut, and sesame) and aero-allergens (House dust mite (HDM), cat and grass). SPT to other foods and aero-allergens was performed when indicated by the history. Sensitisation data to all the different allergens for the pooled cohorts is shown in figure 2.1. Figures 2.2 and 2.3 show the sensitisation data to food and aeroallergens at different ages. Table 2.1 describes the sensitisation rates as the frequency of those with positive SPTs.

Figure 2.1: Sensitisation data in the pooled cohort (n=3469)



* Does not include wheat-grass cross-reactors

Figure 2.2: Sensitisation data to food allergens in the individual cohorts (n=3469)



* Does not include wheat-grass cross-reactors

Figure 2.3: Sensitisation data to aero-allergens in the individual cohorts (n=3469)

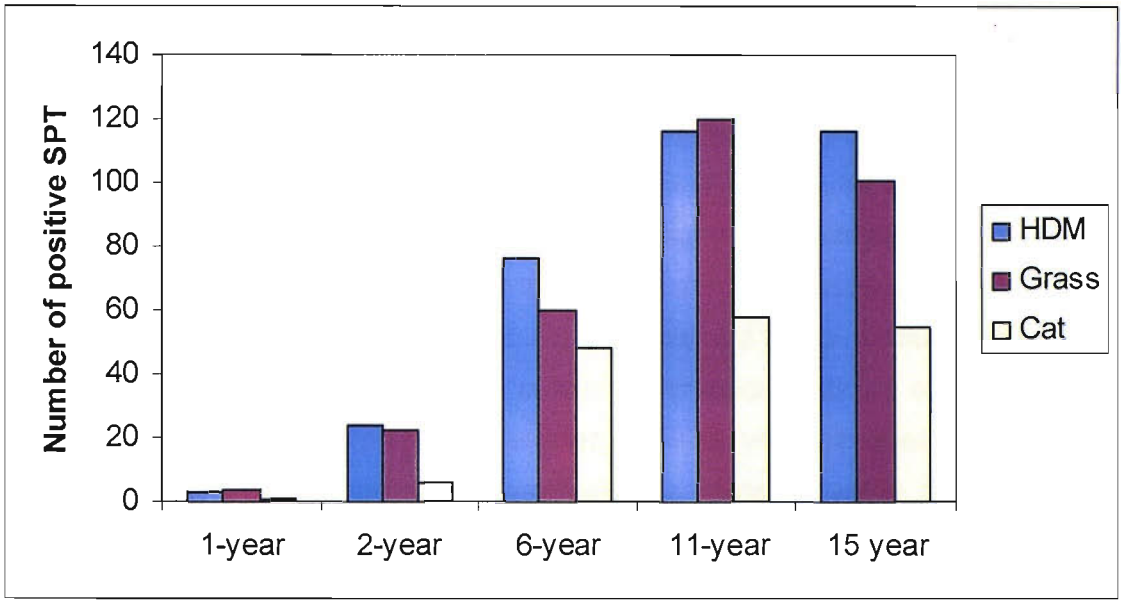


Table 2.1: Sensitisation rates in the five cohorts

Age assessed	Sensitisation rates to any predefined allergen (%) N	Sensitisation rates to any predefined aero-allergen (%) N	Sensitisation rates to any predefined food allergen (%) N
At 1 year	2.6 (20/763)	1.1 (8/763)	2.2 (17/763)
At 2 years	8.2 (54/658)	6.4 (42/658)	3.8 (25/658)
At 6 years	17.6 (123/700)	16.9 (118/700)	3.6* (25/700)
At 11 years	26.0 (181/699)	25.5 (178/699)	5.2* (36/699)
At 15 years	28.2 (183/649)	26.9 (175/649)	4.9* (32/649)
At all ages	**16.2 (561/3469)**	**15.0 (521/3469)**	**3.9 (135/3469)**

* Excludes the wheat-grass cross-reactors

2.3.3 Reported food hypersensitivity and food avoidance

The rate of reported FHS and food avoidance in the different cohorts is shown in table 2.2.

Table 2.2: Rate of reported FHS and foods avoided in the five cohorts

	1 year old cohort	2 year old cohort	6 year old cohort	11 year old cohort	15 year old cohort	Pooled cohort
Reported FHS	By 1 year: 27% (250/927) At 1 year: 7.2% (65/900)	7.5% (72/858)	11.8% (94/798)	11.6% (90/775)	12.4% (94/757)	10.2% (415/4088)
Food avoidance	54.8% (487/900)	32.2% (312/858)	14.6% (177/798)	15.7%) (122/775)	18.8% (142/757)	30.3% (1240/4088)

Not surprisingly, the foods and symptoms reported varied amongst the respective cohorts. During the first year of life, the foods most commonly implicated included cow's milk formula and first weaning foods such as fruits and baby rice. At one year, mothers also reported problems to egg, tomato and fish. As the diet became more varied during the second year of life, problems were reported to a variety of fruits, marmite, rich foods, spicy foods, additives and nuts. The children in the three school cohorts reported adverse reactions to all of the major food allergens including milk, egg, wheat, fish, sesame and nuts. Nuts were the main offending food in the six year old group, additives in the 11 year cohort and milk and dairy in the 15 year cohort. Other foods included: cheese, chocolate, citrus, meat, peppers, pork, pulses, vegetables, caffeine, yeast/yeast extracts, vinegar, bran, Eccles cake, muffins, pizza, sugar/sweets, fatty foods, Wheetos, rice, citrus fruit/non-citrus fruit, meat, vegetables and soya.

The symptoms most commonly reported at one year were gastro-intestinal (vomiting, diarrhoea) and cutaneous (eczema and rashes) with very few reporting respiratory symptoms. Other symptoms reported included sore bottom, catarrh and excessive crying. At two years the parents reported problems such as vomiting, diarrhoea, wheeze, eczema, urticaria, rashes, collapse, cough, hyperactivity and rhinitis. Other symptoms reported included red face and lethargy. Similar symptoms were reported by the parents/children of the three school cohorts. These included hyperactivity, and gastrointestinal problems followed by wheeze, cough, urticaria or other rash, rhinitis, collapse, angioedema, abdominal pain, vomiting and diarrhoea. A large number of children indicated that they simply disliked the food.

With regards to food avoidance, food additives and nuts were the most common food/ingredient avoided at one year. Peanuts and tree nuts were the most common food/ingredient avoided at age two, six and eleven years. Very few mothers avoided additives from the diet of their child at age two, but this was the second most common food ingredient avoided at six years.

Fish was the most commonly avoided food at age fifteen followed by nuts, egg and milk products. The specific reasons for this avoidance were not given in most cases and it was assumed that this is due to the perceived problems with the particular food or food ingredient. However, in some cases foods/ingredients were avoided due to dislike.

2.3.4 Food challenges

This section begins with describing the selection criteria in the pooled cohort and is followed by the results of the challenge outcomes.

2.3.4.1 Selection criteria for open food challenges

Food challenges will be presented based on the pooled cohort (n=4088). Of the 600 parents and/or children (250 one year olds + 72 two year olds + 94 six year olds + 90 eleven year olds + 94 fifteen year olds) reporting a problem with food, 402 children (173 one year olds + 47 two year olds + 64 six year olds + 60 eleven year olds + 58 fifteen year olds) were excluded from undergoing challenges for reasons such as 'only tried food once and tolerated it on second occasion', 'can eat other foods from the same food groups' (e.g. eats cheese and drinks milk, but cannot tolerate yoghurt), inconsistent history, dislike of a particular food but can eat it without any reaction, vomiting after an episode of over eating, reported a problem with hyperactivity to additives, a high-fibre diet causes diarrhoea, the child is afraid of eating peanuts and the parents reported a problem which the child only experienced during infancy, but food is well-tolerated at this stage.

19 children (17 one year olds and 2 fifteen year olds) did not improve on an exclusion diet under dietetic supervision and two parents declined further intervention. Therefore, 179 children (60 one-year olds + 25 two year olds + 30 six year olds + 30 eleven year olds + 34 fifteen year olds) were invited for open food challenges. An additional 24 children (8 one-year olds + 15 two year olds + 1 six year old) identified by means of a positive SPT without prior consumption of the food or a previous positive food challenge) were also invited for food challenges. This lead to a total of 203 infants (68 one year olds + 40 two year olds + 31 six year olds + 30 eleven year olds + 34 fifteen year olds) invited for food challenges.

However, 63 mothers (5 one year + 17 two years + 12 six year olds + 9 eleven year olds + 20 fifteen year olds) declined the food challenges. These children included:

- Six children sensitised to a food without prior exposure.
- Five children sensitised to a food with previous reactions.
- One child with negative SPT to the food but symptoms improved on elimination diet.
- One child with a negative SPT to egg reported a rash after consumption of egg.
- Six children with previous positive food challenges, followed by an increase in SPT size and/or accidental exposure to the food with symptoms.
- Six children with previous positive challenges, who subsequently had introduced the food at home without any reaction.

- One child sensitised to milk and egg at age one, whose symptoms improved on elimination diet, but declined SPT.
- Seventeen children previously diagnosed with FHS to a particular food in hospital.
- One child with a mother who had an allergy to hazelnut, presented with a positive SPT (3.25mm) hazelnut, but had no prior exposure.
- Nineteen parents just simply refused the food challenge.

Therefore 140 children (63 one year olds + 23 two year olds + 19 six year olds + 21 eleven year olds + 14 fifteen year olds) underwent food challenges with 2 children undergoing only DBPCFCs leading to 138 children undergoing OFCs. The foods included in these challenges were milk, egg, peanut, chocolate, sesame, almond, banana, wheat and citrus fruit, strawberry, tomato, fish, corn, melon, hazel nut, raisin, shell fish, cheese, kiwi, tomato, additives, salicylates and soya.

2.3.4.2 Open food challenges

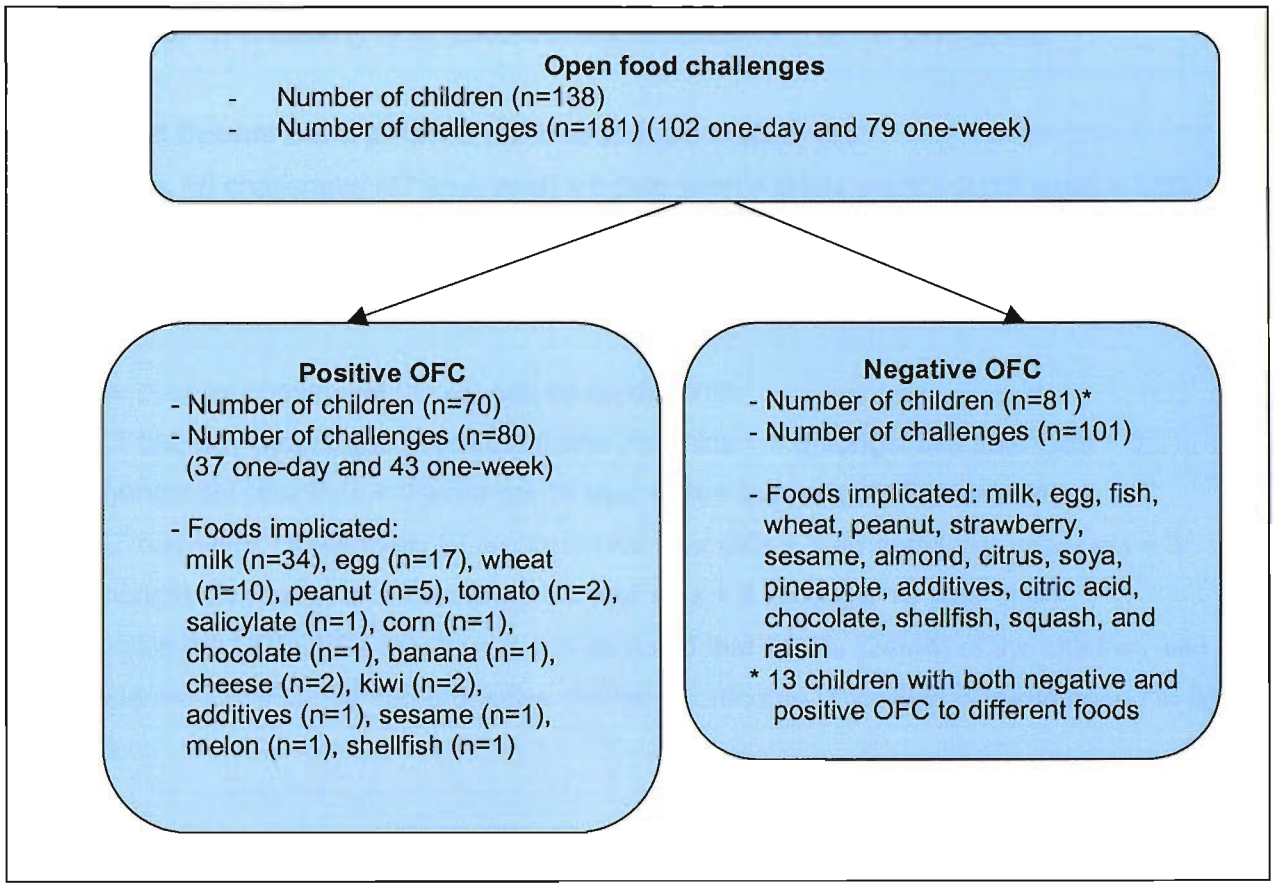
The 138 eligible children who consented to undergo OFCs underwent a total of 181 challenges between them of which 80 challenges were positive in 70 children.

The positive challenges (n=80) can be divided into:

- 37 one-day challenges (18 amongst one year olds + 4 amongst two year olds + 3 amongst six year olds + 7 amongst 11 year olds + 5 amongst 15 year olds)
- 43 one-week challenges (25 amongst one year olds + 6 amongst two year olds + 7 amongst six year olds + 2 amongst 11 year olds + 3 amongst 15 year olds)

Pooling the OFCs together, it can be noted that 50.7% (70/138) of the children who underwent OFCs had a positive challenge outcome. This data is summarised in figure 2.4.

Figure 2.4: Open food challenges performed in the five cohorts



2.3.4.3 Selection criteria for double blind placebo controlled food challenges

All the children with a positive OFC (n=70) were invited for a DBPCFC.

28 mothers declined the DBPCFCs. The reasons for refusing included:

- Seventeen children with severe reactions in past (either upon OFC or accidental exposure) who did not wish to undergo another challenge.
- One child reacted on skin contact with milk (confirmed with OFC) and consumed milk without any reaction.
- Three children had multiple food allergies and other allergic symptoms and the consultant allergist requested no further interventions in these instances.
- One child lived on the mainland.
- Four parents refused the DBPCFCs, but agreed to two open food challenges.
- One mother declined a DBPCFC and decided to introduce wheat into the child's diet despite the positive OFC.
- One DBPCFC was not performed due to the difficulties in performing DBPCFCs for OAS.

A total of 42 children (23 one year olds + 4 two year olds + 6 six year olds + 2 eleven year olds + 7 fifteen year olds) underwent DBPCFCs. Additionally, 2 two year olds underwent only DBPCFC leading to 44 children/parents consenting to the DBPCFCs.

2.3.4.4 Double blind placebo controlled food challenges

In total, 48 challenges (27 [one year] + 6 [two year] + 6 [six year] + 2 [11 year] + 7 [15 year]) were performed in 44 children. Of these, 28 challenges were positive in 24 children (15 [one year] + 1 [two year] + 3 [six year] + 1 [11 year] + 4 [15 year]).

The positive challenges (n=28) can be divided into:

- 11 one-day challenges (9 amongst one year olds + 0 amongst two year olds + 0 amongst six year olds + 0 amongst 11 year olds + 2 amongst 15 year olds)
- 17 one-week challenges (10 amongst one year olds + 1 amongst two year olds + 3 amongst six year olds + 1 amongst 11 year olds + 2 amongst 15 year olds)

Pooling the DBPCFCs together, it can be noted that 54.5% (24/44) of the children who underwent DBPCFCs had a positive challenge outcome. This data is summarised in figure 2.5.

Figure 2.5: Double blind placebo controlled food challenges performed in the five cohorts

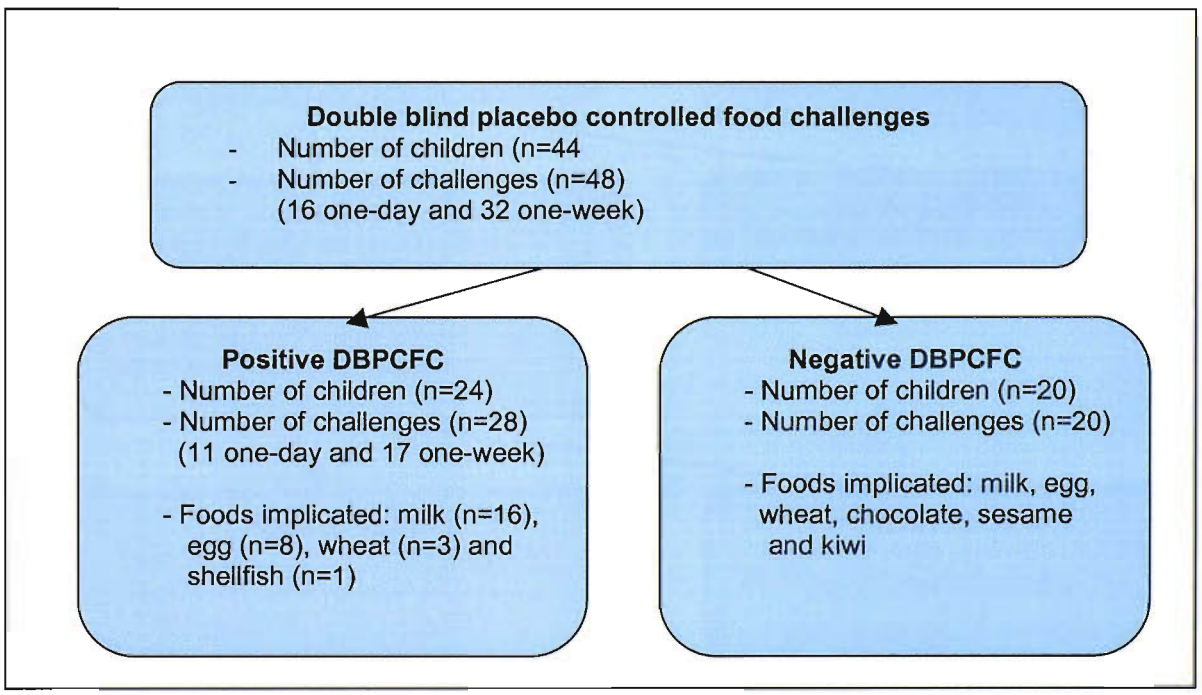
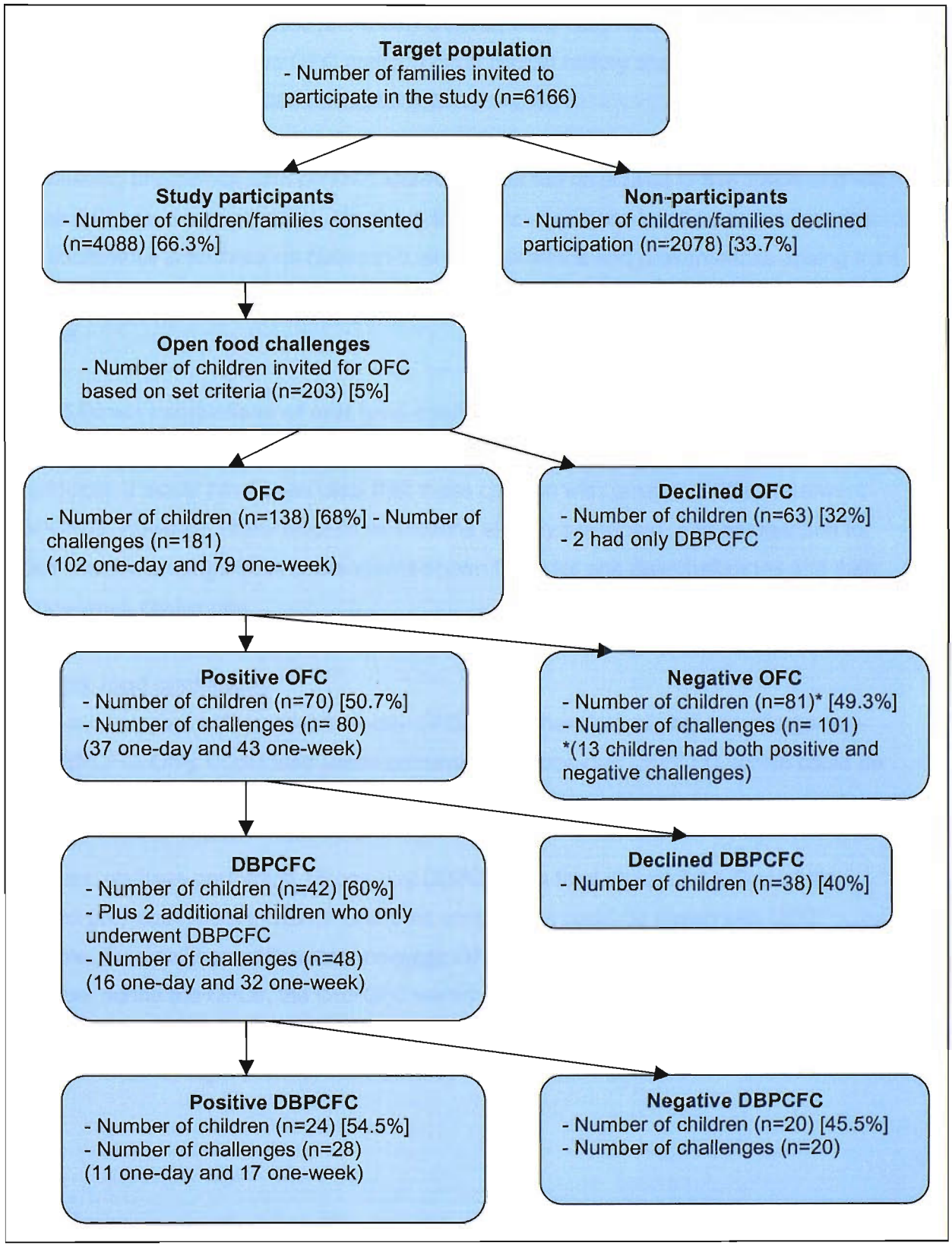


Figure 2.6 describes the flow of all the challenges conducted in the course of this project.

Figure 2.6: Food challenges conducted amongst all children



In summary, using the OFC outcome, FHS was confirmed in 70/4088 (1.7%) children. This however is not a true estimate as a large number of children did not undergo OFCs

due to reasons discussed under 2.3.4.1. Therefore, the prevalence of FHS based on OFC, a good clinical history and positive SPT is 111/4088 (2.7%; 95%CI 2.2 – 3.3). Based on DBPCFCs, 24 (0.6% [24/4088]) children were diagnosed with FHS. However, based on DBPCFC, positive OFC and/or a good clinical history and/or positive SPT the prevalence of FHS is 85/4088 (2.1%; 95% CI 1.7 – 2.6).

Establishing prevalence data on FHS was not one of the objectives of this thesis and will not be addressed in more detail. However, the author has been involved in publications and conference presentations (listed in "List of publications and presentations arising from this study") regarding detailed description of the incidence and prevalence of FHS in these cohorts.

2.3.4.5 Direct comparison of oral food challenge and double blind placebo controlled food challenge

In principle, it would have been ideal if all those children with positive OFCs underwent DBPCFCs. However, many refused for reasons already presented. The comparison for those who did undergo both challenges is shown firstly for one-day challenges and then for one-week challenges.

One-day food challenges

Thirty-seven cases with positive one-day OFCs were therefore eligible to undergo one-day DBPCFC. Only 11 of these cases consented to a one-day DBPCFC, which could be compared with the one-day OFC.

However, we have performed 16 one-day DBPCFCs in total (figure 2.6.). One of the children only underwent a DBPCFC and no comparison could be drawn with OFC outcome. Four children underwent one-week OFCs, but due to the nature of their symptom during the OFCs, the DBPCFC were performed as one-day DBPCFCs. These four challenges are therefore discussed under one-week challenges.
Of these 11 OFC, eight (72.7%) were positive (table 2.3).

Table 2.3: One-day OFCs vs. one-day DBPCFCs performed in the pooled cohort (n=11)

	Food	OFC outcome	Symptoms Experienced	DBPCFC outcome	Symptoms experienced
1	Egg	Positive	Urticaria Rash	Positive	Rash Urticaria
2	Egg	Positive	Rash Itch	Positive	Rash Urticaria
3	Egg	Positive	Urticaria	Positive	Urticaria
4	Egg	Positive	Eczema	Positive	Eczema
5	Egg	Positive	Rash Erythema	Positive	Rash Erythema
6	Egg	Positive	Urticaria	Positive	Urticaria Erythema
7	Egg	Positive	Urticaria	Negative	NA
8	Milk	Positive	Nausea Vomiting	Positive	Nausea Vomiting
9	Sesame	Positive	Vomiting	Negative	NA
10	Prawn	Positive	Urticaria	Positive	Tingling of lips
11	Kiwi	Positive	OAS	Negative	NA

In total, 7 DBPCFCs to egg were performed, of which six were positive. Of the four positive milk OFCs in all cohorts, one challenge was repeated as a DBPCFC and it was positive. The prawn challenge had a positive DBPCFC outcome and the positive sesame OFC had a negative outcome. One of the DBPCFCs to kiwi was negative (n=1) and the other OFC was not repeated as it was decided not to perform any more blinded challenges for the diagnosis of OAS.

One-week food challenges

For the one-week OFCs, comparisons were drawn between 35 challenges. In total however, only thirty two one-week DBPCFCs were performed (figure 2.6). One of these children underwent a DBPCFC only and no comparson could be drawn with an OFC, leading to 31 challenges. As discussed on p.74, four one-day DBPCFCs were preceded by one-week OFCs and they are therefore discussed in this section, leading to 35 challenges. Therefore 35 DBPCFCs were performed of which 20 (57.1%) challenges were positive.

Table 2.4: One-week OFCs vs. one-week DBPCFCs performed in the pooled cohort (n=35)

	Case	OFC outcome	Symptoms experienced	DBPCFC outcome	Symptoms experienced
1	Milk	Positive	Eczema Generally unwell	Positive	Eczema Generally unwell
2	Milk	Positive	Urticaria Rash	Positive	Urticaria Rash
3	Milk	Positive	Eczema Vomiting	Positive	Eczema
4	Milk	Positive	Vomiting Eczema Colic	Positive	Eczema
5	Milk	Positive	Diarrhoea Excessive crying	Positive	Diarrhoea Excessive crying
6	Milk	Positive	Excessive crying Eczema Generally unwell	Positive	Excessive crying Eczema Generally unwell
7	Milk	Positive	Eczema	Positive	Eczema
8	Milk	Positive	Facial rash	Positive	Facial rash
9	Milk	Positive	Diarrhoea Vomiting	Positive	Diarrhoea Vomiting
10	Milk	Positive	Distended abdomen Diarrhoea Vomiting	Positive	Distended abdomen Diarrhoea Vomiting
11	Milk	Positive	Eczema Erythema	Positive	Eczema
12	Milk	Positive	Congested nose	Positive	Congested nose
13	Milk	Positive	Diarrhoea Vomiting	Positive	Diarrhoea Vomiting
14	Milk	Positive	Nasal congestion Abdominal pain	Positive	Nasal congestion Abdominal pain Nausea
15	Milk	Positive	Eczema	Positive	Eczema
16	Milk	Positive	Eczema	Negative	NA
17	Milk	Positive	Diarrhoea	Negative	NA
18	Milk	Positive	Vomiting	Negative	NA
19	Milk	Positive	Eczema Vomiting	Negative	NA
20	Milk	Positive	Eczema	Negative	NA
21	Milk	Positive	Diarrhoea	Negative	NA
22	Milk	Positive	Eczema	Negative	NA
23	Milk	Positive	Diarrhoea	Negative	NA
24	Milk	Positive	Eczema Urticaria Wheeze Cough	Negative	NA
25	Milk	Positive	Diarrhoea	Negative	NA
26	Milk	Positive	Diarrhoea Abdominal pain	Negative	NA
27	Egg	Positive	Eczema	Positive	Eczema
28	Egg	Positive	Urticaria	Positive	Urticaria
29	Wheat	Positive	Rash Vomiting Excessive crying	Positive	Rash Vomiting Excessive crying
30	Wheat	Positive	Eczema	Positive	Eczema

31	Wheat	Positive	Stomach ache Distended abdomen	Positive	Stomach ache Distended abdomen
32	Wheat	Positive	Rash	Negative	NA
33	Wheat	Positive	Constipation Abdominal pain Blood in stools	Negative	NA
34	Chocolate	Positive	Diarrhoea	Negative	NA
35	Additives	Positive	Migraine	Negative	NA

Of the 30 positive open milk challenges, 26 were repeated as DBPCFCs of which 15 challenges were positive. Both of the egg challenges were followed up by a positive DBPCFC. Of the nine wheat challenges, five challenges were repeated double blind, and three were positive. The positive chocolate and additive OFCs had a negative DBPCFC outcome.

We could therefore directly compare the results of OFCs and DBPCFCs in 42 children who underwent 46 challenges (11 one-day and 35 one-week challenges). In total, 60.9% of these challenges (28/46: 8 one-day and 20 one-week challenges) had a positive outcome.

In summary, the positive predictive value of the one-day challenges was: 8 positive DBPCFCs out of 11 positive OFCs: 72.7% (95% CI: 39.0 – 94.0%). Three children had positive OFCs that were not confirmed by DBPCFCs of which 2 of the children presented with subjective symptoms. The positive predictive value of the one-week challenges were: 20 positive DBPCFCs out of 35 OFCs: 57.0% (95% CI: 39.4 – 73.7%). Of the 15 children with positive OFCs, subsequently followed by a negative DBPCFC all 15 presented with subjective symptoms such as generalised rash or flare of eczema, diarrhoea and vomiting.

Of the 31 positive OFCs in children younger than 2 years, 20 (66.7%) had a positive DBPCFC and of the 15 positive OFCs in children older than 2 years, 8 (53.3%) had a positive DBPCFC. However, there was no evidence to indicate that the young children are more likely to have a positive OFC confirmed by a DBPCFC than the older children (Fisher's exact p=0.53).

2.3.4.6 Symptoms of food challenges

This section describes the symptoms experienced during the food challenge in order to establish how well the reported history of symptoms correlated with the outcome of the challenge.

Open food challenges

Of the 102 one-day OFCs performed in the children, 37 (36.3%) one-day challenges were positive. At least one of the symptoms reported by the history was experienced in 25/37 (67.5%) of the challenges.

Of the 79 one-week OFCs performed in the children, 43 (54.4%) one-week challenges were positive. At least one of the symptoms reported by the history was experienced in 34/43 (79%) of the challenges. Although those who underwent the one-day challenges compared to those who underwent one-week challenges were less likely to have a history of symptoms similar to that experienced during the food challenge the difference was not significant ($\chi^2 = 1.36$, $p = 0.24$).

Double blind placebo controlled food challenges

Of the 16 one-day DBPCFCs performed, 11(68.8%) one-day challenges were positive. At least one of the symptoms reported by the history was experienced in 5/11 (45.5%) of the challenges.

Of the 32 one-week DBPCFCs performed in the five cohorts, 17 (53.1%) one-week challenges were positive. At least one of the symptoms reported by the history was experienced in 14/17 (82.4%) of the challenges. Although those who underwent the one-day DBPCFCs compared to those who underwent one-week DBPCFCs were less likely to have a history of symptoms similar to that experienced during the food challenge the difference was not significant ($\chi^2 = 2.65$, $p = 0.10$).

2.3.4.7 Comparison of reported dose with doses needed during challenges

The challenges were further investigated in order to establish how well the reported history of dose reacted to correlated with the actual outcome of the challenges.

Open food challenges

The data on doses reported and doses reacted to is summarised in table 2.5 and 2.6 for one-day and one-week OFC respectively.

Table 2.5: Reported dose and doses used in the one-day OFCs (n=37)

Child's age (yrs)	Food	SPT mm	Dose reported	Symptoms during challenge	Dose reacted to during food challenge	Time to reaction
1	Milk	0	On touch	Urticaria	1 drop topical	5 min
1	Milk	0	230 ml (a bottle of formula = 230 ml)	Wheeze	200 ml	12 hours
1	Milk	1.25	230 ml	Urticaria Rash	Last 2 ml Total 3.5 ml Last 70 ml Total 73.5 ml	15 min 45 min 25 min 70 min
15	Milk	9.5	1-30 ml	Vomiting Generally unwell	0.5 ml 0.5 ml	15 min 10 min
1	Egg	4.5	Did not know	Rash Eczema Generally unwell	Last 2 g Total 7g Last 2 g Total 7g Last 2 g Total 7g	1 hour 2 hours 11 hours 12 hours 23 hours 24 hours
1	Egg	5	Did not know	Urticaria	Labial rub	7 min
1	Egg	7.5	Did not know	Rash Angioedema Urticaria	1 g 1g 1g	10 min 10 min 15 min
1	Egg	5	Did not know	Rash Urticaria Rash	Labial rub 500 mg 500 mg	10 min 6 min 6 min
1	Egg	0	Did not know	Urticaria	Labial rub Urticaria	50 min 25 min
1	Egg	6.75	Did not know	Urticaria Rash	1 g	5 min
1	Egg	0	¼ egg = 10 g	Rash Urticaria	1 g Last 10 g Total 18 g	10 min 15 min 1hr 40 min
1	Egg	0	1 scrambled egg = 40 -50 g	Rash	15 g 18 g	10 min 3hr 30 min
1	Egg	3.5	Did not know	Urticaria Vomiting Irritable	Last 2 g Total 3 g Last 2 g Total 3 g Last 2 g Total 3 g	10 min 30 min 10 min 30 min 10 min 30 min
1	Egg	3	1 scrambled egg = 40 -50 g	Erythema	Last 10 g Total 18 g	16 min 30 min
1	Egg	3.5	Did not know	Urticaria Urticaria Rash	Labial rub 1 g Last2 g Total 3 g	10 min 5 min 5 min 30 min
2	Egg	4	1 g	Urticaria	1 g	15 min
2	Egg	0	1 g	Lip swelling Lip swelling Itch	Labial rub 1g 1g	7 min 5 min 5 min
2	Egg	8	0.5 – 1.0 g	Urticaria "Delayed erythema"	1 g 1 g	5 min 1 hr 5 min
2	Egg	8	Did not know	Urticaria	Labial rub	3 min
6	Peanut	8.25	Did not know	Angioedema Runny nose and eyes	Labial rub	10 min
6	Peanut	5.75	A few peanuts	Pallor Vomiting	Last dose: 1 peanut Total dose: 1 ½ peanut Last dose: 4 peanuts Total dose: 8 peanuts	10 min 1 hr 10 min 5 min 2 hours

11	Peanut	6	Did not know	Angioedema, Nausea	250 mg 250 mg	30 min 5 min
11	Peanut	8.5	Did not know	Nausea, Urticaria, Vomiting	250 mg 250 mg 250 mg	10 min 10 min 35 min
11	Peanut	9.5	Did not know	Tingling tongue Itching - back of throat Nausea, Vomiting	Labial rub 250 mg 250 mg 250 min	5 min 5 min 5 min 45 min
11	Cheese	NA	30 – 60 g cheese	Abdominal pain Vomiting Diarrhoea	30 g 30 g 30 g	2 hours 2 hours 3 hours
11	Cheese	NA	30 – 60 g cheese	Stomach ache Nausea Headache	Last dose: 60g Total dose: 110 g Last dose: 60g Total dose: 110 g Last dose: 60g Total dose: 110 g	8 hours 10 hours 8 hours 10 hours 8 hours 10 hours
1	Tomato	0	½ tomato = 30 – 50 g	Rash	Labial rub	2 hours
11	Tomato	2.75	Few slices	OAS	50 g	10 min
11	Kiwi	2.25	Few slices	OAS	50 g	10 min
15	Kiwi	0	Few slices	Itchy lip and tongue	Last dose: 10 g Total dose: 18 g	5 min 1hr 10 min
1	Wheat	0	Only through breast milk	Vomiting Urticaria Irritable	Last 2 g Total 5 g Last 2 g Total 5 g Last 2 g Total 5 g	40 min 1 hr 20 min 40 min 1hr 20 min 40 min 1 hr 20 min
1	Salicylates	NA	Did not know	Angioedema Stiff/swollen joints	250 ml blackcurrant juice	2 hours
1	Corn	5	Only through breast milk	Urticaria Rash	Last 4 g Total 10 g Last 4 g Total 10 g	30 min 1 hr 15 min 30 min 1 hr 15 min
6	Banana	4	1 banana = 80 - 100 g	Vomiting	Last 12 g Total 40 g	15 min 30 min
15	Melon	0	Did not know	Tingling of tongue and lips	1 g	20 min
15	Sesame	4	Did not know	Swelling of lip Vomited	Labial rub Last dose: 3g Total dose: 6.5 g	5 min 1 min 50 min
15	Prawn	8.5	3-5 prawns = 9-15 g	Urticaria	Labial rub	20 min

Only 4/37 (10.8%) of the mothers reported an amount of food similar to the amount of food triggering the symptoms during the food challenge. In a great majority of the cases, the doses which elicited a reaction, were higher than the dose indicated by the history.

Table 2.6: Reported dose and doses used in the one-week OFCs (n=43)

Child's age (yrs)	Food	SPT mm	Dose reported	Symptoms during challenge	Dose reacted to during food challenge	Time to reaction
1	Milk	0	230 ml (1 bottle of formula = 230 ml)	Eczema	170 ml	Day 1-3[α]
1	Milk	6.5	Amount in breast milk	Rash Excessive crying Itch	10 – 15 ml	Day 1[α] Day 1 Day 1
1	Milk	0	230 ml	Vomiting Eczema	230 ml 560 ml	Day 1-4 Day 5-7
1	Milk	0	230 ml	Vomiting	580 ml	Day 6
1	Milk	0	Amount in breast milk	Diarrhoea Vomiting	120 – 230 ml	Day 6 Day 7
1	Milk	0	230 ml	Diarrhoea	500 ml	Day 2-7
1	Milk	0	230 ml	Abdominal pain Restlessness Rash Sleep disturb	120 – 300 ml	Day 2-4[α] Day 1 Day 4 Day 4
1	Milk	0	230 ml	Rash	230 ml	Day 4-6 [α]
1	Milk	1.25	230 ml	Angioedema Excessive crying Diarrhoea	230 ml	Day 1-2 [α]
1	Milk	0	230 ml	Vomiting	230 ml	Day 3[α]
1	Milk	0	Did not know	Diarrhoea Sore bottom	30 g margarine	Day 1[α]
1	Milk	0	230 ml	Eczema	120 ml	Day 1-2 [α]
1	Milk	0	150 -230 ml	Vomiting	30 ml	Day 1 [α]
1	Milk	0	Any amount	Inflamed nappy area	300 ml	Day 1-7
1	Milk	0	230 ml	Urticaria	420 ml	Day 1-7
1	Milk	0	Variable amounts	Diarrhoea Vomiting	300 ml	Day 2 [α]
1	Milk	6.25	230 ml	Rash	180 ml	Day 1-3[α]
1	Milk	0	Did not know	Eczema	560 ml	Day 4-5 [α]
1	Milk	0	230 ml	Diarrhoea Distended abdomen	Little bits of food	Day 2-6 [α]
2	Milk	0	250 – 500 ml	Itch Erythema Eczema	250 – 500 ml	Day 1-4α Day 1-4α Day 1-4α
2	Milk	0	230 ml	Diarrhoea	230 ml	Day 1-2α
2	Milk	2.5	Did not know	Eczema	2 portions = 500 ml	Day 1-3α
2	Milk	0	Did not know	Diarrhoea	125 – 250 ml	Day 2-3α
2	Milk	0	"Normal amount" ≈ 2- 3 portions	Eczema Urticaria Wheeze Cough	1- 2 portions = 10 g margarine – 250 ml milk	Day 2-7 Day 2 Day 1 Day 2-3
6	Milk	4	100 ml	Eczema Diarrhoea	100 ml 100 ml	Day 2α Day 1α
6	Milk	0	> 250 ml	Congested nose	250 ml	Day 2α
6	Milk	0	"normal amount"	Diarrhoea Vomiting	250 ml	Day 2α Day 2α
6	Milk	0	"any amount"	Diarrhoea Abdominal pain	50 ml	Day 1-2α Day 1-2α

11	Milk	0	> 500 ml	Nasal congestion Abdominal pain	500 -600 ml	Day 3-4α Day 3-4α
15	Milk	0	20 g butter or little bit of milk in tea	Eczema	20 g butter	Day 3-7
1	Egg	0	Did not know	Red facial flush	2.5 g	Day 2 α
1	Egg	2	Did not know	Rash Urticaria	1 g 32 g 67 g	Day 1 Day 6 Day 7
1	Wheat	0	1 Weetabix	Rash Vomiting Excessive crying	3-4 portions wheat	Day 2-4α Day 2 Day 3
1	Wheat	0	1 Weetabix	Rash	1 Weetabix	Day 2
1	Wheat	0	1 Weetabix	Diarrhoea	1 portion of wheat	Day 2-7
1	Wheat	0	As above	Eczema	Amount in breast milk	Day 4-7
2	Wheat	0	3-4 portions wheat	Rash	3 portions	Day 1-7
6	Wheat	0	"any amount"	Diarrhoea Abdominal pain Generally unwell	3-4 portions	Day 1-3 Day 1-3 Day 2-3
6	Wheat	0	Did not know	Eczema	1-2 portions	Day 2-7
15	Wheat	5.25	Did not know	Distended abdomen Tiredness Discomfort Abdominal pain	4-6 portions of wheat per day	Day 2-3 Day 2-3 Day 2-3 Day 2-4α
15	Wheat	0	Bowl of cereal	Abdominal pain Blood in stools	4-6 portions of wheat	Day 2-7 Day 2-7
6	Chocolate	0	1 square	Diarrhoea	1 square	Day 1α
11	Additives	NA	Did not know	Migraine	150 g of jelly sweets with azo-dyes	Day 2-4α

α End of challenges due to positive outcome.

Only 10/43 (23.2%) of the mothers reported an amount of food similar (not exactly equal) to the amount of food triggering the symptoms during the food challenge.

In summary, although those who underwent the one-day challenges compared to those who underwent one-week challenges were less likely to know how much food would trigger a response, the difference was not significant ($\chi^2 = 0.83$, $p = 0.36$).

B) <u>Double blind placebo controlled food challenges</u>

The data on doses reported and doses reacted to is summarised in table 2.7 and 2.8 for one-day and one-week OFCs respectively.

Table 2.7: Reported dose and doses used in the one-day DBPCFCs (n=11)

Child's age (yrs)	Food	SPT mm	Dose reported	Symptoms experienced	Dose	Time to reaction
1	Milk	6.5	Only through breast milk	Urticaria Rash	Last 8 ml Total 12 ml Last 8 ml Total 12 ml	15 min 30 min 15 min 30 min
15	Milk	9.5	1-30 ml	Vomiting Distended abdomen Abdominal pain/Diarrhoea	100 ml 100 ml 100 ml	10 min 2 hours 8 hours
1	Egg	7.5	NA	Urticaria	250 mg	15 min
1	Egg	5	NA	Rash	250 mg	5 min
1	Egg	0	NA Don't know	Urticaria Itch Generally unwell	1 g 1 g 1g	7 min 7 min 7 min
1	Egg	0	Don't know 10 g NA	Urticaria	<1 g	25 min
1	Egg	6.75	NA	Rash Excessive crying Urticaria	500 mg Last 1 g Total 1.5 g Last 1.5 g Total 2.5 g	15 min 15 min 25 min 18 min 1 hr
1	Egg	3	1 scrambled egg = 40 – 50 g	Urticaria Rash	Last 5 g Total 8 g Last 5 g Total 8 g	45 min 1hr 30 min 5 g 8 g
1	Egg	3.5	NA	Urticaria Erythema	Last 15 g Total 25 g Last 15 g Total 25 g	15 min 1 hr 30 min 15 min 1 hr 30 min
1	Egg	2	NA	Urticaria Rash Erythema	20 g Last 40 g Total 60 g Last 40 g Total 60 g	10 min 15 min 55 min 15 min 55 min
15	Prawn	8.5	3-5 prawns = 9 – 15 g	Tingling of lip and tongue	Last dose: 3 g Total dose: 6 g	30 min 45 min

Note that only the children from the one year and 15 year old cohorts underwent one-day DBPCFCs. None of the mothers reported an amount of food similar to the amount of food triggering the symptoms during the food challenge.

Table 2.8: Reported dose and doses used in the one-week DBPCFCs (n=17)

Child's age (yrs)	Study number	SPT Mm	Dose reported	Symptoms experienced	Dose	Time to reaction
1	Milk	0	230 ml (1 bottle of formula = 230 ml)	Itch Rash Sleep disturbed	250 – 400 ml	Day 1 -2 Day 2-7 Day 2-7
1	Milk	0	230 ml	Eczema	230 ml	Day 2-7
1	Milk	0	230 ml	Rash Vomiting	200 ml	Day 4 α Day 4 α
1	Milk	1.25	230 ml	Diarrhoea Excessive crying Generally unwell	480 ml	Day 2-5 α Day 2-5 Day 2-5
1	Milk	0	NA	Excessive crying Eczema Generally unwell	400 - 500 ml	Day 1,3-7 Day 3 Day 6-7
1	Milk	0	230 ml	Itch Eczema	250 – 500 ml	Day 2-4 α Day4
1	Milk	0	230 ml	Urticaria	400 ml	Day 3-7
1	Milk	0	Variable amounts	Diarrhoea Vomiting	250 ml	Day 2-4 α Day 3-4 α
1	Milk	0	230 ml	Abdominal pain Vomiting/Diarrhoea	250 ml	Day 4-5 α
2	Milk	0	230 ml	Eczema Itch	500 ml	Day 1-7 Day 1-7
6	Milk	0	> 250 ml	Blocked nose Generally unwell	200 ml	Day 2-4α Day 2-4α
6	Milk	0	"normal amount"	Diarrhoea Rash	200 ml	Day 2α Day 2α
11	Milk	0	>500 ml	Nasal congestion Abdominal pain Nausea	100 – 200 ml	Day 1-3 Day 2-3 Day 3-6α
15	Milk		20 g butter or little bit of milk	Eczema Itch	20 g milk powder	Day 4-7 Day 4-7
1	Wheat	0	1 Weetabix	Rash Vomiting	5 portions	Day 3 -7 Day 3-6
6	Wheat	0	Don't know	Eczema	1-3 portions	Day 2-7
15	Wheat		NA	Abdominal pain Distended abdomen	3 cupcakes	Day 2-3α Day 2-3α

α End of challenges due to positive outcome.

One mother (6.25%) reported an amount of food similar to the amount of food triggering the symptoms during the food challenge.

In summary, although those who underwent the one-day DBPCFCs compared to those who underwent one-week DBPCFCs were less likely to know how much food would trigger a response, the difference was not significant ($\chi^2 = 1.08$, $p = 0.30$).

2.3.4.8 Practical considerations of food challenges

We aimed to compare the ease of performing OFCs vs. DBPCFCs in terms of being able to keep to the time intervals as recommended by the challenge protocols, number of vehicles and dosages used and adherence to the specified challenge duration.

2.3.4.8.1 Practical considerations during the one-day challenges

Time intervals

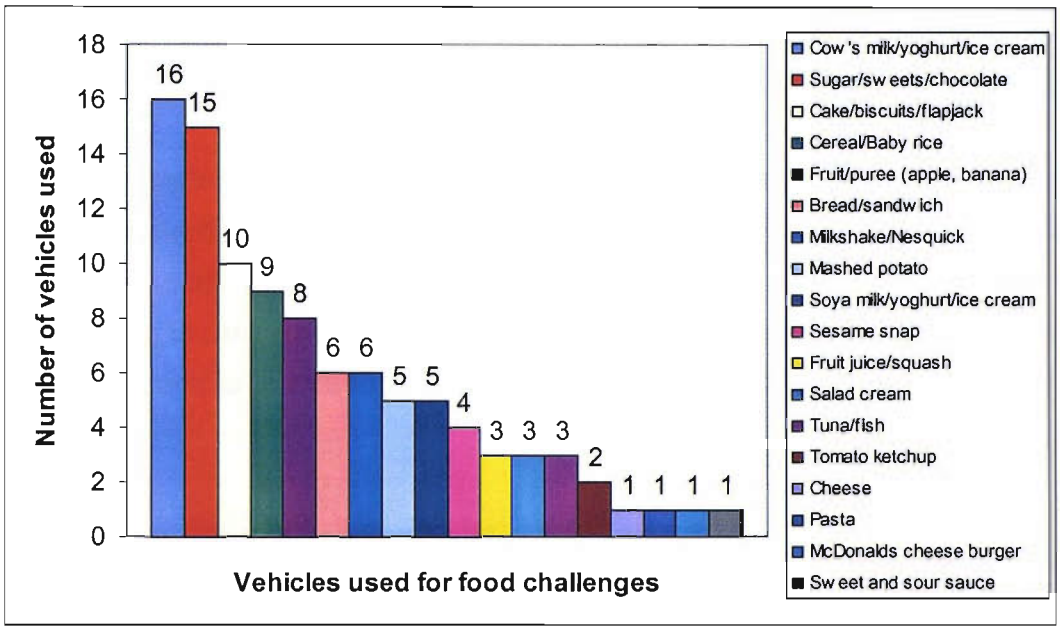
With the OFCs, we were able to keep to time intervals as indicated by the challenge protocols in 65.7% (67/102) of the challenges (22/44 of the one year OFCs [50%] + 7/12 of the two year OFCs [58%] + 8/11 of the six year OFCs [72%] + 17/22 of the 11 year OFCs [77%] + 13/13 of the 15 year OFCs [100%]). It therefore appears that most of the problems with keeping to time intervals were encountered in the younger cohorts as we kept to the time intervals in most cases in the older cohorts. In the one year old cohort, the reasons for not being able to keep to time intervals were: baby falling asleep (n=10), refused challenge food (n=6), positive challenge/challenge discontinued (n=2), baby wanted more food at once (n=3), baby full/had enough (n=1). In the two year cohort the reasons were: Shortened challenge to fit in with history (n=1) and refused challenge food (n=4). For the six and 11 year cohorts the reasons were: uncertain if symptoms developed and needed extra time between doses (n=1), refusal of challenge food (n=2), mother's choice of challenge duration (n=2), needed to adjust time-intervals for OAS challenges (n=2) and a positive challenge outcome (n=1).

With the DBPCFCs, we were able to keep to time intervals in 62.5% (10/16) of the challenges (6/11 of the one year DBPCFCs [54.5%] + 0/1 of the two year DBPCFCs [0%] + 4/4 [100%] of the 15 year DBPCFCs).Once again, it seems that it was easier to keep to the time intervals in the older cohorts than in the younger cohorts. The reasons for not keeping to planned time intervals in the one and two year old cohort included: infant falling asleep (n=1), infants refused challenge food (n=2), positive challenge/challenge discontinued (n=3), child full/had enough (n=1) with one mother providing no reasons.

Number of vehicles used

We used foods as a vehicle to carry the suspecting allergic foods. Different vehicles were used for 61 (61%) of the 102 OFCs in order to ensure the infants/children ate the challenge food. The range of vehicles used in the OFCs is shown in figure 2.7.

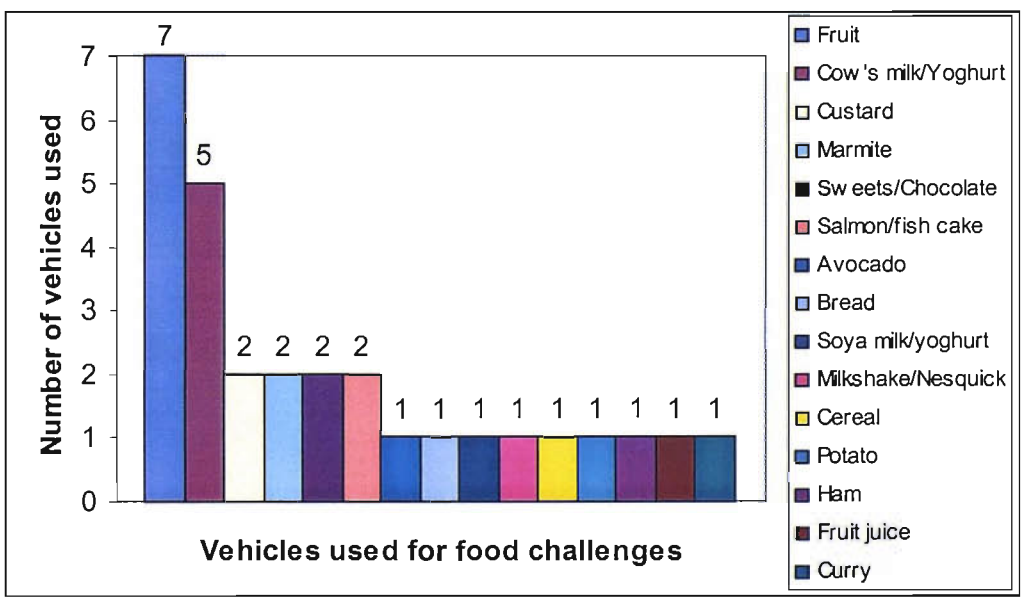
Figure 2.7: Vehicles used in the one-day OFCs



The reasons for using these vehicles were to make the challenge food more palatable, to provide the food as indicated by the history, to hide a certain food e.g. egg from the patient if they did not want to eat this particular food, mother's choice of food to mix with the suspected allergen or if the infant/child refused the challenge food, food as prescribed by the challenge protocols.

With the DBPCFCs, vehicles were used in 15 (93.8%) of the 16 challenges. The range of vehicles used in the DBPCFCs is shown in figure 2.8.

Figure 2.8: Vehicles used in the one-day DBPCFCs



As with the OFCs, the main reasons for using these vehicles was to make the challenge food more palatable, to mask the challenge food for a DBPCFC, or because it was the mother's choice of vehicle.

A range of placebos were used for the DBPCFCs. For the egg challenges these included: egg-free custard, plain yoghurt, white sauce, macaroni cheese, and plain soya yoghurt or potato croquettes. For the milk challenges Neocate/Wysoy plus Duocal or Rice milk smoothies was used as the placebo. A fish mix was used as placebo for the prawn challenge, pumpkin seeds for the sesame challenge and gooseberries for the kiwi challenge.

Number of challenge dosages used

The limit of challenge dose and the upper limit of the number of challenges, dosages needed for each challenge was estimated prior to the challenge taking place.

With the OFCs the adherence rate with the number of challenge dosages indicated on the challenge protocol was 41.25% (42/102). The main reasons for deviation from the challenge protocols were either due to the infant falling asleep or refusing the challenge food. However, in 20 of the 42 (47.6%) OFCs the recommended number of challenge dosages was not used due to a positive challenge rather than difficulties in performing the food challenge.

With the DBPCFCs the adherence rate with the number of challenge dosages indicated on the challenge protocol was 50% (8/16). The main reason for deviation from the challenge protocols was the infant/child refusing the challenge food. However, in 50% of these DBPCFCs (4/8), the recommended number of challenge dosages was not used due to a positive challenge rather than difficulties in performing the food challenge.

2.3.4.8.2 Practical considerations during the one-week challenges

Adherence to challenge duration

The challenge duration for each challenge was specified prior to performing the food challenge.

With the OFCs, we could not keep to the duration of the challenges (7 days) in 41.8% (33/79) of challenges. With 4 of the 33 challenges (12.1%) the reasons for deviation from the challenge protocol included difficulties in performing the food challenge or parents carrying out their own version of the challenge protocol in terms of duration/food chosen.

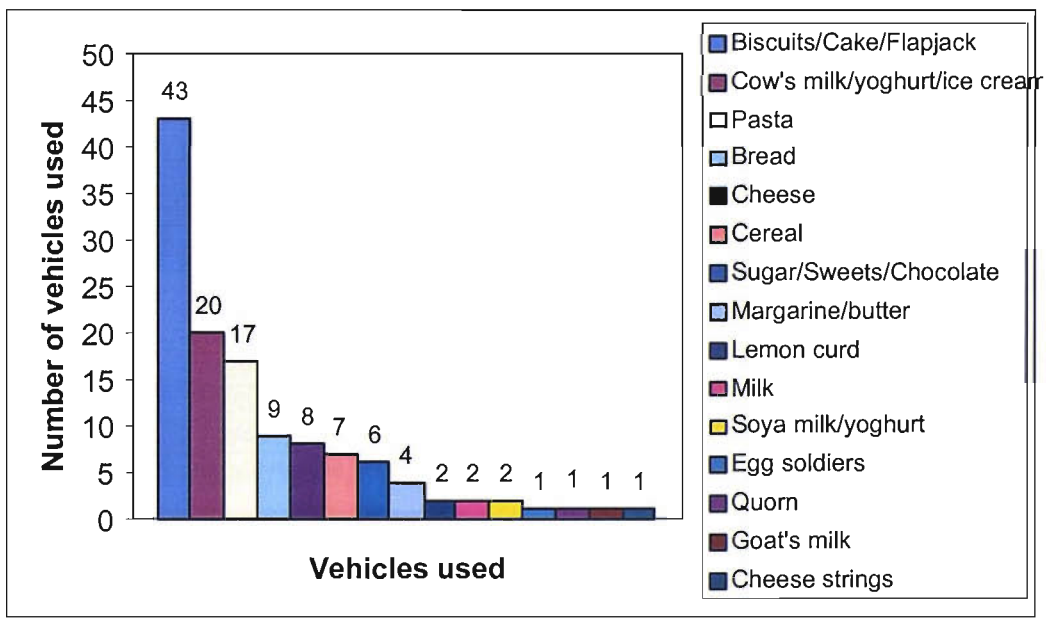
With 29 of the 33 (87.9%) of the challenges we could not keep to the recommended challenge duration due to a positive challenge outcome.

With the DBPCFCs, we could not keep to the duration of the challenges (7 days) in 34.4% of challenges (11/32). With 2 of the 11 challenges (18.2%) the reason for deviation from the challenge duration was: problem with understanding the challenge protocol (n=1) and refusal of the challenge food (n=1). With 9 of the 11 (81.8%) of the challenges we could not keep to the recommended challenge duration to a positive challenge outcome.

Number of vehicles used

We used different vehicles for 51 (64.5%) of the 79 OFCs in order to ensure the infants/children ate the challenge food. The range of vehicles used in the OFCs is shown in figure 2.9.

Figure 2.9: Vehicles used in the one-week OFCs



The main reason for using the vehicles was to offer the suspected allergen in a palatable form to the infants/children. Other reasons for using vehicles included food identified by the history, mother's choice of challenge food or infant refused challenge food.

For the DBPCFCs, we had to use different vehicles in all the cases in order to ensure the infants/children ate the challenge food and to mask the challenge food for the all DBPCFCs.

Vehicles included cereal (cereal mixed with the "milk" for challenge), ice cream, pasta, cake, biscuits, muffins, fruit squash and the infant's usual formula to provide a base for the powdered cow's milk used in the cow's milk formula.

A range of placebos were used for the 32 DBPCFCs. These included Neocate/Wysoy/Goat's milk or soya/rice milk ice cream for the milk challenges and wheat free pasta, biscuits, cake and cupcakes for the wheat challenges. Carob was used for the chocolate challenge and a fruit squash with added artificial colours for the additive challenge.

Challenge dosages used

For the one-week OFCs, the recommended challenge dose was given on average by 68.8% of the mothers. The correct dose was given more often in the older cohorts than the younger cohorts as presented in table 2.9.

Table 2.9: Challenge dose given vs. recommended challenge dose for the one-week OFCs

Cohort	Correct dose given Day 1	Correct dose given Day 2	Correct dose given Day 3	Correct dose given Day 4	Correct dose given Day 5	Correct dose given Day 6	Correct dose given Day 7
One year (n=51)	27/51*;	29/48	26/42	25/40	25/39	24/37	21/34
Two year (n=12)	6/12*	8/11	7/11	6/9	6/7	5/7	5/7
Six year (n=9)	5/9*	4/8	3/4	3/3	3/3	3/3	3/3
11 year (n=3)	2/3*	2/3	1/2	1/2	NA$^{\alpha}$	NA	NA
15 year (n=4)	3/4*	4/4	4/4	4/4	3/3	3/3	3/3

* The denominator will not be the same for days 1-7 as the challenges were stopped on different days due to a positive challenge outcome.

$^{\alpha}$No challenges performed after day 4.

The reasons for not giving the specified challenge dose were: Infant or child full/had enough, refused challenge food, challenge discontinued, hungry infant, mother wanted to start with a smaller challenge dose on the first day of the challenge, child not feeling well.

For the DBPCFCs, the recommended challenge dose was given on average by 71% of the mothers. The reasons for not giving the specified challenge dose included: Baby full/had enough, refused challenge food, amount usually taken, mother gave the child only ½ dose on day one of the challenge, mother not very clear regarding the challenge

procedure used. The correct dose was given more often in the older cohorts than the younger cohorts as presented in table 2.10.

Table 2.10: Challenge dose given vs. recommended challenge dose for the one-week DBPCFCs

Cohort	Correct dose given Day 1	Correct dose given Day 2	Correct dose given Day 3	Correct dose given Day 4	Correct dose given Day 5	Correct dose given Day 6	Correct dose given Day 7
One year (n=16)	10/16*	12/16	10/16	10/16	7/13	6/11	4/11
Two year (n=5)	3/5*	4/5	4/5	4/5	3/5	4/5	4/5
Six year (n=6)	6/6*	5/5	2/3	2/2	1/1	1/1	1/1
11 year (n=2)	1/2*	1/2	1/2	1/2	1/2	1/2	1/1
15 year (n=3)	2/3*	2/3	2/3	2/2	2/2	2/2	2/2

* The denominator will not be the same for days 1-7 as the challenges were stopped on different days due a positive challenge outcome.

2.3.4.9 Factors influencing the choice of open food challenge or double blind placebo controlled food challenge

As discussed in chapter 1, large discrepancies exist regarding the use of OFCs vs. DBPCFCs in the diagnosis of FHS. Clearly, one would like to use the type of challenge that would give an undisputable diagnosis. Factors such as the challenge duration, which could affect cost and staffing level as well as parental acceptance and preference should also be taken into account.

Challenge duration

Challenge duration may have an effect on patient compliance and it obviously does affect the overall cost and staff time required. When the challenge duration for food challenges were compared, the DPBCFCs took on average twice as long as the OFCs. This is presented in more detail in table 2.11.

Table 2.11: Challenge duration of the different type of food challenges in the five cohorts

	Number of challenges	Minimum time	Maximum time	Mean (Std Dev)
One-day OFC	102	54 min	3 hrs 19 min	2 hours (59 min)
One-day DBPCFC	16	2 hr 20 min	8 hrs	5hr 12 min (113 min)
One–week OFC	79	2 days	12 days	5 days (3 days)
One-week DBPCFC	32	9 days	14 days	12 days (1.2 days)

Parental acceptance of food challenge outcome

An important factor to consider when choosing the type of food challenge (OFC or DBPCFC) is whether the parents will accept the challenge outcome. When parents do not accept the challenge outcome, they will either not avoid a food that may lead to allergic symptoms or they will continue avoidance of a food unnecessarily. The data on parental acceptance is summarised in the table 2.12.

Table 2.12: Parental acceptance of food challenge outcome

	Positive accepted	Negative accepted	Positive not accepted	Negative not accepted	Accepted (total)
OFC one-day (n=102)	37	60	0	5	95%
OFC one-week (n=79)	41	29	2	7	88.6%
DBPCFC 1-day (n=16)	11	5	0	0	100%
DBPCFC one-week (n=32)	17	13	0	2	93.8%

With the one-day OFCs, 95% (97/102) parents accepted the challenge outcome. Parents of five children who had negative OFCs did not accept the challenge outcome. In the one year cohort two parents continued to avoid tomato (n=1) and egg (n=1) from their child's diet. In the two year old cohort, one parent continued to avoid citrus from the child's diet by three years of age. In the 11 year cohort, two parents are still avoiding colours (n=1) and additives, particularly monosodium glutamate (n=1) from their child's diet.

With the one-week OFCs: 88.6% (70/79) of the parents accepted the challenge outcome. Parents of two children with a positive challenge and seven children with negative challenges did not accept the challenge outcome. In the one year old cohort, four parents of children with negative OFCs, were still avoiding or partially avoiding the "offending" foods (citrus [n=1], wheat [n=1], egg [n=1], milk [n=1]) by two years of age. In the two year cohort, the mother of a child with a positive wheat challenge, continued to give him wheat as she did not feel the rash he develops caused him any upset. One mother was still avoiding egg by the age of three years despite the negative challenge. In the six year old cohort, one mother did not accept the negative egg challenge outcome, as she still felt egg in biscuits caused her child's eczema to flare. In the 15 year old cohort, two parents did not accept the challenge outcome as the one child is still avoiding chocolate from his diet despite a negative challenge and one mother was not convinced that milk really aggravates the child's eczema despite a positive challenge.

All parents of the 16 children who underwent one-day DPBCFCs accepted the challenge outcome and reintroduced the food in case of a negative challenge or kept avoiding the food in case of a positive outcome.

With the one-week DBPCFCs, 93.8% (30/32) of the parents accepted the challenge outcome. Two of the parents did not accept the challenge outcome. In the two year old cohort, two mothers were still avoiding "lots" of dairy products from the infant's diet at the age of three years despite the negative challenge outcome in both cases.

In summary, the difference between accepting the one-day or one-week OFCs compared to the one-day or one-week DBPCFCs was not statistically significant (McNemar's test $p<2$ and $p<1$ respectively)

Parental preference of food challenge

Referring back to the figures presented under 2.3.4.5, parental preference of food challenges provided the following data: With the one-day food challenges 45.5% (5/11) of the parents, whose children underwent DBPCFCs, preferred the OFCs and 18.2% (2/11) preferred the DBPCFCs. A further 36.4% (4/11) parents were undecided or had no preference. Those who preferred the OFCs stated that they would prefer the shorter time duration, whilst those who preferred the DBPCFCs, felt this type of challenge was more reliable with a smaller chance of being biased. Therefore, the majority of parents preferred the one-day OFCs rather than the one-day DPBFCFCs, but the difference was not statistically significant.

With the one-week food challenges 11.3% (4/35) of the parents preferred the OFCs and 42.9% (15/35) preferred the DBPCFCs. A further 45.7% (16/35) parents were undecided or had no preference. Those who preferred the OFCs stated that they considered the OFCs easier to perform, the children found it more acceptable and the mothers wanted to know what they were giving their children, whilst those who preferred the DBPCFCs, felt this type of challenge was more reliable with a smaller chance of being biased. Hence, in terms of the one-week challenges, the majority of parents preferred the DBPCFCs compared to those preferring the OFCs, but the difference was not statistically significant.

2.4 Discussion

A major problem regarding the diagnosis of FHS is the lack of consensus regarding the gold standard for diagnosis, the DPBCFC. Some clinicians view the use of these challenges as unnecessary in young children and prefer the OFC (Bahna 1994;Hide 1994;Hill & Hosking 1991). Another important factor is the lack of standard procedures in protocols in performing either OFCs or DBPCFCs. An attempt has been made to standardise some of the procedural issues regarding food challenges (Bindslev-Jensen et al. 2004;Bock et al. 1988), but clear, practical guidance is still lacking.

In this chapter, we have investigated the use of OFCs and DBPCFCs in the diagnosis of FHS and compared the two procedures across a number of key issues relevant to food challenges.

The study population for this objective consisted of 4088 children living on the Isle of Wight. 3469 (84.8%) of children underwent SPT with 15.0% and 3.9% children sensitised to any of the predefined aero- or any food allergens respectively. However, a positive skin prick test to a food only indicates sensitisation to that food. The negative predictive value of SPT (>95%) is much higher than its' positive predictive value (50%) (Isolauri & Turjanmaa 1996;Sarnpson & Albergo 1984). SPT could therefore not be considered a good test for excluding IgE-mediated food allergy, but it can only be suggestive of IgE mediated FHS (when positive) due to the high rate of clinically insignificant positive SPTs.

Only 27.4% of the sensitisations to foods in our cohorts were confirmed by either a very good clinical history or a positive food challenge. In a study performed by Pucar et al (Pucar et al. 2001) 18.1% of children with a SPT ≥ 3mm to peanut were diagnosed with a peanut allergy based on a positive food challenge or a clear history. Bock et al (Bock et al. 1978), in a study in children age 5 months to 15 years, showed that 40.8% (31/76) of positive SPT were confirmed by DBPCFC.

Eigenmann and Sampson (Eigenmann & Sampson 1998) compared SPT result with FHS diagnosed by DBPCFC. They found that 71.4% (120/168) children sensitised to foods were clinically allergic. One must however take into account that this was a highly selective group of children with diagnosed eczema.

In a German paediatric study (Roehr et al. 2004a), 46% of children (0-14 years) and 65% of children (15-17 years) had a positive SPT to foods, 9.7% to carrots, 9.2% apple and hazelnut each, 5.4% to soy, 4.3% to wheat and peanut, 2.2% to egg and 0.5% to cow's

milk. Unfortunately the authors used fresh foods for the SPTs rather than standardised allergens and therefore this data cannot be compared to the data in this thesis.

Although SPTs have been performed in the population based studies by Eggesbo et al. (Eggesbo et al. 2001b) the authors did not make it clear how many children in total were sensitised and how many of these were clinically allergic. It was also not clear whether SPT had been performed in all the children, or only those with reported adverse reactions upon milk and egg consumption. They did however establish that of the 9 children with positive egg challenges at 2 ½ years (OFCs or DBPCFCs), 5 (44.4%) children had a positive SPT (≥ 3 mm) to egg (Eggesbo et al. 2001a) and of the 11 children age 2½ years with positive milk challenges, only one (9.1%) child was sensitised.

In our study, of the 17 children with positive egg challenges, 11 (64.7%) were sensitised to egg and of the 34 children with positive milk challenges, only 4 (11.8%) were sensitised. Therefore, in our cohort, more children with egg FHS were likely to be sensitised to egg, but we showed similar numbers for milk as the other study by Eggesbo and colleagues. Bock et al. (Bock et al. 1978) established that 86.2% (25/29) of children (age 5 months – 15 years) with immediate symptoms upon food challenge (< 2 hours) were sensitised to the offending food (milk, egg, nuts, and soya). Host et al (Host & Halken 1990) determined that 47.4% (9/19) children (age 0-3 years) with immediate symptoms were sensitised to milk and 30.4% (7/23) of children with delayed symptoms. In this study 56.8% (21/37) of children with a positive food challenge (one-day) were sensitised to the food (milk, egg, wheat, tomato, banana, corn, salicylate, peanut, cheese, kiwi, melon, sesame, prawn). In contrast only 9.3% (4/43) children with delayed symptoms had a positive SPT to the food (milk, egg, additive, chocolate and wheat). In our study, 21/37 (56.8%) of children who had immediate symptoms upon OFC, showed a positive SPT and only 4/43 (9.3%) of those with delayed symptoms.

Adverse reactions to food were reported by 10.2% of the parents. The reported rate of perceived adverse reactions to food was 25.8% by one year of age, 7.5% at two years, 11.8% at six years, 11.6% at 11 years and 10.2% at 15 years.

Previous studies have looked at parentally reported adverse reactions to food. One cross-sectional study looking at children age 0-17 in Germany, (Zuberbier et al. 2004) found that 61.5% (455/739) children reported adverse reactions to foods, mainly fruit and vegetables. Another study reported the rate of parentally perceived adverse reactions to foods was 35% by two years of age (Eggesbo et al. 1999) with the majority of parents

reporting problems with milk, fruit and vegetables. Bock's study suggested the reported rate of food related problems was 28% by three years of age to foods such as milk, egg, soya, peanut, chocolate, corn, rice and wheat (Bock 1987). In France an estimated 20% of schoolchildren suffer from allergic diseases, with approximately 400 000 children across the country suffering from food allergy. The commonest food allergens reported were egg, peanut, milk, mustard and fish (Molkhou 2003). A population-based study in the Netherlands demonstrated that the prevalence of self-reported adverse reactions to foods among school children (aged 4-15 years) was 7.2% (Brugman et al. 1998). Adler and colleagues (Adler et al. 1991) reported that 56% of adolescent atopic asthmatic children (n=67) had reported some symptoms with foods, with behavioural disturbance being the most common. In that study, the commonest foods implicated were food additives (31%), egg (27%), milk (26%), chocolate (23%) and orange (15%).

The foods most commonly reported to cause problems during the first two years of life in this study included milk, fruits, baby rice, egg, tomato, fish, marmite, rich/spicy foods additives and nuts. In the school cohorts were nuts in the six year olds, additives in the 11 year olds and milk and dairy in the 15 year olds. Therefore, it seems that a wide range of foods are reported to cause adverse reactions to foods.

It has long been known that parents and children avoid various foodstuffs from the child's diet based on health beliefs with sources of dietary advice being the media and family members rather than any medical influence (Ford, Dawson, & Mogridge 1989). In this study, 30.3% of the children were avoiding one more food/ingredient from their diet. Food additives and nuts were the most common food/ingredient avoided at one year. Peanuts and tree nuts were the most common food/ingredient avoided at age two, six and 11 years. Fish was the most commonly avoided food at age 15 years followed by nuts, egg and milk products.

In the Netherlands, in a cohort of 1039 children aged 5-6 years the reported rate of food hypersensitivity was 11.4% and although only 39% of those children were examined, 91.5% of the parents who perceived their child to have food hypersensitivity restricted the child's diet (Bockel-Geelkerken & Meulmeester 1992) with food additives and chocolate being the commonest foods avoided. In the study by Brugman et al (Brugman et al.1998) 7% of school-aged children avoided certain foods or ingredients because of self-reported food hypersensitivities.

Based on the information regarding sensitisation to food as well as reported food related problems, only 5% (203/4088) children were identified for food challenges; 63 declined the OFCs and another two children underwent DBPCFCs, leading to 138 children undergoing 181 OFCs. Seventy children had positive OFCs and were invited to undergo DBPCFCs, of these 28 children declined. DBPCFCs have therefore been performed in 44 (42 + 2 children who underwent DBPCFCs only) and 28 children had positive challenges.

Our number of children identified for food challenges compares with that of two previously conducted population studies. In a population based study by Young et al (Young et al.1994) 2.7% of the recruited study population were identified for food challenges. Host and Halken (Host and Halken 1990) identified 6.7% (117/1749) of children in a population of 0-3 year olds for food challenges. Zuberbier et al (Zuberbier et al. 2004) performed food challenges in 6.5% (267/4093) of the study population (0 – 79 years), but they did not mention how many were initially identified for food challenges.

In short, the prevalence of FHS was estimated in the pooled cohort. The prevalence of FHS based on OFC, a good clinical history and positive SPT is 111/4088 (2.7%; 2.2 – 3.3 CI 95%). Based on DBPCFC, positive OFC that was not repeated double blind and or a good clinical history and/or positive SPT is 85/4088 (2.1%; 1.7 – 2.6 CI 95%).

In the German study, previously referred to 4.2% of children (0 – 17 years) were found to suffer from FHS as assessed by OFCs, SBPCFCs or DBPCFCs (Roehr 2004a). The foods most commonly implicated were apple, kiwi, soy, hazelnut, and wheat. These foods do not compare with the 5 main foods identified in the pooled cohort which were, milk, egg, wheat, peanut, and tomato by OFCs and milk, egg, wheat, and shell fish by DBPCFCs.

Bock (Bock 1987) diagnosed 8% (37/480, CI: 5.5 to 10.5) of infants with FHS by three years of age. This was achieved using either OFCs or DBPCFCs. Unfortunately, no data regarding FHS at one year or at two years is available and therefore we can not compare this data directly with the data obtained in this thesis. Also Bock et al only employed food challenges aimed at identifying immediate type symptoms (IgE mediated food allergy rather than FHS). Overall the foods implicated in Bock's study (Bock 1987) were milk, egg, soy, peanut, chocolate, corn, rice and wheat. These foods are very similar foods to those identified in the one and two year old cohorts in this project.

In the absence of standardised guidelines for performing food challenges, it is suggested that the patient history should be used as an indication for symptoms experienced during food challenge and challenge dose needed to elicit the reaction (Bock et al. 1988). No studies have however evaluated the usefulness of these guidelines previously. We found that between 67.5 – 79% of mothers report at least one symptom that will be experienced during the OFCs and 45.5 – 82.4% during the DBPCFCs. Only 10.8% - 23.2% reported an amount of food similar to the amount of food triggering the symptoms during the OFCs and 0 – 6.25% during the DBPCFCs. Our data therefore suggest that the food reported during the history is a poor indicator of the amount of challenge food that will be needed.

Two studies previously looked at challenge dose and outcome. Sicherer et al (Sicherer, Morrow, & Sampson 2000) investigated the challenge dose eliciting positive food challenges and found that the percentage of children reacting at the first dose (500 mg or less) was as follows: 49% egg, 55% milk, 28% soya, 25% wheat, 26% peanut, and 17% fish. In addition, Bock et al (Bock et al. 1978) found that a variety of dosages led to positive food challenges in children. These studies did however not look at reported patient history in planning and performing the food challenges.

It was the objective of this study to compare the ease of performing OFCs vs. DBPCFCs in terms of being able to keep to challenge protocols (time intervals and number of dosages used), number of vehicles used and reasons for using the vehicles and obstacles in performing the food challenges as there are no published data available in the literature. The data from this work suggest: In terms of the one-day challenges, the DBPCFC may be more difficult to perform in terms of vehicles used and keeping to the recommended protocol. The one-week challenge data indicates that the DBPCFC may be more difficult to perform in terms of vehicles needed. Hill and colleagues (Hill et al. 1993) mentioned that some problems were experienced with adhering to the challenge protocols, mainly due to parents either unwilling to increase the challenge dose rapidly or wanting to increase the challenge dose more quickly in performing one-day or 4-7 day challenges. They did not however give any indication of how often they experienced these problems.
In terms of parental acceptance of food challenge outcome, 95% of parents accepted the one-day OFC outcome and 100% the one-day DBPCFC. In contrast, 88.6% parents accepted the one-week OFC challenge outcome but 93.8% parents accepted the one-week DBPCFC. Only one study previously looked at parental acceptance of food challenge outcome. Kaila et al (Kaila & Isolauri 1997) compared OFCs with DBPCFCs in a population of children (2- 36 months) with suspected cow's milk allergy (although a within

case comparison was not made). More infants were diagnosed with cow's milk allergy after OFCs (56%) than DBPCFCs (44%). One interesting finding in this study was that the parents considered the DBPCFCs a more definite test than the open challenges. In children who underwent OFCs, 20/85 parents disagreed with the challenge outcome (10 with positive and 10 with negative challenges). In contrast with this, in those children who underwent DBPCFCs only 4/71 parents disagreed with the challenge outcome (1 with a positive and 3 with negative challenges) (χ^2 8.192; p=0,004). They did not unfortunately divide their food challenges into immediate and delayed symptoms as in our study.

In a poster presentation at the American Academy of Allergy, Asthma and Immunolgy, Lidman et al (Lidman et al. 2004) reported that in spite of no reaction, 7.7% (2/26) previously peanut allergic continued to completely avoid peanut and 10/26 had peanut less than once a week. However, all 15 patients with negative milk challenge tolerated and continued to regularly consume milk.

Most importantly, we could directly compare the results of OFCs and DBPCFCs in 46 cases (44 children underwent 46 challenges [11 one-day and 35 one-week challenges]. In total, 61% of these challenges (28/46: 8/11 [72.7%] one-day and 20/35 [57.1%] one-week challenges) had a positive outcome.
The positive predictive value of the one-day challenges was 72.7% (95% CI: 39.0 – 94.0%) vs. 57.0% (95% CI: 39.4 – 73.7%) for the one-week challenges. The data therefore suggest that OFCs may be suitable for diagnosing immediate (objective) symptoms, whereas a DBPCFC may be needed for the diagnosis of delayed (subjective) symptoms.

Parents whose children underwent both OFCs and DBPCFCs were asked regarding their preferences. More parents preferred the one-day OFCs (5/11) than the one-day DBPCFCs (2/11). Very interestingly, in terms of the one-week challenges, the majority of parents (15/35) preferred the DBPCFCs compared to only 4/35 parents preferring the OFCs. DBPCFCs take on average twice as long as OFCs, which has implications on financial costs and staffing levels. No comparable data were found in the literature.
Most importantly, we could compare the results of OFCs and DBPCFCs in 42 children who underwent 46 challenges (11 one day and 35 one week challenges). In total, 61% of these challenges (28/46:8/11[72.7%] one-day and 20/35[57.1%] one-week) had a positive outcome. The positive predicted value of the one-day challenges was 72.7% (95% CI: 39.0-94.0%) vs. 57.0% (95% CI: 39.4 – 73.3%) for the one-week challenges. The data therefore suggest that OFCs may be suitable for diagnosing immediate (objective)

symptoms, whereas a DBPCFC may be needed for the diagnosis of delayed (subjective) symptoms.

The lack of evidence based guidelines for the use of OFCs vs. DBPCFCs has been discussed. In this study, there was no evidence to indicate that the young children are more likely to have a positive OFC confirmed by a DBPCFC than the older children (Fisher's exact p=0.53). This indicates that age should not play a role in deciding which type of challenge to use and that this decision should rather be based on the symptoms experienced.

No previous study was found in the published literature addressing this issue. Scrutinising grey literature, a poster presentation by Shinoda et al (Shinoda et al. 2004) looked at the usefulness of SBPCFCs, OFCs or in vitro tests compared to DBPCFCs. These authors reported similar findings to our results that in the case of immediate reactions, it was possible to diagnose food allergies with OFCs in the outpatient clinic because of no discrepancies between OFCs and DBPCFCs. SBPCFCs was necessary for accurate diagnosis in the cases where only subjective symptoms were prevalent. The authors concluded that SBPCFCs should be done at least in the cases of non-immediate reactions (Shinoda et al. 2004).

We have also indicated and discussed previously that the same symptoms reported by history are likely to be experienced during the food challenge. This confirmed the findings by Hourihane et al (Hourihane et al. 2005). These authors also found that the severity of the symptoms during a DBPCFC does not correlate with severity of reported symptoms. This was however not investigated in this thesis.

In conclusion, we have established that 10.2% of parents report adverse reactions to foods in their children. FHS was only confirmed in 27.4 % of children sensitised to food. In terms of the food challenges, we found that that between 67.5 – 79% of mothers report at least one symptom that will be experienced during the OFCs and 45.5 – 82.4% during the DBPCFCs. Only 10.8% - 23.2% reported an amount of food similar to the amount of food triggering the symptoms during the OFCs and 0 – 6.25% during the DBPCFCs.

In terms of the one-day challenges, the DBPCFCs may be more difficult to perform with regards to the use of vehicles to get the children to eat the food. The one-week challenge data indicates that the DBPCFCs may be more difficult to perform in terms of vehicles needed. Parents are equally likely to accept OFCs and DBPCFCs for one-day challenges,

but may be more inclined to accept DBPCFCs outcome for one-week food challenges, although not statistically significant. Also, more parents preferred the one-day OFCs than the one-day DBPCFCs whereas more parents preferred the one-week DBPCFCs than one-week OFCs. One of the most important findings is that we could directly compare the results of OFCs and DBPCFCs in 46 cases. The data suggest that OFCs may be suitable for diagnosing immediate (objective) symptoms, whereas a DBPCFC may be needed for the diagnosis of delayed (subjective) symptoms.

Chapter 3

Reliability and Validity of a Maternal Food Frequency Questionnaire

3.1 Introduction

There are a number of factors which could lead to the development of FHS. These include genetic susceptibility (Kjellman 1977;Kurukulaaratchy et al. 2003), lifestyle factors (Lau et al. 2002;Strachan, Taylor, & Carpenter 1996;von Mutius 1996) and maternal diet (Hourihane, Dean, & Warner 1996;Lack et al. 2003). Current evidence regarding the role of maternal food intake during pregnancy on the development of FHS in the infant has been discussed in detail in chapter 1.

In order to measure maternal food intake during pregnancy, a variety of methods are available. These measures include 24 hour recall diaries (Harrison et al. 2000;Kroke et al. 1999b), 1-7 day food diaries with or without weighted food intake (De Vriese et al. 2001;Kassam-Khamis, Judd, & Thomas 2000;Marshall et al. 2003), food frequency questionnaires (FFQs) (Bingham et al. 1994;Block et al. 1990;Engle et al. 1990) or dietary questionnaires designed for a specific purpose such as the Quality Diet Index (Bodnar & Siega-Riz 2002). The most important factors to take into account when deciding on which dietary intake method to use, are the purpose of the dietary survey, the details of information needed, participant time commitment and resources available.

FFQs are often used in large scale population based studies, as the time used to complete the questionnaire should be kept to a minimum (Kroke et al.1999b;Ocke et al.1997a). FFQs in themselves will vary according to the purpose they are used for. FFQs can be used to determine simple frequency of food intake (Frank et al.1999), or they can be used to determine nutrient intake (Kroke et al. 1999b) based on frequency of food intake in conjunction with estimated portion size. In other words, a FFQ which determines level of fatty acid intake (Lagiou et al. 2004a;Otto et al. 2001), would need much more detail regarding sources and portions of fat in the diet than a questionnaire looking at different types of food eaten (Siega-Riz, Bodnar, & Savitz 2002) during pregnancy. When energy or specific nutrient intake is required from a FFQ, one may be able to determine energy expenditure and compare actual reported energy intake with the calculated energy expenditure (Burley et al. 2000). A comprehensive list of foods is required for this purpose and may not suit the need of all studies utilising FFQs. Therefore, short FFQs have been successfully developed and used to answer a specific question such as calcium intake during pregnancy (Brown & Griebler 1993;Wilson & Horwath 1996).

The strengths of FFQs are that highly trained interviewers are not required, administration is simple, customary eating habits are not influenced, the response rates are high, the respondent burden is light and in principle the relationship between dietary intake and

disease development can be measured (Burley et al. 2000). However, weaknesses such as memory loss of participants and problems in approximate quantification of food intake should not be ignored (Burley et al. 2000).

Also, no dietary measurement is completely without error and FFQ should therefore be tested for reliability and validity. The validity for using FFQs in large scale population based studies (Bingham 1997;Khani et al. 2004;Ocke et al. 1997a), some of which included pregnant women (Lagiou et al. 2004a;Olsen et al. 2001;Robinson et al. 1996;Suitor, Gardner, & Willett 1989) has been assessed in the past and these FFQs were found to be a valid method of determining dietary intake during pregnancy.

The aim of this part of the study (objective 2) was to design and test the reliability and validity of a FFQ that could be used to determine an estimate of the frequency with which some of the main food allergens are consumed.

3.2 Plan of investigation

This chapter will firstly describe the approach to the development of the FFQ and its validation. The results of the validity and reliability study are then presented. The chapter will conclude with a discussion of the findings.

3.2.1 Development of the food frequency questionnaire

Initially, previously used FFQs in pregnancy were scrutinised to assist in the development of this FFQ. When this FFQ was designed there was no validated suitable FFQ available in the literature that suited the purposes of the planned study. Therefore, the initial development of the questionnaire used was informed by two other validated FFQs. The first one determined food intake in a cohort study in Japan (Ogawa et al. 2003). The following frequencies of food consumption were used: never, rarely (1-2 per month), occasionally (1-3 times per week), 4 times per week or more and uncertain. In addition, the FFQ from the European Prospective Investigation into Cancer and nutrition (EPIC) study, (Bohlscheid-Thomas et al. 1997;Ocke et al.1997a) was used as guidance. A copy of the FFQ developed in this study is shown in appendix 3.1.

The FFQ was developed mainly to determine frequency of intake of some of the major food allergens (European Union 2003) namely milk and milk products, egg, wheat, fish (oily and white), shellfish, nuts (peanuts and tree nuts) and seeds. The FFQ also aimed to assess the frequency of avoidance of certain foods such as soya and food additives.

Specific questions regarding fruit and vegetable intake (Stazi et al. 2002), oily fish and food supplements such as fish oils (Dunstan et al. 2003) were included in order to look at the role of these foods/ingredients in the development of FHS. Additionally, we obtained information on the type of diet (normal/vegetarian/vegan/special medical condition) pregnant women were following, which foods they were avoiding, their use of vitamin or mineral supplementation, medication use, smoking habits and exposure or environmental tobacco smoke.

The general dietary advice given during pregnancy includes: limit alcohol intake, avoid smoking, use vitamin and mineral supplementation when indicated (Thomas 2002) and take a folate supplement (400 microgram) per day during the first 12 weeks (Wilson et al. 2003).

Pregnant women are advised to avoid foods containing large amounts of vitamin A such as liver and liver products (Thomas 2002). They are also advised to avoid foods containing bacteria such as pates, unpasteurised blue veined and soft cheeses including Brie, Camembert and Stilton due to the risk of Listeriosis. In order to reduce the risk of Salmonella, raw or undercooked meat, chicken and eggs should be avoided.

There are at present no internationally accepted dietary recommendations for the prevention of FHS during pregnancy apart from the COT report (1998) on Peanut Allergy (Committee on Toxicity of Chemicals in Food: Department of Health 1998). This report was issued in the United Kingdom by the Department of Health and was mainly based on a study performed by Hourihane et al. (Hourihane, Dean, & Warner 1996) and stated that women from atopic families (if either the women herself is atopic or the father or a sibling suffer from allergic disease) may wish to avoid peanut during pregnancy and lactation. This report further emphasised that the advice is precautionary and that non-atopic women should not be discouraged from eating peanuts. The FFQ used for this thesis therefore included questions which asked the pregnant women about their peanut intake and avoidance during pregnancy.

Once developed, the FFQ was pretested with 6 pregnant women as advised by Armstrong et al (Armstrong, White & Saracci 1992). The purpose of the pretesting was to test the FFQ on a similar group of study participants, have the FFQ reviewed by the research nurses and give the author the opportunity to train the research nurses regarding the completion of the FFQ on a sample similar to the study subjects. The pretesting of the

FFQ also gave the author the opportunity to identify problems through feedback from the pre-test subjects and to make the appropriate changes to the questions.

Approval for the study was obtained from the Isle of Wight, Portsmouth and South East Hampshire NHS Local Research Ethics Committee (Reference 04/Q1701/18) (see page 301 for ethical approval letter).

3.2.2 Sample size calculations

Sample size calculation for questionnaire validation is not appropriate. Most previous validation studies recruit between 50 - 100 participants (Bohlscheid-Thomas et al. 1997;Erkkola et al. 2001;Kroke et al. 1999b;Ocke et al.1997a). Therefore, we aimed to recruit 100 women for the validation and reliability study each (Burley et al. 2000). The consensus document (Burley et al. 2000) regarding validation of FFQs considers a study sample of 50 people as sufficient for a validation study.

3.2.3 Validity study

Validation tests the accuracy of the data (measure what it is supposed to measure). "Validity is the strength of the conclusions, inferences or propositions. It is the "best available approximation to the truth or falsity of a given result, proposition or conclusion" (Bohlscheid-Thomas et al. 1997). In the context of this study, a FFQ may be considered valid if it accurately measures or reflects the actual food intake or true behaviour of study participants.

3.2.3.1 Reference method

In order to test the validity, the FFQ should be compared against a reference method (Nelson 1997). A vital component of the validation process is the selection of the appropriate reference method against which to assess the test tool. It is well-recognised that there is a lack of accuracy with most methods of assessing dietary intake and that there is no "gold standard" for determining dietary intake (Ocke et al.1997a). Previous studies used either 24 hour recall questionnaires (Focke et al. 2003;Kroke et al.1999b), 4 day weighed food diaries (Block et al. 1990;Ogawa et al. 2003), 5 day food records (Erkkola et al. 2001) or 7-day diaries (Kaaks & Riboli 1997;Kassam-Khamis, Judd, & Thomas 2000;Khani et al. 2004;Kipnis et al. 2002;Marshall et al. 2003;Millen et al. 2001;van Assema et al. 2001).

Of these methods, using food diaries is the method of choice for validating FFQs as it measures actual food consumption and its errors do not correlate with those of the FFQ

(Bingham 1997;De Vriese et al. 2001;Erkkola et al. 2001). Therefore, 7-day food diaries completed on 4 occasions during pregnancy was our chosen reference method. This enabled us to calculate weekly and monthly food intake.

3.2.3.2 Recruitment of pregnant women for the food frequency validation study

The author and two research nurses approached pregnant women at the ante-natal clinic of St. Mary's Hospital, Isle of Wight at 12-13 weeks in pregnancy. This coincided with a routine ante-natal appointment.

Once the study information was discussed with pregnant women as shown in appendix 3.2, written consent was obtained from those who were willing to participate in the validation study.

At recruitment, detailed information on history of allergic disease and FHS, number of previous pregnancies, and level of education, were obtained from the pregnant women (see appendix 3.3). This information enabled us to compare the women recruited for the validation study with the pregnant women in the FAIR study. A total of 130 pregnant women were recruited for the validation study. Fifty nine dropped out due to a number of reasons such as going on holiday, too busy with other children or lack of interest. A further 14 participants completed only 3 of the 4 food diaries and their information could not be used. Therefore, 57 women completed the validity study

3.2.3.3 Food diaries

The pregnant women completed a 7-day food diary on 4 occasions during pregnancy: Week 12 – 16 (at recruitment); week 20; week 28; week 32.

The four 7-day food diaries were sent to the pregnant women, one week prior to the completion date. In some cases, diary 1 was issued on the day of recruitment.

In order to validate intake of supplementation, avoidance of foods related to pregnancy, foods avoided due to own preference as well as avoidance of soya, additives and other food, we asked the following questions on the food diary:

- Are you taking any supplementation and if so what?
- Are you avoiding any foods, ingredients or supplements and if so, what?
- We used a food diary in order to leave the information "open" i.e. the women could just write down exactly what they were eating, including brand names.

- We were particularly interested in their intake of peanuts and nuts and asked specific questions regarding intake of hidden nuts and foods that may contain traces of nuts.

An example of a completed food diary is shown in appendix 3.4.

The main purpose of the validation study was to validate the frequencies used in the FFQ. The frequencies used included: never/ 1-2 per month or less/ 1-3 per week / 4 times per week or more and uncertain. At 36 weeks of pregnancy, the women were asked to complete the FFQ which was posted to them. The data obtained from the food diaries were transferred by the author onto a FFQ (FFQV1) which was then compared against the FFQ (FFQV2) completed by the pregnant women.

3.2.4 Reliability of the food frequency questionnaire

Reliability tests the test-retest consistency. "Reliability is the consistency of the measurement, or the degree to which the FFQ measures the same way each time it is used under the same condition with the same women" (Bohlscheid-Thomas et al.1997).

3.2.4.1 Recruitment of pregnant women for FFQ reliability study

The author and two research nurses approached pregnant women at the ante-natal clinic of St. Mary's Hospital, Isle of Wight who were > 20 weeks pregnant. This coincided with a routine ante-natal appointment.

Once the study information was discussed with pregnant women as shown in appendix 3.5, written consent was obtained from those who were willing to participate in the reliability study.

At recruitment, detailed information on history of allergic disease and FHS, number of previous pregnancies, and level of education were obtained from the pregnant women. This information enabled us to compare the women recruited for the reliability study with the pregnant women in the FAIR study. In total, we recruited 102 pregnant women and 11 dropped out. The main reasons for dropping out were the early birth of the infant or the mother forgot to complete the FFQ in time. Therefore 91 pregnant women completed the reliability study.

Each pregnant woman completed one FFQ at 30 weeks gestation (FFQR1) and another at 36 week's gestation (FFQR2). The FFQ was sent to them one week prior to the completion date. In allowing 6 weeks between FFQR1 and FFQR2, we aimed to

determine reproducibility of the FFQ. By allowing a much longer period of time, changes in dietary habits may be measured rather than reproducibility (Burley et al. 2000), especially as it is known that taste and food preferences change over the course of the pregnancy (Bowen 1992).

3.3 Statistical analysis

All the data was double entered on SPSS, compared and verified.

Information regarding maternal age, number of children, maternal reported FHS and history of allergic disease, intention to breastfeed, type of diet, education and avoidance of peanuts were determined for pregnant women in the validation and reliability studies in order to compare them with the FAIR birth cohort pregnant women. These comparisons were calculated with one-way ANOVA (for age) and 2x3 tables utilising Chi^2-statistics.

The frequency of food intake was classified into four categories: Never, Moderate, Frequently and Uncertain. The number of subjects who provided identical responses to both validity and or both reliability assessments was used to produce percentage agreement. A clinical decision was made that agreement of 75% or above indicated good validity or reliability. Kappa statistics were also calculated to provide alternative indices of reliability and validity adjusting for chance agreement (Saw & Ng 2001). The results are discussed in the following section.

In analysis the response categories were simplified to never, moderate (1-2 per month up to 1-3 per week), frequently (≥ 4 times per week) and uncertain.

3.4 Results

3.4.1 Characteristics of participants in the validation and reliability study

Fifty seven women completed the validity study by completing four food diaries transferred onto a FFQ (FFQV1) and a FFQ at 36 weeks gestation (FFQV2). Ninety one pregnant women completed FFQR1 and FFQR2 for the reliability study.

The pregnant women recruited for the validity and reliability studies were compared to the FAIR pregnant women and this data is presented in table 3.1.

Table 3.1: Characteristics of pregnant women in the FAIR, Validity and Reliability study

Characteristics	Validity study (n=57) (%)	Reliability study (n=91) (%)	FAIR pregnant women (n=969) (%)	Differences between the three groups ANOVA or χ^2, p-value
Age range	20 - 44 years mean 30 yr 1m	18 - 44 years mean 30 yr 1m	15 – 44 years mean 27 yr 10 m	0.997
First child	31 (54)	37 (41)	402 (42)	3.76, 0.15
Pregnant women with reported FHS	9 (16)	9 (10)	189 (20)	5.39, 0.07
Pregnant women with reported allergic disease	35 (61)	52 (58)	581/937 (62)	0.83, 0.66
Intention to breastfeed	43 (75)	68 (75)	697/937 (74)	0.04, 0.98
Normal diet	54 (95)	84 (92)	851/937 (91)	1.29, 0.55
Reported peanut avoidance during pregnancy	31 (54)	42 (46)	521 (56)	1.97, 0.37
Education level (further and higher)	41 (72)	64 (70)	589 (61)	5.6, 0.59

There was no statistical difference between the three groups.

3.4.2 Validity data

The validity of the FFQ was tested by asking pregnant women to complete food diaries on four occasions during pregnancy and a FFQ at around 36 weeks gestation (FFQV2). The data obtained from the food diaries were transferred onto a FFQ (FFQV1) and compared with FFQV2. The data was divided into two sections, the general information section which included intended method of feeding, type of diet followed, avoidance of pregnancy related food etc (table 3.2) and the second section which included the frequency of food intake (table 3.3).

Table 3.2: Summary of general information obtained from FFQV1 and FFQV2

Questionnaire item	Number (%) responding yes		Number providing the same answer to FFQV1 and FFQV2	Validity index	
	FFQV1 (n=57)	FFQV2 (n=57)	Both V1 &V2	α% Agreement	Kappa
No. of cigarettes smoked per day	6	6	2	40	NA
Taken Folic acid	28 (49)	53 (93)	30	53	0.07
Excluding pregnancy related foods	40 (70)	53 (93)	42	74	0.19
Taken Iron	21 (37)	24 (42)	44	77	0.52
Claim to exclude peanuts	26 (46)	31 (54)	45	79	0.62
Exclude foods due to personal choice	2 (4)	11 (19)	46	81	0.1
Taken Calcium	12 (21)	9 (16)	48	84	0.51
Taken 0ther supplements	3 (5)	7 (12)	51	90	0.35
Taken Multi-mineral	19 (33)	16 (28)	52	91	0.79
Eaten ≥ 5 portions fruit & vegetables daily	6 (11)	9 (16)	52	91	NA
Normal diet	54 (95)	54 (95)	53	93	0.3
Normally smoke	5 (9)	9 (16)	53	93	0.68
Taken Multivitamin	20 (35)	24 (42)	53	93	0.85
Excluded additives	0	2 (4)	55	97	NA
Following medical diet	0	1 (2)	56	98	NA
Excluded soya	0	1 (2)	56	98	NA
Average (min – max				83.8 (40 – 98)	0.45 (0.1 – 0.85)

α% agreement: number of participants providing the same answer to both FFQ1 and FFQ2/total number of participants

With regards to the general information, number of cigarettes smoked per day obtained the lowest score. Kappa statistics are not usually appropriate for numeric data and was therefore not calculated. In contrast, questions with dichotomous answers such as "excluded additives or soya" and "following a special diet due to medical reasons" showed the highest degree of agreement.

An additional question regarding avoidance of hidden nuts and traces of nuts was asked on the food diaries. Only 11% (6/57) of pregnant women reported that they had avoided hidden nuts and only 2% (1/57) had avoided traces of nuts.

Table 3.3: Summary of information regarding frequency of food intake obtained from FFQV1 and FFQV2.

Food item	Questionnaire	Frequency of consumption (n=57)				Validity index	
		Never N (%)	Moderate N (%)	Frequently N (%)	Uncertain N (%)	α% Agreement	Kappa
Egg	FFQV1	0	14 (25)	43 (75)	0	49	0.19
	FFQV2	0	43 (75)	14 (25)	0		
Tree nuts*	FFQV1	18 (32)	37 (65)	2 (4)	0	67	0.31
	FFQV2	11 (19)	40 (70)	5 (9)	0		
Seeds	FFQV1	28 (49)	29 (51)	0	0	67	0.35
	FFQV2	15 (26)	40 (70)	0	2 (4)		
Citrus fruits	FFQV1	1 (2)	32 (56)	24 (42)	0	67	0.35
	FFQV2	1 (2)	34 (60)	21 (37)	1 (2)		
Oily fish	FFQV1	33 (58)	24 (42)	0	0	75	0.52
	FFQV2	28 (49)	27 (47)	1 (2)	1 (2)		
Peanuts*	FFQV1	33 (58)	22 (39)	2 (4)	0	77	0.55
	FFQV2	31 (54)	26 (46)	0	0		
Shellfish	FFQV1	34 (60)	23 (40)	0	0	79	0.56
	FFQV2	36 (63)	21 (37)	0	0		
Milk	FFQV1	0	0	57 (100)	0	91	NA
	FFQV2	0	5 (9)	52 (91)	0		
Wheat	FFQV1	0	0	57 (100)	0	95	NA
	FFQV2	0	3 (5)	54(95)	0		
White fish	FFQV1	4 (7)	53 (93)	0	0	95	0.54
	FFQV2	3 (5)	54 (95)	0	0		
Mean (min – max)						76% (49 – 95)	0.4 (0.19 – 0.56)

α% agreement: number of participants providing the same answer to both FFQ1 and FFQ2/total number of participants

* Of the pregnant women who reported that they never ate peanuts, only 1 avoided traces of nuts and 6 avoided hidden nuts.

Frequency of intake of foods commonly "hidden" in foods such as eggs and seeds and foods eaten infrequently such as tree nuts, obtained the lowest agreement. Oily fish, peanut, shell fish, milk, wheat and white fish intake showed a higher degree of agreement (≥ 75%).

We also asked a question regarding the pregnant women's concern about weight gain as it could be argued that the "concerned" pregnant women may be underreporting. Of the 18 women concerned about weight gain, 16 (88%) consumed milk on a regular basis compared to 35 (90%) of the 39 women not concerned about weight gain. This difference is not statistically significant (Fisher's exact test $p>0.999$). There was no significant difference between these two subgroups regarding frequent consumption of eggs (9/18,

50% vs. 22/39, 56%, p=0.78), wheat (17/18, 94% vs. 34/39, 87%, p=0.65) or fish (1/18, 5% vs. 0/39, 0%, p=0.32).

In summary, the validation of the FFQ was 83.3% (Kappa 0.45) for the general information obtained and 76% (Kappa 0.40) for the frequency of food intake, leading to an average score of 79.7%.

3.4.3 Reliability data

The reliability of the FFQ was tested by asking pregnant women to complete one FFQ at around 30 weeks gestation (FFQR1) and 6 weeks later at around 36 weeks gestation (FFQR2). The data obtained from the two FFQs were compared and are summarised in tables 3.4 and 3.5.

Table 3.4: Summary of general information obtained from FFQR1 and FFQR2

Questionnaire item	Number (%) responding yes		Number providing the same answer to FFQV1 and FFQV2	Validity index	
	FFQR1 (n=91) N (%)	FFQR2 (n=91) N (%)	Both R1 &R2 N	[α]% Agreement	Kappa
Excluding pregnancy related foods	74 (81)	70 (77)	73	80	0.40
Exclude foods due to personal choice	15 (17)	19 (21)	75	82	0.42
Exposed to smoke at home	27 (30)	27 (30)	76	84	0.68
Method of feeding: Intention to breastfeed	55 (60)	58 (64)	77	85	0.75
Taken Iron	30 (33)	34 (37)	77	85	0.66
Claim to exclude peanuts	48 (53)	42 (46)	79	87	0.74
Exposed to smoke at work	11 (12)	9 (10)	54/60*	90	0.57
Taken Medication	75 (82)	72 (79)	82	90	0.68
Eaten ≥ 5 portions fruit & vegetables	12 (13)	15 (17)	83	91	NA
Taken Multivitamin	20 (22)	22 (24)	85	93	0.81
Taken Multi-mineral	11 (12)	11 (12)	85	93	0.81
Taken Folic acid	78 (86)	76 (84)	85	93	0.75
Taken Calcium	9 (10)	8 (9)	86	95	0.68
Normally smoke	40 (44)	39 (43)	86	95	0.89
Stop smoke	16 (18)	15 (17)	36/38[⊕]	95	0.88
Normal diet	87 (96)	84 (92)	87	96	0.71
Excluded soya	5 (6)	3 (3)	88	97	0.74
Excluded additives	7 (8)	6 (7)	88	97	0.75
Cut down on smoke	28 (31)	27 (30)	28/29[∂]	97	0.84
Following medical diet	7 (8)	9 (9.9)	89	98	0.86
Taken other supplements	2 (2)	1 (1.1)	90	99	0.66
Mean (min-max)				91.5 (80 – 99)	0.8 (0.4 – 0.89)

*Only 60 women were working and could therefore have been exposed to smoking at work
[⊕]Only 38 women completed this question on both FFQs (as only 38 indicated to be smoking on both FFQs)
[∂]Only 29 women were asked this question as 38 were smoking and some claimed to have stopped/cut down.
[α]% agreement: number of participants providing the same answer to both FFQ1 and FFQ2/total number of participants

The data in the above table is presented in order of percentage degree of agreement.

Information on excluding pregnancy related foods had the lowest degree of agreement. As in the validity study, questions with dichotomous answers such as excluded additives or soya, cut down on smoking, following a special diet due to medical reasons showed the highest degree of agreement.

Table 3.5: Summary of information regarding frequency of food intake obtained from FFQR1 and FFQR2.

Food item	Questionnaire	Frequency of consumption (n=91)				Validity index	
		Never N (%)	Moderate N (%)	Frequently N (%)	Uncertain N (%)	α% Agreement	Kappa
Citrus fruits	FFQR1	3 (3)	54 (59)	34 (37)	0	66	0.37
	FFQR2	6 (7)	46 (51)	38 (42)	1 (1)		
Tree nuts	FFQR1	26 (29)	58 (64)	7 (8)	0	67	0.33
	FFQR2	29 (32)	59 (65)	2 (2)	1 (1)		
Seeds	FFQR1	39 (43)	50 (55)	2 (2)	0	71	0.44
	FFQR2	43 (47)	47 (52)	0	1 (1)		
Egg	FFQR1	4 (4)	74 (81)	12 (13)	1 (1)	76	0.26
	FFQR2	2 (2)	74 (81)	15 (17)	0		
Oily fish	FFQR1	39 (43)	50 (55)	1 (1)	1 (1)	82	0.66
	FFQR2	44 (48)	45 (50)	1 (1)	1 (1)		
Peanut	FFQR1	51 (56)	37 (41)	2 (2)	1 (1)	82	0.66
	FFQR2	49 (54)	39 (43)	2 (2)	1 (1)		
Wheat	FFQR1	0	13 (14)	76 (84)	2 (2)	82	0.29
	FFQR2	0	11 (12)	80 (88)	0		
Shell fish	FFQR1	63 (69)	27 (30)	0	1 (1)	84	0.63
	FFQR2	65 (71)	26 (29)	0	0		
Milk	FFQR1	0	12(13)	78 (86)	1 (1)	87	0.41
	FFQR2	0	8 (9)	83 (19)	0		
White fish	FFQR1	10 (11)	73 (80)	6 (7)	2 (2)	90	0.68
	FFQR2	12 (13)	77 (85)	2 (2)	0		
Mean (min – max)						79 (66-90)	0.5 (0.26 – 0.68)

α% agreement: number of participants providing the same answer to both FFQ1 and FFQ2/total number of participants

Intake of citrus fruit obtained the lowest score followed by foods (table 3.5) commonly "hidden" in foods such as eggs and seeds and foods eaten infrequently such as tree nuts. Oily fish, peanut, shellfish, milk, wheat and white fish intake showed a higher degree of agreement (≥ 75%).

Again, pregnant women were asked about concern over weight gain as the women who said they were concerned (yes/no answer) may be underreporting. Of the 91 pregnant women, 30 (33%) said that they were concerned regarding weight gain. Of the 30 women concerned about weight gain, 26 (87%) consumed milk on a regular basis compared to 54 (89%) of the 61 women not concerned about weight gain. The difference is not statistically

significant (Fisher's exact test p>0.999). There was no significant difference between these two subgroups regarding frequent consumption of eggs (6/30, 20% vs. 10/61, 16%, p=0.27), wheat (26/30, 86% vs. 54/61, 89%, p>0.99) or fish (1/30, 3% vs. 3/61, 5%, p>0.99).

In summary, the validation of the FFQ was 91.5% (Kappa 0.8) for the general information obtained and 79% (Kappa 0.5) for the frequency of food intake, leading to an average score of 85.3%.

3.4.4 Validity and reliability of individual questions

The purpose of the FFQ was to enable us to look at the relationship of frequency of major food allergen intake and investigate its association to the development of FHS and sensitisation to foods. Only foods and dietary factors with an individual validity and reliability score of >75% were used.

These foods and factors with a validity and reliability score ≥ 75% are summarised in table 3.6 and their relationship with sensitisation to food allergens and FHS at the age of one and two years will be discussed in chapter 4.

If only questions with a validity and reliability or equal or higher than 75% are considered, then one third (31%) of questions cannot be used. Based on ≥ 75% validity and reliability the FFQ shown in table 3.6 will be recommended in future studies. An amended FFQ is shown in appendix 3.6.

Table 3.6: Individual questions with a valid and reliable score

Question	Validity (%)	Reliability (%)	Average (%)
Often eaten oily fish	75	82	79
Often eaten peanut	77	82	80
Taken Iron	77	85	81
Often eaten shell fish	79	84	82
Exclude foods due to personal choice	81	82	82
Claim to exclude peanuts	79	87	83
Often eaten wheat	95	82	89
Average for identified questions	88	90	89
Often eaten milk	91	87	89
Taken Calcium	84	95	90
High (≥ 5 portions) and low (<5 portions) fruit and vegetables	91	91	91
Taken Multi-mineral	91	93	92
Often eaten white fish	95	90	93
Taken Multivitamin	93	93	93
Normally smoke	93	95	94
Taken other supplements	90	99	95
Normal diet	93	96	95
Excluded additives	97	97	97
Excluded soya	98	97	98
Following medical diet	98	98	98

3.5 Discussion

A number of studies previously used FFQ in pregnant women (Bodnar & Siega-Riz 2002;Brown et al. 1996;Erkkola et al. 2001;French, Barr, & Levy-Milne 2003;Fronczak et al. 2003;Hashim & Norliza 2004;Lagiou et al. 2004b;Lagiou et al. 2004a;Olsen et al. 2001;Otto et al. 2001;Robinson et al. 1996;Rogers et al. 2004;Rogers & Emmett 1998;Siega-Riz, Bodnar, & Savitz 2002;Suitor, Gardner, & Willett 1989;Wei et al. 1999;Wild et al. 1996) and found the FFQ to be a useful tool in determining food intake during pregnancy. These studies obtained information on food intake during pregnancy and size of the infant (Lagiou et al. 2004b;Moore et al. 2004), nutritional quality of the pregnancy diet (Bodnar & Siega-Riz 2002;Siega-Riz, Bodnar, & Savitz 2002), pregnancy related changes in diet (Brown et al. 1996), micronutrient intake (French, Barr, & Levy-Milne 2003;Hashim & Norliza 2004;Lagiou et al. 2004a;Otto et al.2001;Rogers & Emmett 1998), relationship between pregnancy diet and disease development (Fronczak et al. 2003), and the usefulness of the FFQ in pregnancy (Olsen et al. 2001;Robinson et al. 1996;Suitor, Gardner, & Willett 1989) (Erkkola et al. 2001;French, Barr, & Levy-Milne 2003;Wei et al. 1999).

As none of these FFQs are tailored towards maternal diet focusing on the major allergen consumption, a FFQ was designed to determine general information regarding food intake, use of supplementation, avoidance of foods and smoking habits during pregnancy.

The main purpose of this FFQ was to determine frequency of intake of the foods containing the major food allergens. FFQs need to be validated and their reliability must be established in order to ensure accurate data is collected. The validity of the FFQ was determined as 79.9% and its reliability was 85.3%. The validity and reliability of questions with dichotomous response categories of yes/no answers were higher than questions with continuous response categories requiring actual numbers of cigarettes smoked and number of portions of fruit eaten. Also, frequency of foods eaten more often was more valid and reliable than foods not eaten very often. To ensure relevance, appropriate questions with a validity and reliability of ≥ 75% will be used to assess the relationship between maternal food intake and development of FHS. Using these criteria, 33% (7/21) questions were excluded. There are three important factors that should be taken into account when testing validity and reliability.

The reference method: A vital component of the validation process is the selection of the appropriate reference method against which to assess the test measurement.
It is well-recognised that there is a lack of accuracy with most methods of assessing dietary intake and that there is no "gold standard" for determining dietary intake (Ocke et al. 1997a). Previous studies have used 24 hour recall questionnaires (Focke et al. 2003) (Kroke et al. 1999b), 4 day weighed food diaries (Block et al. 1990;Ogawa et al. 2003), 5 day food records (Erkkola et al. 2001) and 7 day diaries (Kaaks & Riboli 1997;Kassam-Khamis, Judd, & Thomas 2000;Khani et al. 2004;Kipnis et al. 2002;Marshall, et al. 2003;Millen et al. 2001;van Assema et al. 2001) as in this study. Of these methods, the use of food diaries is the method of choice for validating FFQs as they measure actual food consumption and its errors do not correlate with those of the FFQ (Erkkola et al. 2001). De Vriese et al. (De Vriese et al. 2001) showed that the 7 day food diary gives similar results for fat intake as the FFQ and is therefore an appropriate method of validating FFQs. In support of this, Bingham et al. concluded that repeated food diaries compared well with information obtained from biomarkers and 16 day weighed diaries (Bingham et al. 1994;Bingham 1997).

The use of another dietary method as a reference for validating a FFQ has been seriously criticised by Kipnis et al. (Kipnis et al. 2002). They established the dietary assessments such as the FFQ, 24 hour recalls, 4 day food diaries and 7 day food diaries could lead to over reporting of protein intake when compared to urinary nitrogen excretion. It is therefore argued by some researchers that more that one method of validation should be used e.g. a dietary method plus a biomarker (Frankenfeld et al. 2002;Kroke et al. 1999b;Ocke et al. 1997b;Siega-Riz, Bodnar, & Savitz 2002).

Ultimately the reference method used will depend on the purpose of the FFQ. If for example only frequency of food intake is required then this is what should be determined by the chosen reference method. Very few studies in the past used both methods for validation. According to a systematic review carried out by the authors of the Consensus Document on Validation, 75% of FFQs were validated against another dietary method, 13% of FFQs against a dietary method and biomarker and 12% against a biomarker only (Burley et al. 2000). For validating our FFQ, we felt that the degree of information only warranted the use of another dietary reference method without any need for biomarkers.

Under or over reporting: Under reporting is particularly a problem in women with a history of frequent dieting, self-reported binge eating and dissatisfaction with body weight. This could be less of a problem in pregnant women, a group that are less likely to be concerned about weight. Our FFQ does not enquire quantities of foods eaten, which may lead to less underreporting. Furthermore, Caan et al. established that subjects that are not undergoing any intervention as our study, are more likely to accurately report food intake than those in intervention trials (Caan et al. 2004). One method of testing under or over reporting is to calculate BMR by means of the Scofield or Harris Benedict formula and compare reported energy intake with actual requirements (Kroke et al. 1999a;Kroke et al. 1999b). We did not feel that this method was appropriate for the validation and reliability study as it is not the policy of hospital to regularly weigh pregnant women and we did not need this level of detail. Nevertheless we incorporated a question regarding concern about weight gain during pregnancy to test for underreporting. Our results suggested there was no underreporting.

Method of administration: When a large number of open questions are used the questionnaire should ideally be interviewer administered (Kassam-Khamis, Judd, & Thomas 2000;Moore et al. 2004). Using closed questions with answers divided into specific frequencies that do not overlap or leave gaps are better suited for self-completion (Burley et al. 2000). In order to minimise participant input, we have used closed questions which could be easily answered.

In summary, in this part of the study (objective 2), we have validated and tested the reliability of a FFQ measuring maternal food intake during pregnancy. This FFQ can be used to assess the frequency of food intake for four major food allergens, during pregnancy and the development of FHS in the infant. We have aimed to take all possible factors into account to ensure adequate validation and reliability.

Chapter 4

Maternal dietary factors associated with the development of food hypersensitivity in the infant

4.1 Introduction

Maternal food intake during pregnancy and breastfeeding as well as feeding and weaning practices, may play a role in the development of food hypersensitivity (FHS) and need further investigation.

A small number of studies have looked at maternal dietary intake during pregnancy and its role in the development of allergic disease. These included food avoidance during pregnancy (Falth-Magnusson & Kjellman 1992;Lilja et al. 1988;Vance et al. 2004), intake of fruit and vegetables (Stazi et al. 2002), peanut consumption (Hourihane, Dean, & Warner 1996;Lack et al. 2003), maternal fat intake and fatty acids (Dunstan et al. 2003;Ushiyama et al. 2002) and the role of probiotics (Kalliomaki et al. 2001). None of these studies found a conclusive relationship between the factors studied and the development of FHS or allergic disease.

In the UK, the main study in this area was a cross-sectional study which investigated maternal peanut consumption in relation to development of peanut allergy in the child (Hourihane, Dean, & Warner 1996). This study led to the recommendations of the COT report (Committee on Toxicity of Chemicals in Food: Department of Health 1998). The COT report recommends that women from atopic families (either the woman herself, the father or a sibling suffer from allergic disease) may wish to avoid peanut during pregnancy and breastfeeding. It is unclear at present how this message has been interpreted and implemented by health care professionals, pregnant and breastfeeding women. Interestingly, Van Odijk and colleagues found that some pregnant women in Sweden avoided peanuts during pregnancy for allergy prevention, even though this is not recommended in Sweden. This avoidance of peanut was also unrelated to atopic status of these families (van Odijk et al. 2004).

The avoidance of allergenic foods during breastfeeding has also been investigated and a reduction in some manifestations of allergies (mostly eczema) has been reported. However, a number of methodological issues make it difficult to draw any major conclusions from these studies (Arshad, Bateman, & Matthews 2003;Chandra, Puri, & Hamed 1989;Hattevig, Sigurs, & Kjellman 1999).

Breastfeeding duration and the development of allergic disease or FHS also need further investigation. The American Academy of Pediatrics recommends exclusive breastfeeding for high risk infants for six months (Committee on Nutrition 2000). A recent review paper by a group of experts set up by the European Academy for Allergy and Clinical

Immunology recommended a period of exclusive breastfeeding for 4 -6 months (Muraro et al. 2004b).

The American Academy of Pediatrics recommends that solid foods should not be introduced into the diet of high-risk infants until six months of age, with dairy products delayed until one year, eggs until two years, and peanuts, nuts, and fish until three years of age (Committee on Nutrition 2000). A European Academy of Allergy and Clinical Immunology Task force recommends that solids and cow's milk should not be introduced for the first four months (Muraro et al. 2004b). The British Dietetic Association (Food Allergy and Intolerance Interest group: BDA 2004) recommends weaning from six months of age, with those foods more likely to precipitate food allergies introduced, singly and with caution.

The above data highlights a lack of clarity regarding maternal dietary intake and feeding and weaning practices in the development of allergic disease and FHS *per se* for infants born into families with a history of allergic disease. It is therefore important to determine if these factors do play a role in the development of FHS.

The aim of the objective (objective 3) addressed in this chapter is to determine the role of maternal dietary intake, feeding and weaning practices in the development of FHS in the infant.

4.2 Methods

In order to determine whether dietary factors during pregnancy and breastfeeding, as well as weaning practices could affect the development of FHS in the infant, data from the following sources have been used: (FAIR project page 58).

- Recruitment and birth questionnaire which included family history of atopy on the study participants
- The food frequency questionnaire (FFQ) completed during pregnancy at 36 weeks gestation. Based on the results of the validation and reliability study (discussed in detail in chapter 3), only the questions with clinically acceptable validity and reliability were used for the purpose of this objective (Table 3.6)
- Follow-up questionnaires at 3, 6, 9, 12 and 24 months regarding avoidance of foods during breastfeeding as well as breastfeeding and weaning practices

- Follow-up questionnaires at 3, 6, 9, 12 and 24 months to obtain prospective information on reported problems to foods and food ingredients and skin prick test (SPT) results at 12 and 24 months
- Food challenge outcomes

4.3 Results

The results section is divided into seven parts. The first part (section 4.3.1) presents data on the families of the birth cohort, the second part presents data on the birth cohort's data (section 4.3.2), and the third part looks at maternal dietary intake during pregnancy and development of FHS in the infant (section 4.3.3). This is followed by reports on the role of maternal food avoidance during lactation (section 4.3.4), feeding practices during the first two years of life (section 4.3.5), weaning practices during the first two years of life (section 4.3.6) and infant food avoidance and exposure to food allergens (section 4.3.7) during the first two years of life.

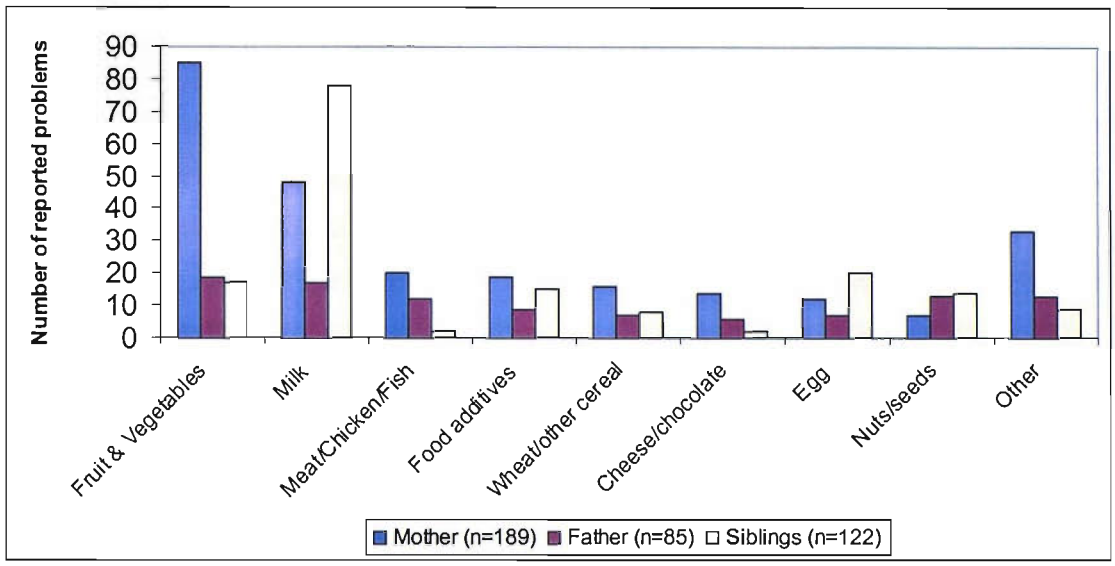
4.3.1 Description of families of the birth cohort

Data were obtained from 969 families of the birth cohort whose babies were born between 1 September 2001 and 31 August 2002.

The age of the pregnant women ranged from 15 – 44 years with a mean age of 27 years and 10 months. Of the 567 pregnant women with other children, 122 (21.5%) reported adverse reactions to food and food ingredients in one or more of their other children. One hundred and eighty nine (19.5%) of the pregnant women and 322 (33.2%) of the families (mother, father, sibling) reported to have a problem related to ingestion of food or food ingredients.

The foods most often reported to cause adverse reactions in the families are summarised in figure 4.1.

Figure 4.1: Foods most often reported to cause adverse reactions in the families of the birth cohort



The main symptoms relating to adverse reactions to food reported by the pregnant women in the past were diarrhoea, bloating, vomiting, abdominal pain, migraine, urticaria and rashes. Some also reported the foods caused mouth ulcers, wheeze and asthma. The fathers reported vomiting, diarrhoea, throat tightness, urticaria, migraine, abdominal pain and wheeze/asthma. The siblings mainly experienced symptoms such as rashes, vomiting, hyperactivity, diarrhoea, eczema, urticaria, angioedema and wheeze.

4.3.2 Description of the birth cohort infants

500 boys (51.6%) and 469 (48.4%) girls comprised the birth cohort (755 vaginal and 211 caesarean deliveries). On the day of birth, 733 (75.6%) babies were breast fed, 230 (23.7%) were bottle fed, 4 babies (0.4%) received bottle and breast milk and 1 child was fed parentally (TPN). This rate of breastfeeding on the first day of life (75.6%) is higher than the rate of those who stated that they intended to breastfeed the baby when asked at 36 weeks gestation (65.1%).

4.3.3 Maternal dietary intake during pregnancy

Information regarding dietary habits during pregnancy was obtained from 937 (96.7%) pregnant women at 36 weeks gestation using the FFQ.

Eight hundred and thirty four (89%) of the pregnant women followed a normal diet, 67 (7.2%) reported to follow a vegetarian diet and two (0.2%) followed a vegan diet, 28 (3%)

pregnant women were on special diet due to medical reasons and six women did not indicate the type of diet they followed.

Five hundred and twenty one women (55.6%) reported they had avoided peanuts during pregnancy. However, 71 (13.6%) of these ate peanuts accidentally and 5 reported that they were uncertain about accidental intake. Therefore in total, 445 (47.5%) women reported complete avoidance of peanuts, another 57 (6.1%) did not exclude peanut but never actually ate any and 360 (38.4%) did eat peanut. It is quite likely that women who reported complete avoidance were actually exposed to traces/hidden nuts as indicated in chapter 3.

Twenty four women (2.6%) excluded soya from their diets. A further 46 (4.9%) claimed to have excluded additives from their diets. 190 (19.6%) women avoided some food during pregnancy by own choice. These foods mainly included coffee or caffeine containing drinks, alcohol, cheese, citrus foods and spicy food.

241 (25.7%) pregnant women took a multivitamin, 160 (17.1%) a multi-mineral, 109 (11.6%) calcium, 440 (47%) iron, 3 cod liver oil, 1 fish oil and 6 took evening primrose oil supplementation during pregnancy. Only 130 (13.9%) of pregnant women ate ≥ 5 portions of fruit and vegetables per day.

The pregnant women were also asked regarding frequency of food intake of the main allergenic foods during pregnancy as summarised in table 4.1.

Table 4.1: Reported frequency of food intake during pregnancy (n= 937)

	Never N (%)	Moderate N (%)	Frequent N (%)	Uncertain N (%)
Milk	2 (0.2)	97 (10.4)	381 (88.7)	7 (0.8)
Wheat	1 (0.1)	75 (8)	857 (91.5)	4 (0.4)
White fish	107 (11.4)	782 (83.5)	44 (46.5)	4 (0.4)
Shell fish	562 (60)	370 (39.5)	2 (0.2)	3 (0.3)
Oily fish	500 (53.4)	425 (45.4)	9 (1)	3 (0.3)
Peanut	502 (53.6)	414 (44.2)	16 (1.7)	4 (0.4)

The majority of the pregnant women consumed milk (88.7%) and wheat (91.5%) frequently and white fish moderately (83.5%). In contrast, adding together the categories "never" and "moderate" showed a low intake of shell fish (99.5%), oily fish (98.8%) and peanut (97.8%). With regards to egg intake, as reported in chapter 3, the question on egg intake showed a low validity and reliability and although 94% women reported to

consume egg moderately to frequently, this data is not included in table 4.1 as it is niether valid nor reliable.

4.3.3.1 Maternal dietary intake during pregnancy and infant's sensitisation to food allergens

At one year

Information on maternal dietary intake during pregnancy and infant sensitisation to foods was available on 77.6% (752/969) of the birth cohort. At one year only a small number of children were sensitised to food allergens and statistical inferences could not be made. Only 2 children were sensitised to milk, 3 to peanut and 2 to fish at the age of one year. Additionally, 14 children were sensitised to egg, 2 to sesame and 1 child was also sensitised to corn, potato and rice, but we did not have valid and reliable information on frequency of intake of these foods by the mother. In this small number of children, food intake during pregnancy did not appear to influence the development of sensitisation to food allergens (table 4.2). Interestingly, for peanut and fish, maternal consumption of those infants sensitised to these foods, fell within the lower range of intake, and for those sensitised to milk maternal consumption fell within a higher range.

Table 4.2: Maternal dietary intake during pregnancy and infant's sensitisation to food allergens at one year

SPT	Maternal reported rate of food consumption during pregnancy				
	Never N (%)	Moderate N (%)	Frequently N (%)	Uncertain N (%)	Total
Milk					
Positive	0	0	1(50.0)	1(50.0)	**2**
Negative	1(0.1)	77(10.3)	668(89.1)	4(0.5)	**750**
Peanut					
Positive	1(33.3)	2(66.7)	0	0	**3**
Negative	406(54.4)	322(43.1)	15(2.0)	4(0.5)	**747**
Fish					
Positive	0	2(100.0)	0	0	**2**
Negative	86(11.5)	622(82.9)	38(5.1)	4(0.5)	**750**

At two years

Information on maternal dietary intake during pregnancy and sensitisation to foods was available for 67% (650/969) of the birth cohort at two years. At the age of two years, 5 children were sensitised to milk, 1 to wheat, 13 to peanut and 3 to fish. Additionally, 14 children were sensitised to egg and 5 to sesame but we did not have information on frequency of intake of these foods by the mother. As with the one year data, in this small number of children, food intake during pregnancy did not appear to influence the development of sensitisation to food allergens (table 4.3).

Table 4.3: Maternal dietary intake during pregnancy and infant's sensitisation to food allergens at two years

SPT	Maternal reported rate of food consumption during pregnancy				
	Never N (%)	Moderate N (%)	Frequently N (%)	Uncertain N (%)	Total
Milk					
Positive	1(20.0)	0	3(60.0)	1(20.0)	**5**
Negative	0	59(9.1)	585(90.7)	1(0.2)	**645**
Wheat					
Positive	0	0	1(100.0)	0	**1**
Negative	0	48(7.4)	598(92.3)	2(0.3)	**648**
Peanut					
Positive	7(53.8)	5(38.5)	1(7.7)	0	**13**
Negative	353(55.5)	270(42.5)	10(1.6)	3(0.5)	**636**
Fish					
Positive	0	2(66.7)	1(33.3)	0	**3**
Negative	77(11.9)	536(83.1)	30(4.7)	2(0.3)	**645**

4.3.3.2 Maternal dietary intake during pregnancy and infant's food hypersensitivity

At one year

FHS was diagnosed in 39 children by one year. This was based on OFC (n=35) and a clear history and/or positive SPT (n=4). The results of the children with FHS based on OFC with relation to reported food intake of the mother during pregnancy is summarised in table 4.4. Of the 39 children, 22 suffered from milk hypersensitivity, 4 from wheat hypersensitivity (one child suffered from wheat and milk hypersensitivity). Additionally 14 children suffered from FHS to foods for which we did not have any information on maternal dietary consumption such as egg, corn and salicylates. In this small number of children, frequency of food intake during pregnancy did not appear to influence the development of FHS. Interestingly for milk and wheat hypersensitivity maternal consumption of these foods fell within the higher range of intake as with sensitisation.

Table 4.4: Maternal dietary intake during pregnancy and infant's FHS at one year

FHS	Maternal reported rate of food consumption during pregnancy				
	Never N (%)	Moderate N (%)	Frequently N (%)	Uncertain N (%)	Total
Milk					
Positive	1(4.5)	0	18(81.8)	3(13.6)	**22**
Negative	1(0.1)	97(10.6)	813(88.9)	3(0.3)	**914**
Wheat					
Positive	0	0	4(100.0)	0	**4**
Negative	1(0.1)	75(8.0)	853(91.4)	4(0.4)	**933**

At two years

An even smaller number of children underwent food challenges at the age of two years as food challenges were not performed in the case of accidental exposure with symptoms or an increase in SPT size. FHS diagnosed by OFC at age two was defined as all children with a positive OFC at one year who had not outgrown their FHS or those with newly diagnosed FHS with a positive OFC at age two or a positive SPT and clear history (n=22).

Table 4.5: Maternal dietary intake during pregnancy and infant's FHS at two years

FHS	Maternal reported rate of food consumption during pregnancy				
	Never N (%)	Moderate N (%)	Frequently N (%)	Uncertain N (%)	Total
Milk					
Positive	1(10.0)	2(20.0)	6(60.0)	1(10.0)	**10**
Negative	1(0.1)	95(10.2)	825(88.9)	7(0.8)	**928**
Wheat					
Positive	0	0	3(100.0)	0	**3**
Negative	1(0.1)	75(80.3)	854(91.4)	4(0.4)	**934**

Of the 10 children with positive OFCs to milk, 1 mother never ate milk or milk containing foods during pregnancy, 2 mothers had a moderate milk intake, 6 mothers frequently ate milk and 1 was uncertain. Of the 3 children with positive OFCs to wheat, all 3 mothers frequently ate wheat and wheat containing foods. Twenty two children were suffering from FHS to foods such as egg, tomato, corn, potato and salicylates for which we did not have information on frequeny of food intake.

4.3.3.3 The role of other maternal dietary intake related factors during pregnancy

Maternal fatty acid and fruit and vegetable intakes were also investigated. There was no association between fatty acid intake and infant sensitisation or FHS. The fruit and vegetable intake showed that there was no statistical significant difference between sensitisation to foods and recommended fruit and vegetable (5 portions or more per day) intake. However, the recommended fruit and vegetable intake significantly reduced the rate of FHS as diagnosed by OFC (table 4.6) and DBPCFC (not presented) at age one year. This data therefore suggest that fruit and vegetable intake may affect the development of FHS although this needs to be confirmed by future studies.

Table 4.6: Fruit and vegetable intake and the development of FHS at one and two years

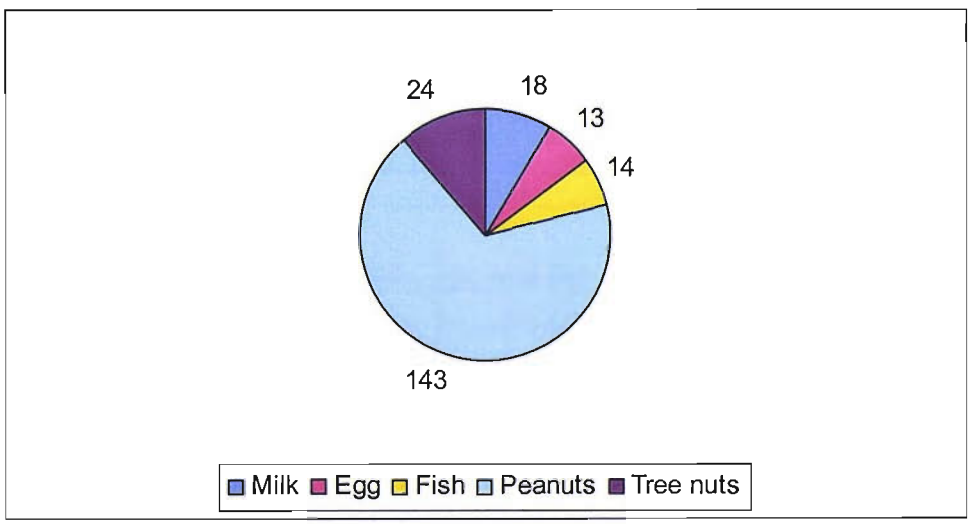
	Adequate intake N (%)	Insufficient intake N (%)	p-value (Fisher's exact test)
Positive SPT to any food 1 yr	2 (13.3)	15 (86.7)	0.75
Positive SPT to any food 2 yrs	6 (24)	19 (76)	0.61
FHS based on OFC 1 yr	12/39 (30.8)	27/39 (69.2)	0.002*
FHS based on OFC 2 yrs	6/22 (27.2)	16/22 (72.8%)	0.11

* Statistically significant

4.3.4 Maternal food avoidance during breastfeeding

During breastfeeding, information was obtained regarding food avoidance (n=927; 95.7%). No information regarding food intake (how often and how much) was obtained at this stage. Six hundred and fourteen mothers (66.2%) breastfed the infant for ≥ 1 week. These mothers were asked regarding any food avoidance during breastfeeding. In total, 265/614 (43.1%) mothers reported to avoid one or more foods from their diets. These foods included a wide variety of foods such as the major food allergens, citrus, meat, spicy foods, onion, brassica family, shell fish and strawberries. Of the 265 mothers, 173 avoided some of the main allergenic foods, with 39 avoiding more than one of the main food allergens (figure 4.2).

Figure 4.2: Avoidance of the major allergenic foods during breastfeeding (n=173)



Eighteen (1.9%) mothers avoided milk during breastfeeding, but only six mothers managed to completely avoid milk from the infant's diet as 12 children had a formula feed containing cow's milk at some point during the first three months. There were 143 (15.4%) mothers who avoided peanut during breastfeeding (101 of these avoided peanut during pregnancy) and 24 (2.6%) avoided tree nuts. Thirteen mothers (1.4%) avoided egg and 14

(1.5%) avoided fish. None avoided wheat or sesame. The reasons given for food avoidance were: following a vegetarian/vegan diet (n=18), advised to avoid certain foods during breastfeeding (n=147), dislike of certain foods (n=9), baby's allergy (n=8), mother's own allergy (n=10) and other reasons (n=105) including baby colicky, allergy prevention, fattening foods, high iron content, other child allergic and religious or personal reasons.

4.3.4.1 Maternal food avoidance during breastfeeding and infant's sensitisation to food allergens

The relationship between maternal food avoidance during breastfeeding and infants sensitisation to foods and FHS is summarised in tables 4.7 to 4.8.

Table 4.7: Maternal food avoidance during breastfeeding and infant's sensitisation to food allergens at one year

Food	Avoiders (infants with positive SPT)	Non- avoiders (infants with positive SPT)
Milk	0	2
Egg	0	14
Fish	0	2
Peanut	1	2
Any food	5	12

Table 4.8: Maternal food avoidance during breastfeeding and infant's sensitisation to food allergens at two years

Food	Avoiders (infants with positive SPT)	Non- avoiders (infants with positive SPT)
Milk	0	5
Egg	0	14
Fish	0	3
Peanut	2	10
Any food	9	15

Of the children sensitised to milk, egg and fish at one and two years, none of the mothers avoided the particular food during breastfeeding. Three children were sensitised to peanut at age one, 1 mother avoided peanuts and 2 did not. At the age of two, 13 children were sensitised to peanut, 2 mothers avoided peanut and 10 did not avoid peanut. We did not have any data on peanut consumption from one of the mothers.

Of the 17 children sensitised to any food allergen at age one, 12 mothers did not avoid any foo and 5 mothers did avoid some foods during breastfeeding. Of the 24 children sensitised to any food allergen at age two, 15 mothers did not avoid any foods and 9 did.

4.3.4.2 Maternal food avoidance during breastfeeding and infant's food hypersensitivity

At one year

Of the six mothers who avoided milk during breastfeeding, none of their children developed milk hypersensitivity and of the 921 mothers who did not, 22 children developed milk hypersensitivity based on OFC. For egg, none of the avoider's children developed egg hypersensitivity and 17 of the non-avoiders did. 17 of the avoiders' children developed FHS and 22 of the infants born to those mothers who did not avoid foods during pregnancy developed FHS. This information is summarised in table 4.9.

Table 4.9: Maternal food avoidance during breastfeeding and infant's FHS based on OFC at one year

Food	Avoiders infant's with FHS	Non-avoiders infant's with FHS	p-value (Fisher's exact test)
Milk	0	22	1.0
Egg	0	17	1.0
Any food	17	22	1.0

Of the children with FHS to milk and egg none of the mothers avoided the particular food during breastfeeding. None of the mothers avoided wheat and sesame and we could therefore not look at the relationship between wheat avoidance and development of FHS.

At two years

Of the six mothers who avoided milk during breastfeeding, none of their children developed milk hypersensitivity and of the 921 mothers who did not, 10 children developed milk hypersensitivity. Also for egg and fish, none of the avoider's children developed egg or fish hypersensitivity and 12 (egg) and 1 (fish) of the non-avoiders did. Seven of the infants born to those mothers who avoided any foods during breastfeeding developed FHS and 15 infants of those who did not avoid foods during pregnancy. This information is summarised in table 4.10

Table 4.10: Maternal food avoidance during breastfeeding and infant's FHS based on OFC at two years

Food	Avoiders infant's with FHS	Non-avoiders infant's with FHS	p-value (Fisher's exact test)
Milk	0	10	1.0
Egg	0	12	1.0
Fish	0	1	1.0
Any food	7	15	0.380

Of the children with FHS to milk, egg and fish none of the mothers avoided the particular food during breastfeeding. None of the mothers avoided wheat and sesame and we could therefore not look at the relationship between wheat avoidance and development of FHS.

4.3.5 Infant feeding practices during the first two years of life

Information regarding feeding practices was obtained from 927 (95.7%) mothers at 3 months, 913 (94.2%) at six months, 900 (92.8%) at nine months, 900 (92.8%) at 12 months and 858(88.5%) at two years. Feeding practices regarding method of feeding, duration of breastfeeding and introduction of formula feeding are summarised in table 4.11.

Table 4.11: Feeding practices during the first two years of life

	3 months (n=927) N (%)	6 months (n=913) N (%)	9 months (n=900) N (%)	12 months (n=900) N (%)	2 years (n=858) N (%)
Exclusive breastfeeding	165 (17.8)	0	0	0	0
Exclusively formula feeding	406 (43.8)	0	0	0	0
Mixed feeding	100 (10.8)	0	0	0	0
Breastfed and solids introduced	33 (3.6)	99 (10.7)	73 (8.1)	105 (11.7)	0
Formula fed and solids introduced	195 (21.0)	702 (76.9)	768 (85.3)	NA	NA
Mixed feeding and solids introduced	28 (3.0)	112 (12.3)	59 (6.6)	NA	NA

The mean duration of breastfeeding was 125 days and the mean timing of introduction of infant formula feeding was 38 days.

Different types of formulas were used in the infants' diet at different stages. The formulas used at different ages are summarised in table 4.12.

Table 4.12: Formulas used at 3, 6 and 9 months

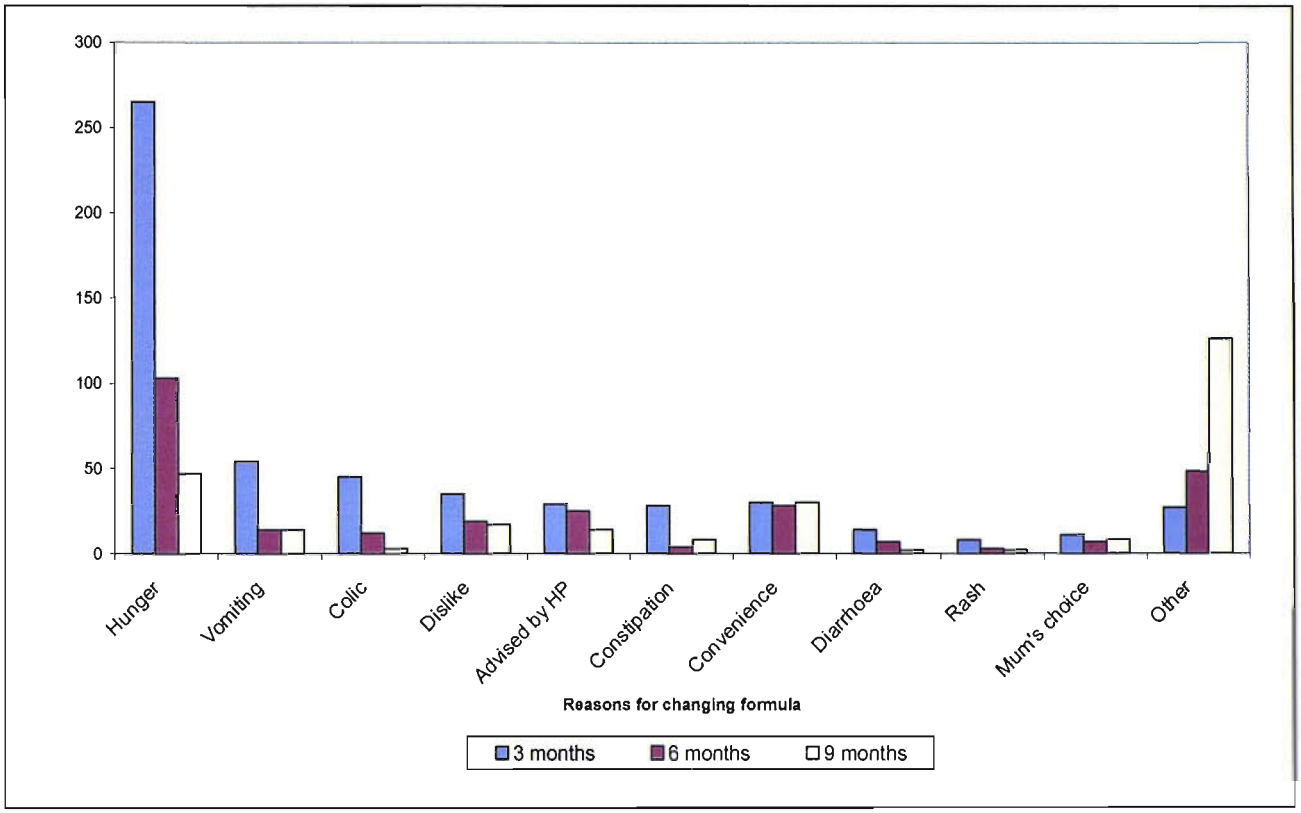
Formulas used	3 months (n=729) [α]	6 months (n=814) [β]	9 months (n=827)
Whey based	408	274	182
Casein based	347	392	282
Follow-on	0	81	260
Soya	24	24	29
Partial hydrolysate	16	14	12
Extensive hydrolysate	2	3	4
Amino acid	4	4	4
Organic	9	13	12
Other milk e.g. specialist feeds, formulas bought abroad	5	4	7
Uncertain	3	7	3
Premature formula	3	0	0
Energy dense	1	3	1
Cow's milk	0	2	31

[α]93 infants were using one or more formula concurrently. [β]7 infants were concurrently using more than one formula.

At three months, mothers were asked their reasons for choosing a certain formula. The main reasons included own preference (n=429), advised by health professional (n= 164), other health professional (n= 25), advised by family and friends (n=41), formula given in hospital or baby clinic (n=68) and nutritional composition of the formula (n=41). Other reasons included treatment or prevention of allergy, availability and cost and preference of organic formula.

In this cohort, 58.5% (426/728) of mothers changed formulas during the infant's first three months of life, 32.1% (262/814) between three and six months and 32.3% (267/827) between six and nine months. Mothers were asked regarding their reasons for changing formulas and the main reasons are summarised in figure 4.3.

Figure 4.3: Reasons for changing infant formulas at 3, 6 and 9 months



35.2% (326/937) mothers continued with breastfeeding after three months and 23% (211/913) mothers continued after 6 months. The main reasons for discontinuation of breastfeeding were too little milk, hungry baby who feeds constantly, and discomfort to mother whilst feeding. Interestingly, going back to work was not one of the main reasons as expected and often claimed by health professionals.

4.3.5.1 Infant feeding practices in relation to sensitisation to foods and development of food hypersensitivity

Information regarding the role of feeding practices and the development of sensitisation to foods and FHS was obtained from the questionnaires completed at 3, 6, 9, 12 and 24 months. This information is summarised in tables 4.13 to 4.17. In order to investigate the role of breastfeeding on the development of sensitisation to foods and FHS the following criteria were considered: exclusive breastfeeding at three months, any breastfeeding at six and nine months, any breastfeeding for longer than nine months and "ever" breast fed.

Table 4.13: Exclusive breastfeeding at three months and its association with sensitisation to the predefined food allergens and FHS

	Exclusive breastfeeding	Not exclusively breastfed	p-value (Fisher's exact test)
ONE YEAR			
Positive SPT	3	14	1.0
Negative SPT	147	581	
FHS	10	29	0.20
No FHS	155	733	
TWO YEARS			
Positive SPT	5	19	1.0
Negative SPT	119	497	
FHS	7	15	0.09
No FHS	158	747	

* FHS based on OFC and history for tables 4.13 – 4.17

Table 4.14: Any breastfeeding at six months and its association with sensitisation to the predefined food allergens and FHS

	Any breastfeeding at 6 months	No breastfeeding at 6 months	p-value (Fisher's exact test)
ONE YEAR			
Positive SPT	5	12	0.78
Negative SPT	186	543	
FHS	11	27	0.44
No FHS	200	657	
TWO YEARS			
Positive SPT	7	17	0.64
Negative SPT	159	461	
FHS	7	14	0.29
No FHS	204	688	

Table 4.15: Any breastfeeding at nine months and its association with sensitisation to the predefined food allergens and FHS

	Any breastfeeding at 9 months	No breastfeeding at 9 months	p-value (Fisher's exact test)
ONE YEAR			
Positive SPT	3	13	0.73
Negative SPT	113	612	
FHS	9	28	0.10
No FHS	123	740	
TWO YEARS			
Positive SPT	4	19	0.77
Negative SPT	96	519	
FHS	3	17	1.0
No FHS	129	751	

Table 4.16: Any breastfeeding at 12 months and its association with sensitisation to the predefined food allergens and FHS

	Any breastfeeding at 12 months	No breastfeeding at 12 months	p-value Fisher's exact test)
ONE YEAR			
Positive SPT	3	14	0.45
Negative SPT	89	641	
FHS	6	30	0.43
No FHS	99	746	
TWO YEARS			
Positive SPT	4	21	0.54
Negative SPT	77	536	
FHS	3	17	0.72
No FHS	102	759	

Table 4.17: "Ever" breastfed and its association with sensitisation to foods and its association with sensitisation to the predefined food allergens and FHS

	"Ever" breast fed	Never breast fed	p-value (Fisher's exact test)
ONE YEAR			
Positive SPT	16	1	0.22
Negative SPT	571	154	
FHS	29	9	1.0
No FHS	677	208	
TWO YEARS			
Positive SPT	19	5	1.0
Negative SPT	488	127	
FHS	18	3	0.44
No FHS	688	216	

There was no statistical difference in terms of sensitisation to food allergens or development of FHS and breastfeeding practices in any of the above groups.

4.3.6 Weaning practices during the first two years of life

More than a quarter (27.6% [256/937]) of mothers had introduced solids into the infant's diet by three months of age, 82.1% (750/913) before 17 weeks (45.6% - 416/913 before 16 weeks) and all mothers by six months. At six months 64% of (562/913) mothers were avoiding some foods from the infant's diet. The corresponding figures for 9, 12 and 24 months were: 58.4% (526/900), 54.8% (487/900) and 32.2% (312/858).

4.3.6.1 Infant weaning and feeding practice in relation to food sensitisation and food hypersensitivity

Fewer children weaned before 16 weeks developed sensitisation to foods at one and two years. This was also true for FHS at one year (table 4.18). The data was not confounded by maternal education, family history of allergic disease, maternal history of allergic disease or breast-feeding duration.

Table 4.18: Infant weaning and its association with sensitisation to the predefined food allergens and FHS

	Weaning before 16 weeks	Weaning after 16 weeks	p-value (Fisher's exact test)
ONE YEAR			
Positive SPT	3	14	0.03*
Negative SPT	329	399	
FHS	10	28	0.02*
No FHS	406	468	
TWO YEARS			
Positive SPT	9	15	0.53
Negative SPT	280	339	
FHS	7	14	0.28
No FHS	409	482	

* Statistically significant

4.3.7 Avoidance and introduction of the major allergic foods during the first two years of life

With regards to the avoidance and introduction of the major food allergens, information was obtained prospectively at 3, 6, 9 months and 1 and 2 years.

The data for each child was tracked during the first two years of life and are presented in section 4.3.7.1 and 4.3.7.2.

For the purpose of this study, exposure to food allergens is defined as those children that were either exposed to the food or not during breastfeeding and the first two years of life (section 4.3.7.1).

Age of introduction of food allergens is defined as the age that the foods were introduced into the weaning diet. It therefore does not take into account exposure during breastfeeding (section 4.3.7.2).

4.3.7.1 Exposure to the major allergenic foods during the first two years of life via breast milk or weaning diet and its association with infant's sensitisation to food and FHS

Data regarding complete food avoidance of foods during the first year of life as obtained during breastfeeding, three, six, nine and 12 months based on the questions "which foods have you avoided during breastfeeding", "have you given your child" and "which foods are you avoiding from your child's diet" are presented in table 4.19.

Table 4.19: Number of infants with no reported exposure to the major allergenic food proteins

Food	6 months (n=913)	9 months (n=900)	1 year (n=900)	2 years (n=858)
Cow's milk	1	0	0	0
Egg	4	0	0	0
Wheat	0	0	0	0
Fish	1	1	1	1
Peanut	74	46	40	20
Tree nut	11	8	5	4
Sesame	0	0	0	0

Ideally we wanted to look at whether exposure to the major allergenic foods at different ages had an effect on sensitisation and development of FHS to that particular food. As such a small number of children did not have exposure to the major allergenic foods, during breastfeeding or in the first 12 months of life, statistical analysis was not indicated.

At one year, one child sensitised to milk was not exposed to cow's milk before the age of six months. Of the children sensitised to egg (n=14) and fish (n=2), none of the mothers avoided these foods during breastfeeding and the infants were therefore all exposed to these foods before the age of three months.

At age two, a similar pattern was seen for milk and egg as age one. Thirteen children were sensitised to peanut and information on peanut avoidance was available on 12 children. Of these 12 children, 10 mothers never avoided peanut (including pregnancy), one mother avoided peanut until the infant was three months olds, and one mother until the infant was six months old.

At one year, 22 children were diagnosed with milk hypersensitivity and 17 with egg hypersensitivity. None of the mothers of these children avoided milk or egg. A similar pattern was seen at age two regarding food avoidance and development of FHS as at age one.

In summary, there were very few children who were sensitised to foods or developed FHS to a particular food in the group whose mothers avoided the food during breastfeeding and the infants first three to six months of life. All the children with sensitisation to foods or FHS at age one and two years of age were exposed to the food before three months except for peanut sensitisation.

4.3.7.2 Age of introduction of the major allergenic foods during the first two years of life

Age of introduction of the allergic food was based on the information gained from the questionnaires i.e. "foods not introduced and foods avoided". Therefore, in order to establish the relationship between timing of introduction of a food and the development of sensitisation or FHS, we looked at what has been given to the infant and avoided from the infant's diet at each time point (table 4.20).

Table 4.20: Pattern of introduction of the major food allergens

Food	6 months (n=913)		9 months (n=900)		1 year (n=900)	
	Introduced N (%)	Not introduced N (%)	Introduced N (%)	Not introduced N (%)	Introduced N (%)	Not introduced N (%)
Cow's milk	906 (99.3)	7 (7.7)	900 (100)	0 (0.0)	900 (100.0)	0 (0.0)
Egg	794 (87.0)	119 (13.0)	832 (92.4)	68 (7.6)	882 (98)	18 (2.0)
Wheat	878 (96.2)	35 (3.8)	896 (99.6)	4 (0.4)	900 (100.0)	0 (0.0)
Fish	886 (97.0)	27 (3.0)	889 (98.8)	11 (1.2)	896 (99.5)	4 (0.5)
Peanut	595 (65.2)	318 (34.8)	533 (59.2)	367 (40.8)	674 (74.9)	226 (25.1)
Tree nut	629 (68.9)	284 (31.1)	586 (65.1)	314 (34.9)	790 (87.8)	110 (12.2)
Sesame	912 (99.9)	1 (0.1)	895 (99.4)	5 (0.6)	900 (100.0)	0 (0.0)

Age of introduction of food and its association with sensitisation to the predefined food allergens

Of the two children sensitised to milk at age one, one child was given milk by 3 months and another by six months. Of the 14 children sensitised to egg, nine were given egg or egg containing foods by six months, two children by nine months and three children by one year. The two children sensitised to fish were given fish by six months. The three children sensitised to peanut were given peanut in weaning foods by six months (n=1) and nine months (n=2). Sesame was given in weaning foods by the age of nine months (n=2 sensitised). The majority of children 56.5% (13/23) were exposed to the food allergen before six months and all before one year.

Of the five children sensitised to milk at two years of age, four children were exposed to milk by three months and another by six months. Of the 14 children sensitised to egg (1 missing), 10 children were given egg or egg containing foods by six months, one by nine months and two by one year. One child was sensitised to wheat and had wheat in weaning foods only at 12 months. The three children sensitised to fish were given fish by six months. The 13 children sensitised to peanut (1 missing) were given peanut in weaning foods by six months (n=6), nine months (n=5) and one year (n=1). Sesame was given in weaning foods by the age of 6 months (n=5 sensitised). The majority of children 70.7% (29/41) were exposed to the food allergen before 6 months and all before one year.

Age of introduction of food and its association with development of food hypersensitivity

Twenty two children were diagnosed with milk hypersensitivity based on OFC at one year of age. Twenty one children were given milk by three months of age and all the children had milk by six months. The four children with OFCs to wheat at the age of one year were given wheat by six months (n=3) and 12 months (n=1). Of the 17 children diagnosed with egg hypersensitivity based on OFC (n=16) at age one, 14 children were given egg in weaning food by six months. Based on OFC the majority of the children, 90.7% (39/43), had eaten the food they developed FHS to by age six months.

Ten children were diagnosed with milk hypersensitivity based on OFC at two years of age. Seven of these children were given milk by three months of age and all of the children had milk by six months of age. The three children with OFCs to wheat at two years of age were given wheat by six months (n=2) and 12 months (n=1). Of the 12 children diagnosed with egg hypersensitivity based on OFC nine children were given egg in weaning food by six months. The one child with fish hypersensitivity was given fish by 6 months. Based on OFC the majority of the children, 90.7% (39/43) had eaten the food they developed FHS to by age six months 84.6% (22/26).

In summary, the majority of children with sensitisations to foods (76% of those sensitised at age one and 69.5% of those sensitised at age two) and all of those who developed FHS to a particular food, were given the particular food allergen before 6 months of age as part of their weaning diet.

4.4 Discussion

In total, 969 families were recruited to the birth cohort used for this project. Adverse reactions to food were reported by 33.2% of the families. The foods most often reported to cause problems by the mothers were fruit and vegetables, milk and food additives, fruit and vegetables, milk and nuts by the fathers and milk, egg and fruit and vegetables by the siblings.

The birth cohort study sample consisted of 500 boys and 469 girls. During pregnancy 89% of mothers followed a normal diet and 47.5% avoided peanuts. The majority of pregnant women had consumed milk (88.7%) and wheat (91.5%) containing foods ≥ 4 times per week and between 53.4 and 60.0% of mothers reported never eating oily fish or shell fish. 46.5% mothers ate white fish frequently i.e. ≥ 4 times per week.

Maternal food intake during pregnancy and its association with infant's sensitisation to foods or FHS at one or two years of age could not be statistically assessed as very few children developed FHS and became sensitised to foods. At one year of age, 2 children were sensitised to milk, 3 to peanut, 14 to egg, 2 to sesame and 2 to fish. 39 children were diagnosed with FHS by means of OFC and history. At two years of age, 5 children were sensitised to milk, 13 to peanut, 14 to egg, 1 to wheat, 3 to fish and 5 to sesame. Twenty two children were diagnosed with FHS by means of OFC and history at 2 years of age.

In this small sample maternal dietary intake during pregnancy did not appear to influence the development of sensitisation to food allergens or FHS. This study is unique as it is an observational study of an unselected population investigating the role of maternal food intake during pregnancy by means of a validated FFQ.

Previously conducted observational studies looking at maternal intake during pregnancy have focused mainly on peanut consumption (Hourihane, Dean, & Warner 1996;Lack et al. 2003) in the development of allergic disease in the infant. Hourihane et al (Hourihane, Dean, & Warner 1996) found that in utero exposure to peanut can trigger sensitisation, in particular where there is a family history of atopy. In contrast Lack and colleagues (Lack et al. 2003) determined that in utero sensitisation of the foetus to peanuts did not seem to be a factor in the development of peanut allergy. Unfortunately, both studies are guilty of recall bias and the questionnaires used to determine this information is not described in any detail and unlikely to have been validated.

Previous intervention studies in this area included three studies that looked at maternal dietary manipulation and the development of atopy in high risk families. One study found that maternal avoidance of milk and egg from 28 weeks of pregnancy, increased the prevalence of egg allergy up to the age of five years (Falth-Magnusson & Kjellman 1992). Another study found that maternal intake of egg during the last trimester did not affect IgE production (Lilja et al. 1988) and the third study found that egg avoidance from 20 weeks gestation reduced the prevalence of atopy (Vance et al. 2004). In addition, two of the studies clearly indicated that maternal food consumption affected IgG production (Lilja et al. 1988;Vance et al. 2004). It is also known that neonates have low serum IgE levels, and the IgG in the newborn's serum is essentially of maternal origin (Holt & Jones 2000). This indicates that maternal food consumption during pregnancy affects IgG production and raised the question whether food intake during pregnancy may affect the development of FHS.

As this was not the case in our study, it could perhaps be explained by the fact that we studied a non-selective group of children rather than a high risk subgroup. It is known that there is a maternal effect on the immunoglobulin profile and the development of allergic disease in the infant and that infants born to mothers suffering from atopic disease are more at risk of becoming allergic (Litonjua et al. 1998).

Two studies previously looked at omega-3 fatty acid intake and fruit and vegetable intake in pregnancy. In our group of mothers, omega-3 fatty acid intake as determined by oily fish consumption (> 1-2 per week) and omega-3 fatty acid supplements, did not show any correlation with development of sensitisation to foods or FHS at age one and two years, which contradicts the data from Dunstan et al (Dunstan et al. 2003). This could be explained by the fact that Dunstan et al. supplemented mothers with a higher dose of omega-3 fatty acids (3.7g per day) than consumed by the pregnant women in our study. Oily fish consumption as defined in our study (1-2 per week) would have provided only 2-3g omega-3 fatty acids 1-2 per week (British Nutrition Foundation 2005), rather than a daily consumption of 3.7g.

Fruit and vegetable intake (≥ 5 portions per day) were significantly associated with reduced FHS at age one year (based on OFC). This confirms the data by Stazi et al (Stazi et al. 2002) which indicated that low maternal intake of fruit (less than three portions per week) was associated with a positive SPT to six allergens, of which milk was the only food allergen. Some studies have looked at the effect of anti-oxidants on the development of epithelial cells of the human lung (Wisnewski et al. 2005). It is also suggested that

reduced maternal dietary antioxidant intake during pregnancy might be associated with the impaired lung development that is associated with wheeze, asthma, and reduced lung function later in life (Martindale et al. 2005). The possible mechanisms for the role of fruit and vegetables in the development of FHS are still unclear.

In terms of breastfeeding, 52% of mothers who breastfed avoided certain foods from their diets for a variety of reasons. 1.9% mothers avoided milk during breastfeeding, 15.4% mothers avoided peanut (101 of these avoided peanut during pregnancy) and 2.6% avoided tree nuts. None avoided wheat or sesame, 1.4% avoided egg and 1.5% avoided fish.

Food allergens such as milk, egg, wheat and peanut (Cant, Marsden, & Kilshaw 1985;Palmer, Gold, & Makrides 2005;Stuart et al. 1984;Troncone et al. 1987;Vadas et al. 2001), have long been known to be detectable in breast milk. It is however, uncertain whether this might lead to sensitisation or tolerance of these foods in the breast fed infant, or what variables affect these two possible outcomes. Our data suggests that maternal food avoidance during breastfeeding led to fewer children who became sensitised or developed FHS to that particular food compared with those whose mothers did not. This data however could not be assessed statistically due to the small numbers who became sensitised and developed FHS.

No intervention studies in an unselected population such as ours have been performed as yet, primarily because a very large population will be needed to show a significant effect of the intervention. However, a number of randomised controlled trials in high-risk infants have investigated the effect of different dietary allergy prevention programs during breastfeeding or pregnancy and breastfeeding. In agreement with our data, these studies found that avoidance of milk, egg, fish, peanuts and soya for 3 months (Hattevig, Sigurs, & Kjellman 1999) for the full duration of breastfeeding (Arshad et al. 1992;Chandra 1989) reduced the prevalence of eczema (Chandra, Puri, & Hamed 1989;Hattevig, Sigurs, & Kjellman 1999), allergic disorders (Arshad et al. 1992) and wheeze and nocturnal cough at eight years (Arshad, Bateman, & Matthews 2003). In addition, Arshad et al (Arshad et al. 1992), found reduced sensitisation to food allergens at 12 months.

Three quarters of mothers (75.6%) attempted breastfeeding on the day the infant was born, but this was reduced to any breastfeeding of 35.2% at 3 months, 23.1% at 6 months and 9.7% at 9 months. The main reasons given for discontinuation of breastfeeding were too little milk, hungry baby or discomfort/pain during feeding. Other studies found that the

main reason for continuation of breastfeeding was the emotional bond between mother and child (Hills-Bonczyk et al. 1994;Kendall-Tackett & Sugarman 1995) and health benefits (Gijsbers et al. 2005). For discontinuation it was a concern about the child's nutrition (Gijsbers et al. 2005), return to work (Williams et al. 1999), lack of social acceptance (Rempel 2004) and expecting another child (Sugarman & Kendall-Tackett 1995).

A variety of formulas were used during the first year of life, starting with whey based, and followed by casein-based and follow-on formulas. Reasons for choosing a formula were mainly own preference, advised to by health professional or family member or formula given in hospital. The main reasons for changing formulas were hungry babies and advice by a health professional.

In this group of children, breastfeeding duration did not seem to affect the prevalence of FHS at all. Numerous studies have attempted to examine the role of breast-feeding in the development of allergy. Differences in methodology and inevitable flaws in design make these studies difficult to compare, and no single definitive study has yet been published. Methodological differences include whether a study is prospective or retrospective, interventional versus observational or self-selective versus randomised studies. Other flaws include small sample size, lack of randomisation, short breastfeeding duration and definition of "exclusive" breastfeeding. Definition of the clinical outcomes in studies and the age at which the study participants were evaluated also differs greatly.

Studies looking at the effect of breastfeeding on the development of allergic disease, can be divided into those showing a protective effect and those showing no protective effect. Five studies indicate that breastfeeding for at least 12 weeks prevented some symptoms of allergic disease. Only two studies (Saarinen et al. 1999;Saarinen & Kajosaari 1995) found that breastfeeding prevented food allergy and only one of these studies (Saarinen et al. 1999) diagnosed food allergy by means of food challenges. There are, however, also a number of studies in unselected cohorts which have shown that breastfeeding increases the risk of allergic symptoms, (Bergmann et al. 2002;Pratt 1984;Sears et al. 2002;Wright et al. 2001) but none of these looked at the effect of breastfeeding on FHS. The different finding of these studies could perhaps be explained by differences in composition of breast milk: firstly, the lower omega-3 fatty acid levels of the serum and breast milk of atopic mothers vs. non-atopic mothers may play a role in the development of asthma and eczema of the infant (Yu, Duchen, & Bjorksten 1998). Secondly, the reduced levels of soluble CD14 and omega-3 fatty acids in breast milk could also favour

the development of atopy in the infant (Jones et al. 2002). As mentioned in chapter 1, we may in future find that breastfeeding may be more effective in preventing allergies, based on the mothers own atopic status and the composition of the breast milk as the most important determining factors (Jones et al. 1998).

More than 80% of mothers had introduced solids before the infant was 17 weeks old, 45.6% before the infant was 16 weeks old, and 27.6% before the infant was 12 weeks old. All mothers had introduced solids into the infant's diet before 6 months.
Our data support the results from previous studies. Hamlyn and colleagues (Hamlyn et al. 2002) found that about 49% of mothers introduced solid foods even before 16 weeks and 21% of mothers recruited into the Millennium Baby Study (Wright, Parkinson, & Drewett 2004) weaned infants before the age of 3 months and only 6% after 4 months.

Weaning age significantly affected the prevalence of sensitisation to foods and FHS at one year of age. Surprisingly, children weaned on or after 16 weeks were more likely to develop FHS (p=0.02) and sensitisation to foods (p=0.04). It is difficult to explain why solid food introduction before 16 weeks led to less FHS and sensitisation. Our data is in contrast with previous studies looking at weaning age and development of FHS. Two previous studies found that introduction of solids before 3-4 months of age increases the risk of developing allergic disease in unselected (Fergusson, Horwood, & Shannon 1990;Morgan et al. 2004;Wilson et al. 1998) and high risk children (Kajosaari 1991). Zutavern et al. reports in a very recent study (Zutavern et al. 2006) that weaning after 4 months reduced the prevalence of atopic dermatitis, but delaying introduction of solid foods after 6 motnhs did not provide any additional benefits. However, in support of our data, another stidy by Zutavern et al. (Zutavern et al. 2004) showed that introduction of solids after 6 months increased the risk of allergic disease and FHS.
The question regarding tolerance to food allergens is not a simple one to answer as the processes governing tolerance to food allergens or aeroallergens are still poorly understood. It seems that a number of factors can influence the balance between tolerance and sensitisation such as: weaning age plus dose and frequency of food given (Strobel 1995), genetic background (Bergmann et al. 1997), although not proven for FHS per se, nature of antigen and dose of antigen (Dearman et al. 2000), immunological status of the infant (e.g. virus infection) and maturity of the immune system (Miller et al. 1994;Taylor et al. 2004). Early introduction leading to tolerisation could be a possible mechanism, but it is unlikely that development of FHS will ever be attributed to one single factor and this needs to be investigated in future prospective studies.

57.4% of mothers avoided certain foods from the infant's diet during the first year of life. These mainly included the main allergenic foods, meat and citrus fruits.
A Swedish study looking at breastfeeding practices of atopic mothers found that 45% of parents avoided gluten till 4 months, 23% egg and 33% fish during the infant's first year of life (van Odijk et al. 2004). In our study, looking at avoidance in the whole cohort, we found that 3.8% mothers avoided wheat until six months, 2.1% avoided egg and 0.5% avoided fish until one year.

Data regarding exposure to food allergens were based on avoidance during breastfeeding, avoided and not given at age three, six, nine and 12 months in order to determine which children have not been exposed to certain food allergens after birth. From this data, it does seem that children who were not exposed to a certain food allergen before the age of three to six months, were less likely to become sensitised or develop FHS to the particular food at age one and two. The data was also scrutinised for peanut avoidance during pregnancy, breastfeeding and the infant's first year of life and none of the children who were not exposed to peanut during the first year of life became sensitised to peanut. Also, all children with sensitisation to foods or FHS were exposed to the food before 3 – 6 months of age, except for a few children with peanut sensitisation (n=3).

Age of introduction of food defined as when food was given in the weaning diet for the first time, showed that the majority of children sensitised to foods were given the particular food before 6 months of age. All of those who developed FHS to a particular food, were given the offending food before 6 months of age as part of their weaning diet.

In this study, we have therefore found contradicting results regarding the effect of weaning age on the development of sensitisation and FHS and exposure to food allergens and age of introduction of the main allergenic foods on the development of sensitisation and FHS.

Those children who were weaned before 16 weeks had significantly less sensitisation and FHS at one year, perhaps indicating early tolerisation. However, in terms of the major allergenic foods, we found that early introduction (between 3-6 months) led to more sensitisation and FHS to these particular foods. This may indicate that although early weaning could lead to tolerisation in general, the main allergenic food proteins may behave differently and that age of introduction to these needs special investigation. It is known that proteins vary substantially with respect to their inherent allergenic potential i.e. that the main allergenic food proteins behave differently to other food proteins. These

characteristics are: (1) size of the protein, (2) glycosylation status, (3) resistance to proteolytic digestion, (4) overall immunogenicity, (5) the way in which proteins are processed by antigen-presenting cells and the form in which peptides are presented to the immune system. These features will ultimately determine whether a protein will have the characteristics to stimulate the type of immune response leading to sensitisation or tolerance (Dearman et al. 2000;Kimber, Stone, & Dearman 2003).

In conclusion, this study found that maternal dietary intake during pregnancy, omega-3 fatty acid intake, and breastfeeding duration did not appear to influence the development of sensitisation to food allergens or FHS. Fruit and vegetable intake (≥ 5 portions per day) during pregnancy were however significantly associated with reduced FHS at age one (based on OFC) and age one and two. In addition, food avoidance during breastfeeding showed that fewer children whose mothers avoided a food, became sensitised or developed FHS to that particular food compared with those who did not.

The most interesting finding of this study is that weaning before 16 weeks significantly reduced sensitisation to foods and development of FHS. However, all of those who developed FHS to a particular food, were given the offending food before 6 months of age as part of their weaning diet. This could be due to early tolerisation in general when weaned early, but indicate that the main allergenic food proteins react differently with the immune system leading to sensitisation upon early introduction.

Chapter 5

Dietary experiences and feeding practices of atopic and non-atopic mothers.

5.1 Introduction

It is unclear whether the dietary, feeding and weaning practices of women with a personal or family history of allergic diseases differ from those without any personal or family history of allergy.

If dietary habits of women who are atopic themselves or who are from families with an atopic history differ, then this may partially explain why children from atopic families are more likely to develop allergic diseases themselves.

Apart from the maternal diet, the role of weaning and introduction of solid foods in the development of allergic disease and FHS is also unclear at present. Few studies suggest that introduction of solids before 3-4 months of age increases the risk of developing allergic disease in unselected (Fergusson, Horwood, & Shannon 1990;Morgan et al. 2004;Wilson et al. 1998) and high risk children (Kajosaari 1991). Introduction of solids after 6 months has also been shown to increase the risk of allergic disease and FHS (Zutavern et al. 2004). In contrast, another study by Zutavern et al (Zutavern et al. 2006) showed that introduction of solid foods after 4 months decreased the prevalence of atopic dermatitis, but delaying solid foods beyond 6 months did not provide any additional benefits.

Three studies previously looked at the role of family atopy on breastfeeding duration and reported no difference between atopic and non-atopic families (Kull et al. 2002;van Odijk, et al. 2004;Wilson et al. 1998). Two further studies investigated whether a family history of allergic disease had any effect on weaning practices. Van Odijk and colleagues found no difference between timing of introduction of solids or introduction of highly allergic foods in the atopic and non-atopic families (van Odijk et al. 2004). In contrast, Schoetzau and colleagues (Schoetzau et al. 2002) found that mothers of infants with a family risk of eczema had delayed solid food feeding beyond the first 6 months more frequently than mothers of subjects without a family history.

The purpose of objective 4 in this project was to add to the body of evidence in this area and assess our findings in the light of other studies.

The aim of this chapter is to report on this objective and assess whether maternal dietary, feeding and weaning practices of FAIR birth cohort mothers with a personal or family history of allergic disease differed from mothers without any history of allergy.

5.2 Methods

In order to obtain the information needed for this objective, the following research tools have been used:

- Recruitment and birth questionnaire to obtain family history of atopy and descriptive data on the study participants
- Validated FFQ to determine food intake during pregnancy
- Questionnaires at 3, 6, 9, 12, and 24 months to obtain prospective information regarding breast/bottle feeding and weaning and feeding practices.

In this study atopic and non-atopic families are defined based on a reported history of allergic disease using the ISAAC questions (von Mutius 1996).

5.3 Results

5.3.1 Baseline information of mothers with and without a personal or family history of atopy

Data were obtained from 969 families with babies born between 1 September 2001 and 31 August 2002. In total, 806 (83.2%) of the families (mother, father or sibling) and 581 (60%) of the pregnant women reported a history of allergic disease. Atopic mothers reported a personal history of FHS more often than non-atopic mothers (141/581 [24.3%] vs. 48/388 [12.4%]; 95%CI, p=<0.001, χ^2= 22.6). 91/338 (26.92%) atopic mothers and 31/229 (13.54%) non-atopic mothers reported a problem with food in their children (95%CI, p=<0.001, χ^2= 14.5). There was no difference between the atopic and non-atopic families with regards to the type of delivery, infant's sex and breastfeeding practices at birth.

5.3.2 Dietary habits of mothers with and without a personal or family history of atopy during pregnancy

At 36 weeks gestation, information regarding history of atopic disease and eating practices during pregnancy were obtained from 937 (96.7%) mothers. Amongst these, 779/937 (83.1%) families and 556/937 (59.3%) mothers reported a history of allergic disease.

The dietary habits of mothers with or without a maternal or family history of allergic disease were compared for the variables outlined in table 5.1.

Table 5.1: Variables assessed to establish the dietary habits of mothers with and without a personal or family history of atopy during pregnancy

Variables investigated
Intention to feed
Type of maternal diet (e.g. normal diet, vegetarian, vegan or a special medically indicated diet)
Foods avoided from their diets
Vitamin/mineral supplementation
Fruit and vegetable intake
Smoking history
Exposure to major allergenic foods (e.g. milk, egg, wheat, fish, peanuts, tree nuts and seeds)

Dietary practices were very similar for most of the factors looked at. Pregnant women with a family history of atopic disease were more likely to smoke (37.6% vs. 29.4% [p=0.01, χ^2 6.7]) and to take a multi-mineral supplement (19.4% vs. 13.6% [p=0.02, χ^2 5.3]) during pregnancy. Pregnant women with a maternal history of atopy were less likely to have an intention to breastfeed (73% vs.81% [p=0.04, χ^2=4.4]) and to stop smoking during pregnancy (31.3% vs. 48.9% [p=0.02; χ^2=5.29]).

5.3.3 Maternal food avoidance during lactation in relation to a maternal or family history of atopy

Data was available on 927 (95.7%) mothers at three months of whom 773 (83.4%) reported a family history and 558 (60.2%) reported a maternal history of allergic disease. 613 (66.2%) mothers breast fed the infant for ≥ 1 week, but history of allergic disease was only available in 611 families. Dietary information was only obtained from those mothers who breast fed for ≥ 1 week.

Using the follow-up questionnaire, maternal avoidance of the main allergenic foods during lactation was explored in relation to history of atopy and there was no difference between mothers with and without a history of atopy.

5.3.4 Infant feeding and weaning practices in relation to a maternal or familial history of atopy

Information regarding feeding and weaning practices was obtained from 927(95.7%) mothers at 3 months, 913 (94.2%) mothers at 6 months, 900 (92.8%) at 9 months, 900 (92.8%) at 12 months and 858 (88.5%) at 2 years.

Of the 913 who completed the questionnaires at 6 months 756 (82.8%) reported a family history of atopy and 545 (59.6%) a maternal history.
Of the 900 who completed the questionnaires at 9 months, 748 (83%) reported a family history of atopy and 538 (59.8%) a maternal history.
The corresponding figures at 1 and 2 years were 748 (83.4%) and 539 (59.9%) at one and 713 (83.1%) and 516 (60.1%) at two years.

We explored a range of factors relating to feeding and weaning practices at 3, 6, 9, 12 and 24 months between those with a history of atopy and those without. These variables are described in table 5.2. At each follow-up, information was also obtained regarding maternal smoking habits and cat and dog ownership. Tables 5.3 and 5.4 show the significant factors based on a familial and maternal history of atopy respectively.

Table 5.2: Variables assessed to determine feeding practices in relation to a maternal or familial history of allergic disease

Variables investigated
Breastfeeding history (e.g. duration exclusive or partial)
Method of feeding (e.g breast, infant formula, both)
Time of introduction of solids
Foods avoided from the infant's diet
Use of commercial baby foods
Reported food related problems
Reported symptoms of allergic disease
GP consultation regarding infant's medical problems
Parental smoking
Pet ownership
Additional information at 24 months
Reported peanut consumption during pregnancy
Acknowledgement of the COT report
Dietary changes on the basis of the COT report

Table 5.3: Statistically significant factors (using the $\chi 2$ test) at 3, 6, 9, 12 and 24 months in relation to the familial history of atopy

	Reported familial history of atopy N (%)	No reported familial history of atopy N (%)	p-value
3 months			
Exclusive breastfeeding at 3 months	141 (18.2)	14 (9.1)	*0.008*
6 months			
Not weaned onto peanuts	275 (36.4)	43 (27.4)	*0.03*
Rate of reported history of allergic symtpoms for the index child	616 (81.5)	105 (66.9)	*0.00*
9 months			
Rate of reported history of allergic symptoms for the index child	559 (74.7)	92 (60.5)	*0.001*
12 months			
No differences were found	-	-	-
24 months			
Rate of reported food related problem for the index child	66 (9.3)	6 (4.1)	*0.04*

At 3 months, more mothers with a family history of allergic disease were still exclusively breastfeeding (18.2% vs. 9.1%; p=0.008). Mean breastfeeding duration however was very similar (61 vs. 62 days).

It was also the mothers from allergic families who were more likely to avoid peanut from the infant's weaning food (36.4% vs. 27.4%; p=0.03). At 6 and 9 months, mothers from atopic families were more likely to report symptoms of allergic disease (not necessarily food related) in the infant (81.5% vs. 66.9%; p=<0.001 [6 months]) and (74.7% vs. 60.5%; p=0.001 [9 months]).

At 12 months no statistically significant differences were found between the two groups.

At 24 months, the only significant difference between the groups was the rate of reported food related problems (9.3% vs. 4.1%; p=0.04).

Table 5.4: Statistically significant factors (using the $\chi 2$ test) at 3, 6, 9, 12 and 24 months in relation to the maternal history of atopy

	Reported maternal history of atopy N (%)	No reported maternal history of atopy N (%)	p-value
3 months			
Maternal smoking	166 (29.7)	76 (20.6)	*0.002*
Dog ownership	140 (25.1)	64 (17.3)	*0.005*
6 months			
Rate of reported food related problems for the index child	52 (9.5)	31(8.4)	*0.02*
Rate of reported symptoms of allergic disease for the index child	446 (81.8)	275 (74.7)	*0.01*
GP consultation rate	117/434 (27.0)	96/268 (35.8)	*0.02*
9 months			
GP consultation rate	170/402 (42.3)	78/237 (32.9%)	*0.02*
Rate of reported symptoms of allergic disease for the index child	415 (77.1)	236 (65.2)	*0.001*
Maternal smoking	151 (28.1)	77 (21.3)	*0.02*
12 months			
Maternal smoking	171 (31.7)	81 (22.4)	*0.01*
Parental smoking	266 (49.4)	155 (42.9)	*0.03*
24 months			
Maternal smoking	157 (30.4)	76 (22.2)	*0.008*
Rate of reported food related problem for the index child	57 (11.0)	15 (4.4)	*0.001*
Acknowledgement of the COT report	190 (36.8)	154 (45.0)	*0.03*

The data indicated that the rate of maternal smoking was higher amongst atopic mothers than non-atopic mothers (29.7% vs. 20.6%; p=0.002 [3 months]), (28.1% vs. 21.3%, p=0.02 [9 months]), (31.7% vs. 22.4%, p=0.01 [12 months]) and (30.4% vs. 22.2%; p=0.008 [24 months]). At six months, this difference was not significant (25.8% vs. 21%, p=0.21).

Atopic mothers were more likely to report a food related problem at 6 (9.5% vs. 8.4%; p=0.02) and 24 months (11% vs. 4.4%, p=0.001). At both 6 and 9 months, atopic mothers reported a significant higher rate of symptoms of allergic disease (81.8% vs. 74.7%; p=0.01 [6 months] and 77.1% vs. 65.2%; p=0.001 [9 months]) in the infant and visited the GP or Paediatrician more frequenty (27% vs. 35.8%; p=0.02 and 42.32% vs. 32.9%; p=0.02 [9 months]) than non-atopic mothers.

At 24 months, less atopic mothers reported to have heard about the COT report than non-atopic mothers (36.8% vs. 45%; p=0.03), but interestingly this did not have an effect on peanut intake or avoidance.

5.4 Discussion

A number of studies have previously looked at factors that could influence maternal dietary intake during pregnancy as well as infant feeding and weaning practices during the first few years of life. Maternal dietary intake can be influenced by taste preferences over the course of pregnancy (Bowen 1992), maternal dietary knowledge (French, Barr, & Levy-Milne 2003), race (Siega-Riz, Bodnar, & Savitz 2002) and income (Wei et al.1999). Factors such as concerns over nutritional content of the infant diet may affect weaning age (Dungy, Losch, & Russell 1994). Convenience, maternal age (Maehr et al. 1993) and education during pregnancy (Skinner et al. 1997) could influence the choice between breast and formula feeding and breastfeeding duration may be determined by maternal education and age (Michaelsen et al. 1994). Only a small number of studies, however looked at the role of a family history of atopy on feeding practices (Kull et al. 2002;van Odijk et al. 2004;Wilson et al. 1998) and only one purely observational study has investigated the effect of a family history of atopy on weaning practices (van Odijk et al. 2004) who found that familial atopic status did not affect weaning practices. No study previously looked at the effect of maternal history of atopy on dietary intake during pregnancy or feeding and weaning practices during the infant's first 2 years of life.

In order to shed more light on this objective, data were obtained from 969 families with babies born between 1 September 2001 and 31 August 2002. In total, 806 (83.2%) of the families (mother, father or sibling) and 581 (60%) of the pregnant women reported a history of allergic disease. This is higher than reported in previously conducted studies, reporting a family history of 53.9% (Morgan et al. 2004), 66.5% (van Odijk et al. 2004) and 38.0% (dual heredity) (Bergmann et al. 2002). However, the definition used for atopy varied widely in these studies, explaining the large differences in the figures. We defined atopy according to the ISAAC questions used (von Mutius 1996) which is broad and includes all types of allergic manifestations.

At 36 weeks gestation, information regarding history of atopic disease and eating practices during pregnancy were obtained from 937 (96.7% mothers). 779/937 (83.1%) families and 556/937 (59.3%) mothers reported a history of allergic disease.

Dietary practices were very similar for a number of the factors looked at. Women with a family history of atopic disease were however significantly more likely to smoke and to take a multi-mineral supplement during pregnancy. Pregnant women without a maternal history of allergic disease were more likely to intend to breastfeed and to stop smoking during pregnancy. We also found that higher numbers of atopic mothers smoked at 3 (p=0.002), 9 (p=0.02), 12 (p=0.01) and 24 (p=0.008) months. It was not the aim of this thesis to correlate maternal smoking with development of allergic disease. The evidence on smoking and its association with atopy is quite confusing. Some studies report an increase in allergic symptoms with parental smoking (Arshad et al. 2005;Cantani & Micera 2005), while other studies found no effect of maternal (Purvis et al. 2005) or parental smoking (Lack et al. 2003) and some even found a protective effect on the development of allergic disease (Kuyucu et al. 2004).

Only one study previously looked at maternal dietary intake during pregnancy in relation to family history of atopy, obtaining information on avoidance of peanuts during pregnancy, and found it to be unrelated to a family history of allergic disease (van Odijk et al. 2004). There are no studies reported in the literature investigating the role of maternal history of atopy on dietary intake during pregnancy.

At 3 months, data were obtained from 927 (95.7%) mothers of whom 773 (83.4%) reported a family history and 558 (60.2%) reported a maternal history of allergic disease. In terms of food avoided during lactation, no difference was found between mothers with and without a maternal or family history of atopy. This is surprising as one would expect that where there is a history of atopy it is likely that expecting women may change their dietary habits. Unfortunately, there are no comparable studies available in the literature for us to compare our findings with.

The relationship between feeding and weaning practices at 3, 6, 9, 12 and 24 months and a maternal or family history of allergic diseases, showed very few significant differences.

Comparing mothers with a family history of allergic disease to those with no family history, we found that in the case of an atopic family history, mothers were more likely to breastfeed exclusively at 3 months than those with no family history. Our data confirms the similar findings by other groups (Halken et al. 2000;Schoetzau et al. 2002) who found that the higher the atopic risk in the family, the greater the mothers' willingness to breast-feed exclusively for the first 4 months of the infant's life. These studies were however performed in high risk children only who were graded according to different levels of

atopic status e.g. single or double heredity. Only one study investigating the effect of atopic status on breastfeeding practices was conducted previously and found (van Odijk et al. 2004) that there was a slightly higher proportion of children with a non-atopic background that were breastfed exclusively at age 4 and 6 months than children with atopic background. The findings from this study are in contrast to our findings. This could be due to different criteria for defining atopy. We found an 83% reported atopic rate compared to the 25% in the study by van Odijk et al (van Odijk et al. 2004). The high drop-out rate in this Swedish study, selection bias by the large number of nurses involved and the fact that the data was collected retrospectively, could also have influenced the data. Ludvigsson and colleagues (Ludvigsson et al. 2005) recently published a study looking at the effect of breastfeeding on the development of atopic dermatitis, but did not present figures to indicate breastfeeding duration in atopic and non-atopic mothers.

We did not find any difference in breastfeeding duration between mothers with or without a maternal or familial history of allergic disease. Our data is therefore in agreement with previous studies that found there was no difference in breastfeeding duration between atopic and non-atopic families (Kull et al. 2002;van Odijk et al. 2004;Wilson et al. 1998). It is often suggested that the conflicting data regarding the protective effect of breastfeeding on the prevention of allergic disease, could be due to the fact that perhaps those with the highest degree of atopic heredity will tend to be breastfeeding for the longest period. This implies that when we are looking at the effect of breastfeeding on allergy prevention, the breastfeeding group may naturally include more of those highest at risk as they are the group that breastfeed for a longer period. Our data does not support this hypothesis.

Reported rate of peanut avoidance from the infant's diet and symptoms of allergic disease in the infant were higher in the atopic group at 6 months. In the study by van Odijk et al. (van Odijk et al. 2004) only 5/467 mothers gave the infants peanuts during the first year of life, even though it is not recommended to delay introduction of peanuts in Sweden. They did not find any relationship between peanut avoidance and a family history of allergy.

Mothers with a family history of allergic disease reported symptoms of all types of allergic disease more often in their infants compared to those mothers with no family history ($p=<0.001$ at 6 months and $p=0.001$ at 9 months), but this difference was lost after 9 months. This could reflect a possible higher degree of anxiety and worries amongst those with a history of atopic disease. However, at 24 months, mothers with a family history of allergic disease specifically reported food related problems more often in the infants than

those with no history (p = 0.04). This may however be a chance finding as this was only found once in the 5 time points that the data were obtained.

In other previous studies looking at food related problems (Bock 1987;Brugman et al. 1998;Roehr et al. 2004b;Young et al. 1994), the data was not correlated with a family history of allergic disease. In terms of reported symptoms of allergic disease, chronic itchy rash and wheeze in children were reported more often by parents with a family history of atopy (Tan et al. 2005). Interestingly, in another population based study (Alspac) (Wadonda-Kabondo et al. 2004) there was a strong association between parental eczema and reported childhood atopic dermatitis.

For those with a maternal history of allergic disease we found a higher number of atopic mothers owned a dog at three months. This is in contrast with the data from Almqvist et al (Almqvist et al. 2003) who reported that dogs were less common in families with parental atopy (3.3%) than those without (5.9%) parental atopy. Other studies that investigated pet ownership reported that pet ownership decreased with a higher socio-economic status (Bergmann et al. 2000). In addition, a number of studies looked at pet ownership and the development of allergic disease (Austin & Russell 1997;Benn et al. 2004;Butland, Strachan, & Anderson 1997;Svanes et al. 1999), but this was not the aim of this thesis.

Atopic mothers (maternal history) were more likely to report a food related problem at 6 months and 24 months. At both 6 and 9 months, atopic mothers reported higher rates of symptoms of allergic disease in the infant (p=0.01 at 6 months and p=0.001 at 9 months) and visited the GP or Paediatrician more often than non-atopic mothers (p=0.02 at 6 months and p=0.02 at 9 months).

We have therefore seen an increase in reported problems of allergic disease and visits to the GP or Paediatrician, in both the groups with a maternal or family history of allergy. This may highlight an important area of health service provision. More studies in this area are needed to determine whether we really found a higher rate of allergic manifestations in these children or whether it was over reporting from this particular group of parents. This may indicate that parents from allergic families are more likely to report symptoms of allergic disease in their infants. The discrepancy between symptoms of allergic disease and diagnosed allergic disease has been reported by a number of studies (Bock 1987;Roehr et al. 2004b;Zuberbier et al. 2004). This study is however the only study comparing reported rates in atopic and non-atopic families and mothers. The finding

therefore suggests the need for better education and support of this particular group of parents during pregnancy and the infant's first years of life.

At 12 months, the infants from the atopic families were more likely to have a positive SPT to food (2.1% vs. 0.7%), positive SPT to any allergen (2.7% vs. 0.7%), a positive OFC (4.5% vs. 3.3%) and a positive DBPCFC (3.7% vs. 2.0%). Children from atopic mothers presented with the following sensitisation and FHS data: a positive SPT to food (2.4% vs. 1.1%), positive SPT to any allergen (3.2% vs.1.1%; p=0.04), a positive OFC (4.3% vs. 4.4%) and a positive DBPCFC (3.7% vs. 3.0%). The only characteristic that reached statistical significance was sensitisation to any allergen in infants born from atopic mothers. However this difference was lost at 24 months.

Another interesting finding is that, less atopic mothers reported to have heard about the COT report than non-atopic mothers (36.8% vs. 45%; p=0.03), but this did not have an effect on maternal peanut intake or avoidance. This could indicate that the message was not conveyed clearly and therefore not understood correctly. On the other hand it may indicate that knowledge of a risk, does not necessarily prompt a response. In terms of the COT report specifically, the wording (mother *may wish* to avoid peanut) might have caused confusion and affected the compliance of mothers. This implies that when recommendations like these are made, the message should be clearly worded and health professionals conveying the message should be sufficiently educated.

Chapter 6

General discussion

This chapter aims to discuss the key points of this thesis and reflects on how individual objectives were achieved. The main strength of the study is the number of novel factors that have been researched. These include:
Comparison of OFCs and DBPCFCs in the diagnosis of FHS.
Reporting on the practical issues surrounding food challenges.
Validation of a FFQ which assesses frequency of intake of four major food allergens.
An extensive comparison of dietary, feeding and weaning practices in the development of FHS.
A study of the role of a personal or family history of allergic disease on the dietary, feeding and weaning practices.

More precisely, OFCs and DBPCFCs were compared in 5 different cohorts of children ranging from 6 months to 15 years, which enabled the author to look at the use of food challenges in children of different ages with different symptoms. Great care was taken in preparing the food for the OFCs and DBPCFCs. The blindness of the challenges was tested in children of the same ages as those in the study and the parents involved. Preparation of foods for the one-week DBPCFC has not been performed previously and is considered impossible by a number of researchers and clinicians.

The project aimed to address 1) how maternal diet, feeding and weaning practices influenced the development of FHS, 2) what was the best approach for the diagnosis of FHS, 3) the role of a personal or family history of atopy in dietary practices.

In order to do this, valid tools were needed to ensure that the outcome measure is an appropriate one. We were surprised at the paucity of information in this area. There was not any validated FFQ investigating maternal consumption of food allergens during pregnancy. As a result, during the course of this study, an appropriate FFQ was developed to determine frequency of maternal intake of some of the main food allergens during pregnancy.

Numerous opinions exist in the literature regarding the need for the time consuming DBPCFC when it is possible to perform an OFC in less time and with less effort. Most experts advise, primarily by opinion, that the DBPCFC is considered a gold standard (Niggemann et al. 2005). Niggemann (Niggemann 2004) recommends that a positive OFC should be followed by a DBPCFC in the diagnosis of atopic dermatitis. However, this thesis is the first to compare the two formats as indeed no previous study has been

published looking at the use of OFCs vs. DBPCFCs in the diagnosis of immediate (mostly objective) symptoms and delayed (mostly subjective) symptoms, apart from a poster presentation by Shinoda et al (Shinoda et al. 2004). The author found that the positive predictive value of the one-day OFCs was higher than the one-week OFCs. The data therefore suggest that OFCs may be suitable for diagnosing immediate (mostly objective) symptoms, whereas a DBPCFC may be needed for the diagnosis of delayed (mostly subjective) symptoms. Supporting our data, Shinoda et al (Shinoda et al. 2004) found that OFCs are suitable for the diagnosis of objective symptoms, but that SBPCFCs are needed for the diagnosis of subjective symptoms.

It is often recommended that OFCs are suitable for children under three years and DBPCFCs should be the method of choice in children over three years (Bahna 2003;Bindslev-Jensen et al. 2004;Muraro 2001;Niggemann et al. 2005). We could not find any evidence to indicate that younger children are more likely to have a positive OFC confirmed by a DBPCFC. This indicated that age should not play a role in deciding which type of challenge to use and that the choice of challenge type should be based on the symptoms reported by the history. In support of this, we found that the symptoms reported by the parents or children were indeed the symptoms likely to be experienced during the food challenges. This confirmed the findings by Hourihane et al (Hourihane2005) who found that similar symptoms were experienced during the DBPCFCs as reported by the history. The reported symptoms were however more severe than the symptoms experienced during the DBPCFCs.

The challenge dose needed to either confirm or refute a diagnosis of FHS is another much discussed point in performing food challenges with a lack of consistency in the literature. The discrepancy between the advice given in guidance papers and challenge dose used for research and clinical purposes has been discussed in the introduction of this thesis. Briefly, for immediate type allergies, guidance papers recommend 15 – 20 g of challenge food as dried food or 60-100 g wet food (Bock et al. 1988) whereas others provided vague, difficult to interpret guidance (Metcalfe & Sampson 1990) or no guidance regarding an exact amount of food (Bindslev-Jensen et al. 2004). Some researchers or clinicians use a *total* of 8-10g of the dried food for challenge purposes (Sampson 2001b;Sicherer, Morrow, & Sampson 2000) whereas others used 18g (Bock 1987;Bock & Atkins 1990;Eigenmann & Calza 2000;Isolauri & Turjanmaa 1996;May 1976;Niggemann et al. 1999). The latest position paper by EAACI recommends that the top dose should be "the normal daily intake in a serving of the food in question, adjusted for the age of the patient" (Bindslev-Jensen et al. 2004). However, very little information is available regarding

normal daily intake of a particular food for particular age groups. For diagnosing delayed type FHS, there are no specific recommendations regarding the dose used when performing food challenges, apart from the amount reported by the history (Bock et al. 1988). The dietitian therefore often has to rely on the diet history to determine a normal daily intake for a child, with mothers often being vague historians. In this study, it was found that less than a quarter of mothers indicated sufficient amounts of challenge foods during history taking for the OFCs with even lower figures for the DBPCFCs. There are however, no studies available to either refute or confirm our findings.

The use of OFCs vs. DBPCFCs also has practical implications (Niggemann et al. 2005). We found that the DBPCFCs were more difficult to perform than the OFCs, mainly due to restrictions in food preparation to ensure the challenge is truly blind. According to the data from this thesis the DBPCFCs take on average twice as long as OFCs. Taking into account that the age of the patient did not affect challenge outcome and the DBPCFCs are more difficult and time-consuming to perform, this project recommends the use of OFCs for immediate reactions and the use of DBPCFCs for delayed symptoms. There are no studies in the literature comparing the practical issues surrounding performing food challenges such as time taken to complete, and staffing levels required to compare our data against. Hill and colleagues (Hill et al. 1993) briefly mentioned that some problems were experienced with adhering to the challenge protocols, mainly due to lack of parental co-operation, but no details were given. The use of OFCs vs. DBPCFCs has implications on financial costs and staffing levels and may even affect patient attendance at future food challenges to establish development of tolerance.

It is known that advice will only be followed by patients if it is credible and accepted by the patient. The number of parents accepting the one-day OFCs (95%) outcome was very similar to those accepting the DBPCFCs (100%). In contrast, parents were more likely to accept the one-week DBPCFCs (93.5%) than the one-week OFCs (88.6%). In terms of parental preference, just as with parental acceptance, more parents preferred the one-day OFCs (45.5%) than the one-day DBPCFCs (18.2%) with the rest of the parents having no preference (36.3%). However, more parents preferred the one-week DBPCFCs (42.9%) than the one week OFCs (11.4%) with the remainder of the parents showing no preference. Our data confirms findings from a study by Kaila et al. (Kaila & Isolauri 1997) which found that the parents considered the DBPCFC a more definite test than the open challenges. Parental acceptance may however also be influenced by the food the children were challenged with. Lidman et al (Lidman et al. 2004) reported that in spite of no reaction, 7.7% (2/26) previously peanut allergic continued to completely avoid peanut and

10/26 had peanut less than once a week. However, all 15 patients with negative milk challenge tolerated and continued to regularly consume milk.

In chapter 3, the development and validation of a FFQ was reported on. The FFQ was used to estimate the frequency with which some of the main food allergens were consumed. All possible factors were taken into account to ensure adequate validity and reliability (Burley et al. 2000). This FFQ is the first FFQ looking at consumption of food allergens and will hopefully be used by future researchers.

Based on the FFQ, in chapter 4, it was found that maternal dietary intake during pregnancy, as well as omega-3 fatty acid intake did not appear to influence the development of sensitisation to food allergens or FHS. Our data regarding omega-3 fatty acids, contradicts the data from Dunstan et al (Dunstan et al. 2003). This could be explained by the fact that Dunstan et al. supplemented mothers with a higher dose of omega-3 fatty acids (3.7g per day) than consumed by the pregnant women in our study. Fruit and vegetable intake (≥ 5 portions per day) during pregnancy was however significantly associated with reduced FHS at age one year. Supporting our data, Stazi et al (Stazi et al. 2002) indicated that low maternal intake of fruit (less than three portions per week) was associated with a positive SPT to six allergens, of which milk was the only food allergen. The reason for this is unclear. However, it can be postulated that the anti-oxidants in fruit and vegetables, may have an effect on the immune system. Clearly this hypothesis needs to be further investigated.

It was also reported (chapter 4) that breastfeeding duration does not affect the prevalence of FHS. No previous study looked at breastfeeding duration and FHS per se and as such this data cannot be compared. Only two previously conducted studies (Saarinen et al. 1999;Saarinen & Kajosaari 1995) found that breastfeeding prevented food allergy and only one of these studies (Saarinen et al. 1999) diagnosed food allergy by means of food challenges.

The author also investigated the role of maternal food intake during lactation on the development of infant's sensitisation to foods and FHS as it is known that food proteins are detectable in breast milk and can be passed from the mother to the infant (Palmer, Gold, & Makrides 2005;Vadas et al. 2001). The data suggests that maternal food avoidance of the major food allergens during breastfeeding led to fewer children becoming sensitised or developing FHS to that particular food compared with those whose mothers did not. In agreement with our data, these studies found that food avoidance during

lactation reduced the prevalence of sensitisation to food allergens (Arshad et al. 1992), eczema (Arshad et al. 1992;Chandra 1989;Chandra, Puri, & Hamed 1989;Hattevig, Sigurs, & Kjellman 1999), and allergic disorders(Arshad, Bateman, & Matthews 2003). However, even though there are no studies refuting our data, a recent review paper by the EAACI still concludes that there is no evidence for maternal dietary intervention during pregnancy or lactation in the prevention of allergic disease (Muraro et al. 2004b). This is due to the major differences in inclusion criteria and methodologies of the mentioned studies. One of the most interesting findings of this thesis was that weaning before 16 weeks significantly reduced sensitisation to foods and development of FHS. In contrast, all of those who developed FHS to a particular food, were given the offending food before 6 months of age as part of their weaning diet. This could be due to a number of factors affecting tolerisation and sensitisation such as weaning age and dose/frequency of consumption (Strobel 1995), genetic factors (Bergmann et al. 1997), immunological factors (Miller et al. 1994;Taylor et al. 2004) and nature of the food proteins (Dearman et al. 2000;Kimber, Stone, & Dearman 2003).

Chapter 5 showed that apart from a very limited number of factors, dietary practices of pregnant and breastfeeding women and weaning of their infants, for the groups with and without a history of atopy were very similar. The differences included that women with a family history of atopic disease were more likely to take a multi-mineral supplement during pregnancy. Pregnant women without a maternal history of allergic disease were more likely to intend to breastfeed. At 3 months, mothers with a family history of allergic disease were more likely to breastfeed exclusively, which confirms the data of other groups who looked at level of atopic risk versus willingness to breastfeed (Halken et al. 2000;Schoetzau et al. 2002).

Not surprisingly, reported rate of peanut avoidance from the infant's diet and reported symptoms of allergic disease in the infant were higher in the families with a history of atopy at 6 months, probably due the COT report (1998) (Committee on Toxicity of Chemicals in Food: Department of Health 1998). Only one study previously looked at maternal peanut intake during pregnancy and found that it was unrelated to a family history of allergic disease (van Odijk et al. 2004). Another interesting finding is that, less atopic mothers reported to have heard about the COT report than non-atopic mothers (36.8% vs. 45%; p=0.03), however this did not have an effect on peanut intake or avoidance. It therefore seemed that the COT report may have affected introduction of peanut into the infant's diet, but had no effect on maternal intake during pregnancy or lactation.

Having discussed the main findings, there are a number of limitations, which need to be mentioned. One possible limitation of the study is the low uptake of the DBPCFCs. Only 58% (46/80) of those with positive OFCs consented to DBPCFCs. The reasons for these refusals are discussed in chapter 2. Ideally, all the questionnaires used to obtain information on family history of atopy, feeding and weaning practices should have been validated, but this was not possible due to the time constraints of the study. Asking questions about concern over weight (on the FFQ) is not an ideal indicator of underreporting (chapter 3). BMR/PAL ratio would have been more useful. However, in order to establish over or underreporting, we would have had to obtain information on pre pregnancy weight, weight gain during pregnancy and portion sizes of foods eaten. This would have increased the participant burden and could have potentially influenced our participation rate. We therefore opted to use the question of concern over the weight gain as a proxy.

6.1 Implications for clinical practice

We showed that OFCs are suitable for diagnosis of immediate (objective) symptoms and DBPCFCs are required for diagnosis of delayed (subjective) symptoms. This is based on the challenge outcome as well as parental preference and acceptance of the challenge outcome. This is a positive finding as DBPCFCs, which are costly and tedious, may not be required for diagnosis of immediate type allergies. Less dietitian, nursing and physician time will therefore be required. However, it seems that DBPCFCs will be needed for the diagnosis of delayed symptoms; which will have a huge implication on planning of the food challenges and food preparation.

The challenge data showed that the history indicated by the family is reliable in indicating the symptoms that may be experienced during the challenge, helping the clinician to decide whether a hospital or home challenge will be needed. However, other methods for deciding on the challenge dose will be needed as the history is not reliable.

Another important clinical finding is that pregnant women from both atopic and non-atopic families avoided peanuts from their diets. The COT report (1998) had no effect on the intake/avoidance of peanuts during lactation in the atopic group. One needs to make sure that the advice based on the COT report (1998) is clear and well understood. This is important to ensure that some women do not avoid peanuts unnecessary, as is currently happening.

The breastfeeding and weaning data showed that a small number of mothers in both groups breast fed beyond three months and that a large number of mothers introduced solids before 17 weeks. This needs to be addressed as the WHO recommend weaning should ideally not commence before 26 weeks, but definitely not before 17 weeks i.e. 4 months.

6.2 Recommendations for future research

A study with a larger number of OFCs followed by DBPCFCs need to be conducted. It will be useful the repeat some negative OFCs by DBPCFCs in order to determine the sensitivity and specificity of OFCs. A standardised protocol to determine at which point a challenge should be considered positive should be designed and tested. More studies are needed to look at challenge doses in the diagnosis of FHS for both immediate and delayed type allergies. Our FFQ could be used as the basis of designing a FFQ, which could determine frequency of intake of all the allergens, as well as the amounts ingested. More studies are needed regarding omega-3 and fruit and vegetable intake during pregnancy and its effect on the development of FHS and allergic disease. More research, especially large scale multi-centre studies is needed to look at the effect of dietary avoidance during lactation, the effect of weaning practices and timing of introduction of the major food allergens on the development of FHS and allergic disease. The COT report (1998) reads that women with a family history of allergic disease may wish to avoid peanuts during pregnancy and lactation. It is important to establish why mothers may not wish to avoid peanuts from their own diet, but delay introduction into the infant's diet.

In conclusion, in this thesis the use of OFCs vs. DBPCFCs in children was investigated and it was found that OFCs are perhaps more suited for the diagnosis of immediate (objective) symptoms and the DBPCFC for delayed (subjective) symptoms. We also validated a FFQ and looked at the effect of dietary intake during pregnancy and weaning and feeding practices on the development of FHS. The only factors found that could perhaps affect the development of FHS, were fruit and vegetable intake during pregnancy and age of introduction of solid foods. Dietary practices during pregnancy and breastfeeding of mothers with either a personal or family history of atopy did not differ. Mothers with a family history of allergic disease were however, more likely to breastfeed exclusively at three months and avoid peanuts from the infant's diet at six months. The strength of the study lies in the number of novel factors that has been studied, but more studies are needed to confirm our data.

Appendices

Appendix 1.1 Guidelines in Clinical Decision Points for Food Hypersensitivity

	MILK			EGG			PEANUT		
	Spes IgE (kU_A/L)	**Grade**	**SPT**	**Spes IgE (kU_A/L)**	**Grade**	**SPT**	**Spes IgE (kU_A/L)**	**Grade**	SPT
Reaction highly probable (challenge may not be needed)	>15[χ]	3 – 6	8* 5[α] 3-4[ϕ]	>7[χ]	3-6	7* 4[α] 3-4[ϕ]	>14[χ]	3-6	**8*** **6[α]**
Reaction probable (challenge needed)	0.35 – 15	1-2	3-8	0.35 – 7	1-2	3-7	0.35 – 14	1-2	**3-8**
Young children under 1-2 year (reaction highly probable)	>5**	3 – 6	6*	>2***	2-6	5*	NA	NA	**4***
Reaction unlikely (home or physician challenge)	**<0.35**	**0**	**NA***	**<0.35**	**0**	**NA***	**<0.35**	**0**	**NA***
	Fish			**Soy**			**Wheat**		
	Spes IgE (kU_A/L)	**Grade**	**SPT**	**Spes IgE (kU_A/L)**	**Grade**	**SPT**	**Spes IgE (kU_A/L)**	**Grade**	SPT
Reaction highly probable (challenge may not be needed)	>20[χ]	4-6	NA	>30[χ] - 60	5-6	3[α]	>26[χ] - 80	6	**NA**
Reaction probable (challenge needed)	0.35 – 20	1-3	> 3	0.35 – 60	1-4	>3	0.35 – 80	1-5	**>3**
Young children under 1 year (reaction highly probable)	NA	NA	NA	NA	NA	NA	NA	NA	**NA**
Reaction unlikely (home or physician challenge)	**<0.35**	**0**	**NA***	**<0.35**	**0**	**NA***	**<0.35**	**0**	**NA***

Specific IgE levels taken from (95% predictive values) : Bock, S. A. & Sampson, H. A. 2003, "Evaluation of Food Allergy," in *Pediatric Allergy: Principles and Practice*, D. Y. M. Leung et al., eds., Mosby Inc., Missouri, pp. 478-487.

SPT taken from (For each a skin weal diameter at, and above, which negative reactions did not occur):

* Sporik, R., Hill, D. J., & Hosking, C. S. 2000, "Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children", *Clin.Exp.Allergy*, vol. 30, no. 11, pp. 1540-1546.

[α] Eigenmann PA, Sampson HA. Interpreting skin prick tests in the evaluation of food allergy in children. *Pediatr Allergy Immunol* 1998; 9(4):186-191.

[χ] Sampson, H. A. 2001, "Utility of food-specific IgE concentrations in predicting symptomatic food allergy", *J.Allergy Clin.Immunol.*, vol. 107, no. 5, pp. 891-896.

[χ]Sampson, H. A. & Ho, D. G. 1997, "Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents", *J.Allergy Clin.Immunol.*, vol. 100, no. 4, pp. 444-451.

** Boyano-Martinez, T., Garcia-Ara, C., Diaz-Pena, J. M., & Martin-Esteban, M. 2002, "Prediction of tolerance on the basis of quantification of egg white-specific IgE antibodies in children with egg allergy", *J.Allergy Clin.Immunol.*, vol. 110, no. 2, pp. 304-309.

*** Garcia-Ara, C., Boyano-Martinez, T., Diaz-Pena, J. M., Martin-Munoz, F., Reche-Frutos, M., & Martin-Esteban, M. 2001, "Specific IgE levels in the diagnosis of immediate hypersensitivity to cows' milk protein in the infant", *J Allergy Clin Immunol.*, vol. 107, no. 1, pp. 185-190.

[ϕ] Verstege, A., Mehl, A., Rolinck-Werninghaus, C., Staden, U., Nocon, M., Beyer, K., & Niggemann, B. 2005, "The predictive value of the skin prick test weal size for the outcome of oral food challenges", *Clin Exp.Allergy*, vol. 35, no. 9, pp. 1220-1226.

Milk, Egg, Soya and Wheat Free Diet Sheet

FAIR Study
The David Hide Asthma and Allergy
Research Centre

THIS INFORMATION WAS PROVIDED AS AN ILLUSTRATED BOOKLET TO THE PARENTS AND CHILDREN

This diet sheet will help you to avoid foods containing milk, egg, soya and wheat.

To avoid these foods look for the following ingredients on food labels:

MILK

Milk solids, non-fat milk solids, skimmed milk powder, cream, artificial cream, cheese, yoghurt, margarine, butter, buttermilk, lactose, whey, hydrolysed whey protein, hydrolysed whey sugar, whey syrup sweetener, casein, caseinate, hydrolysed casein, lactose.

EGG

Egg protein, dried egg, egg albumin, **egg** lecithin, egg yolk, fresh egg, pasteurised egg.

WHEAT

Wheat flour, bread, breadcrumbs, wheatbran, wheat binder, hydrolysed whey protein, wheatgerm, wheat gluten, **wheat starch** (used in some gluten-free products), wheat thickener, whole-wheat.

SOYA

Soya, soya bean, soya flour, soya margarine, soya milk, soya, yoghurt, soya sauce, soya lecithin (E322).
(Chinese, Thai and Oriental dishes, Ready meals).

You will also need to avoid **goat's milk and sheep's (ewe's) milk** as the proteins in these milks are very similar to those in cow's milk.

The following pages will give you more information on foods which may or may not contain milk, egg, soya or wheat.

Appendix 2.1 **Milk, egg, soya and wheat free diet sheet**

MILK and MILK PRODUCTS

Avoid:
Cow's milk (full fat, semi-skimmed, skimmed), dried,
evaporated or condensed milk, coffee whiteners e.g.
Coffee Mate, Coffee Compliment.
Milks with added vegetable fat such as Five Pints, cream,
artificial cream, ice cream, yoghurt, mousses, cheese (also vegetarian cheese), cheese spread, cottage cheese, quark and
lactolite milk.
Butter, margarine and soya margarine, shortenings, Kosher margarine and Ghee.
Any goat's, sheep's or soya milk and their products.

Allowed:
Milks
Infant formulas such as Nutramigen, Prejomin, Pregestimil, Pepti Junior or Neocate.

Suitable milk substitutes for children over 2 years:
Rice milk (calcium added), oat milk, coconut milk, almond milk.

Chocolate
All plain or dark chocolates e.g. Lindt dark chocolate(85%), Scotts Real Dark, Sainsbury's "Taste the Difference" dark chocolate.

Margarines & Spreads
"Pure" Organic or Sunflower oil, Sainsbury's Dairy Free spread, Vitaquelle, Vitasieg or any margarine made with vegetable oil.

Oil
Any oil.

EGG

Avoid:
Egg, Meringues, Quiches, Egg Custards, Scotch Egg,
Yorkshire Pudding, Pancakes, Quorn (vegetarian product).

Allowed:
Egg replacers e.g. Ener-G.

BREAKFAST CEREALS

Avoid:
Weetabix, Shredded Wheat, Branflakes, Shreddies, Coco Pops, Weetos, Ready Brek, Special K, Muesli and any other containing milk, egg, wheat or soya.

Allowed:
Homemade muesli made with oat flakes, cornflakes, rice crispies, porridge oats (not Ready Brek) millet flakes.

Appendix 2.1 **Milk, egg, soya and wheat free diet sheet**

Special Products:
Glutano: Corn flakes and muesli.

Barkat: Organic porridge flakes.

OTHER CEREALS

Avoid:
Wheat, semolina, wheat flour, spelt.
Pastas e.g. spaghetti, macaroni, lasagne and cous cous.

Allowed:
Rice, rice pasta (usually found with the Chinese Cook-in Sauces)
corn, corn pasta, corn flour, Pollenta, corn meal, maize, oats,
sago, tapioca, millet, Quinoa, buckwheat, modified starch may be eaten freely.

Special Products Available:
Pasta:
Glutano *Spaghetti, Macaroni, Spirals, Tagliatelle, Animal shapes.*

Schar *Fusilli, Rigati, Penne, Pipette.*

Orgran *Gourmet corn pasta, Buckwheat spiral pasta, Corn lasagne.*

Flour:
Juvela *Gluten-free Harvest mix.*

Trufree Bread mix, Pastry Mix and Cake mix.

Schar *Mix C—for cooking.*

Orgran Self raising flour.

Baking Powder:
Glutafin baking powder, **Sainsbury's** baking powder.

Quick Snack Pots:
Barkat Mexican Rice pot meal, Rice and Tomato pot meal.

Trufree Potato and Vegetable Quick Snack
Rice and Lentil Quick Snack.

Appendix 2.1 **Milk, egg, soya and wheat free diet sheet**

BREAD and CRISPBREAD

Avoid:
All breads, e.g. wholemeal, granary, brown, white, Danish etc.
Chapatti, naan, pitta, croissants, any cakes or fruit loaves.

Allowed:
Rice cakes, corn and rice cakes.

Special Products Available

Bread:
Barkat *Sliced white rice bread, Sliced brown rice bread.*
White rice pizza crust, Brown rice pizza crust.

Trufree Part-baked white loaf, part-baked 2 white rolls.

Schar *Ertha sourdough bread.*

Orgran Gourmet Pesto Bread Mix.

Crispbread:

Glutano *Crispbread.*

Juvela *Gluten-free Crispbread.*

MEAT, MEAT PRODUCTS and PULSES

Avoid:
Sausages (may **contain rusk**), beef burgers, soya,
soya beans, tinned meat, pate, meat pastes, meat pies,
pastry also ready meals unless known to be milk, egg, soya and wheat free.

Allowed:
Plain fresh, frozen and smoked meats e.g. beef, lamb, pork, chicken, turkey, ham, bacon, liver, kidney
NB – Beware: Some sliced meats contain milk - **check the label.**
Heinz: Baked Beans, Chicken Curry, Beans in Tomato Sauce, Barbecue Beans, Curried Beans, Healthy Balance Baked Beans, Organic Baked Beans.
Heinz:
John West Corned Beef - plain, mixed peppers and onions, Stewed steak with no added gravy.
Nestle: Herta Chirozo, Kabanos, Parisian Ham (Original and Beechwood Smoked).

Appendix 2.1 **Milk, egg, soya and wheat free diet sheet**

FISH and FISH PRODUCTS

Avoid:
Fish fingers, fish cakes, fish in sauce, fish in batter or breadcrumbs.
Ready meals - unless they are known to be milk, egg, soya and wheat free.

Allowed:
Plain, fresh, frozen and smoked fish.
Plain tinned fish in brine or oil (not soya oil) e.g. sardines, mackerel, crab, prawn.

Heinz:
John West Mackerel in Spicy Tomato Sauce,
Pilchards, Sardines, Sild in Tomato Sauce,
Tuna Light Lunch: French Style, Mediterranean
Tomato Salsa.

FRUIT

Avoid:
Fruit crumbles, pies, fools, trifle and fritters

Allowed:
All fresh, frozen and tinned fruit
Heinz - Weight Watchers Fruit Spreads

VEGETABLES

Avoid:
Vegetables tinned in sauce,
Instant potato, flavoured crisps (check the label, some are suitable),
Vegetable salads, coleslaw (unless it is homemade and you have checked all the ingredients),
Egg fried rice,
Mashed potatoes (unless home-made with suitable fat and "milk" alternative).

Allowed
All fresh, frozen or tinned plain vegetables (without sauce).
Potatoes, allowed crisps, sweet potato.
Pulses e.g. peas, beans and lentils.
Heinz: Canned tomato, tomato puree, ketchup.

BISCUITS, CAKES and DESSERTS

Avoid:
All cakes and biscuits, unless from a specialised product range free of milk, egg, soya, and wheat. Instant custard mix,
dessert mixes, mousses etc.

Allowed:
Jelly.

Birds: Original custard powder.
Nestle: Creamola or Creamola Rice products made from allowed ingredients.

Special Products Available
Biscuits:
Glutano *Shortcake ring biscuits*, Hazelnut cookies, Ginger cookies, Tartlets.

Cakes:
Schar *Margherita cake mix – A.*

Puddings, Crumbs, Snack Bars
Orgran All purpose crumbs, Lemon Sponge Pudding mix, Chocolate sponge pudding mix, Fruit filled blueberry bars, Fruit filled apricot bars.

SUGAR, PRESERVES and CONFECTIONERY

Avoid:
Lemon curd, soft centre sweets, milk chocolate, ice cream filled lollies.

Allowed:
Sugar, jam, marmalade, honey (for children older than 1 year), golden syrup, treacle, boiled sweets, lollies, pastilles, gums, ice lollies.

Nestle

Ice Lollies:	Fruit Pastille Lollies, Mr Men Fruit, Orange Maid, Slammer, Traffic Cone.
Confectionery:	Fruit Gums (standard)
	Fruit Pastilles (standard)
	Jellytots (standard)
	Mike's Bursting Eyeballs
	Minties - spearmint
	Polos - original, spearmint,
	Sugar free XXX mints
	Wonka - Oompas

BEVERAGES

Avoid:
Milkshake mixes, chocolate and malted drinks. Build-up, Complan, vending machine hot drinks and instant hot Chocolate.

Allowed:
Fruit juice, squash, fizzy drinks, soda water, sports drinks e.g. Lucozade. Tea, coffee, Cadbury's drinking chocolate, cocoa and Nesquick.

Appendix 2.1 **Milk, egg, soya and wheat free diet sheet**

MISCELLANEOUS

Avoid:

Creamed, tinned and packet soups, sauces and spreads, e.g. chocolate spread, salad cream, mayonnaise, gravy mixes,
Oxo, ready meals, artificial sweeteners, baking powder,
Monosodium Glutamate.

Allowed:

Home-made soup from allowed ingredients, gelatine, yeast, Marmite, Bovril, Vegemite, salt, pepper, herbs, spices,
Vinegar.
Sainsbury's baking powder, baking powder from specialist companies.

Heinz: Apple sauce, Mustard, Pickle and Chutney, Ketchup.
Big Soup: Beef and Vegetable, Beef Broth, Thick Beef Broth, Tomato and Lentil Soup.
Weight Watchers Soup: Mediterranean Tomato and Vegetable Soup.
Nestle: Apple sauce, Gravy Browning, Pickle, Rich and Fruity Sauce. Waistline - Creamy Dressing, Vinaigrette.

See also our list of Milk free, Egg free, Soya free and Wheat free Baby Foods.

Helpful telephone/websites numbers:

BOOTS	0115 950 6111	www.wellbeing.com
HJ Heinz	020 7402 2272	
Farley's	020 7402 2272	
Organix	0800 393 511	www.babyorganix.co.uk
Hipp organic	0845 0501351	www.hipp.co.uk
Cow and Gate	01225 767 381	
Milupa	01225 711511	www.milupa.co.uk
Co-op	0800 317827	
Sainsbury	0800 636 3622	
Tesco	0800 505 555	
Somerfield	0117 935 9359	
Safeway	020 8970 3622	
Nestle	00800 63785385	www.nestle.co.uk

Appendix 2.1 **Milk, egg, soya and wheat free diet sheet**

Special Dietary Products

Gluten Free Foods:		
Glutano	020 8953 4444	www.glutenfree-foods.co.uk
Barkat	020 8953 4444	www.glutenfree-foods.co.uk
Nutricia:		
Glutafin	01225 711801	www.glutafin.co.uk
Trufree	01225 711801	www.trufree.co.uk
Juvela	0151 228 1992	www.juvela.co.uk
Shar		www.schaer.com
Orgran	020 8450 9411	www.orgran.com
Dietary Specialities	07041 544 044	www.nutritionpoint.co.uk
Useful address:		
Barbara's Kitchen	01443 229304	www.barbaraskitchen.co.uk

PLEASE DOUBLE CHECK ALL THE PRODUCTS LISTED IN THIS DIET SHEET AT ALL TIMES AS RECIPES AND INGREDIENTS CHANGE FREQUENTLY.

Carina Venter **Carole Gant**

Allergy Research Dietitians
FAIR Study

Tel: 01983—534178

The David Hide Asthma & Allergy Research Centre
St. Mary's Hospital
Newport
Isle of Wight
PO30 5TP

Direct Tel. No. (01983) 534113

Food Allergy and Intolerance Research
Information Sheet to Parents of the 'Newborn Cohort'
(Recruitment)

Dear Parent(s)

We would like to inform you about an exciting new research planned to involve all babies born on the Isle of Wight between 1st September 2001 and 30th August 2002. The purpose of this project is to establish how common a problem food allergy and food intolerance is amongst children.

You may have heard about a previous large study carried out by the staff of The David Hide Asthma and Allergy Research Centre at St Mary's Hospital. In that study all children born on the Isle of Wight between January 1989 and February 1990 were seen regularly at the Centre to establish the natural history of asthma and the findings from the study has been widely published in medical and scientific journals.

We have been successful in obtaining a research grant from the government's Food Standards Agency to find out how common is food allergy and intolerance in children. Part of the study is establishing the incidence of food allergy and intolerance amongst very young children (in the first three years of their life). To gain an accurate picture of how frequently these problems occur, it is really important that we have information on as many children as possible. Scientifically it would be more valid if we could include every child born within the study period.

You will be having your child within the study period (between 1st September 2001 and 30th August 2002) and we would like you to consider being a part of this study.
If you decide to take part in the project, we do hope that you will be completing the study. However, it is important to know that you will be free to withdraw at any time without giving a reason.
If you don't want to take part in the study at all, this decision will not in any way influence the care you receive.

If you decide to take part in the study, we have listed below what it would involve.

Before Birth and Delivery
Completion of a questionnaire on family history of allergies and a dietary questionnaire.
A sample of blood would be taken from the cord at delivery by your midwife.

During the First Year of Baby's Life
The dietitian will contact you by telephone or post at 3, 6, and 9 months to ask about any feeding problems. If you have any concerns it will be possible for you to contact the Allergy Centre for advice from the doctor or dietitian.

At 1, 2, and 3 years of Age

Each year we will invite you to the Allergy Centre to complete a questionnaire, and if you are willing, we will give the baby a skin prick test to see if he/she is allergic to any foods. This is a painless procedure that is carried out routinely at the Allergy Centre on babies, children and adults of all ages. The nurses of the Centre are very experienced in skin testing having carried out thousands of these tests over recent years.
The test involves drawing on the baby's arm and placing on it several drops of allergens. The top layer of skin is then very gently pricked through the liquid allowing a tiny amount in to the skin. If there is a positive reaction a little itchy wheal will appear after 10 minutes. This will disappear fairly soon after the test.

If at any visit you report that your child has a problem with a food, or has a positive skin test reaction you will be invited to the Allergy Centre where we will investigate the problem further.

We do hope you will feel able to take part in this really important study to help us better understand food allergy. If you have any questions please ring The David Hide Asthma and Allergy Research Centre – 534113 and speak to one of the study team who are:

Jane Grundy (Research Nurse)
Bernie Mealy (Research Midwife)
Carina Venter (Research Dietitian)

The David Hide Asthma & Allergy Research Centre
St. Mary's Hospital
Newport
Isle of Wight
PO30 5TG

Direct Tel. No. (01983) 534113

Food Allergy and Intolerance Research

Consent Form

Please delete as appropriate

Have you read the Study Information Sheet? Yes / No

Have you been given information on who to contact if you want to ask more questions about this study? Yes / No

Have you received enough information about the study? Yes / No

Do you understand that you are free to withdraw from the study:

- At any time?
- Without having to give a reason for withdrawing? Yes / No

I agree to take part in this study. Yes / No

I agree for cord blood to be taken after delivery Yes / No

I also give consent for my GP ..... to be informed of our participation in the study.

The undersigned certify that the Information Sheet has been read and understood by the patient.

_____	_____	_____
Patient Name (in block letters)	Signature	Date

_____	_____	_____
Investigator Name	Signature	Date

Study No. _____

Appendix 2.4

Study No. _____

FAIR Study

Recruitment Questionnaire: Family history of atopy

Name & Address
Hospital Number
Date of Birth

Date seen			/ /	
Expected date of delivery			/ /	
Is this pregnancy	Single		Multiple	
NHS Number				

Tel No: (Home)	Other contact:
(Work)	
(Mobile)	

Consultant	
Community Midwife	Clinic
Health Visitor	Clinic
GP	Surgery

Family history of atopy

1. Has any of the following persons ever had asthma?

Mother					Father					Any sibling				
Yes[1]	No[2]	D/K[3]	Yes[1]	No[2]	D/K[3]	Yes[1]	No[2]	D/K[3]	N/A[-100]					

2. Has any of the following persons ever had hayfever?

Mother					Father					Any sibling				
Yes[1]	No[2]	D/K[3]	Yes[1]	No[2]	D/K[3]	Yes[1]	No[2]	D/K[3]	N/A[-100]					

3. Has any of the following persons ever had an itchy rash which was coming and going for at least six months?

Mother					Father					Any sibling				
Yes[1]	No[2]	D/K[3]	Yes[1]	No[2]	D/K[3]	Yes[1]	No[2]	D/K[3]	N/A[-100]					

4. Has any of the following persons ever had wheezing or whistling in the chest at any time in the past?

Mother					Father					Any sibling				
Yes[1]	No[2]	D/K[3]	Yes[1]	No[2]	D/K[3]	Yes[1]	No[2]	D/K[3]	N/A[-100]					

5. Has any of the following persons ever suffered from an itchy, stuffy or runny nose and/or swollen, itchy eyes when they did not have a cold?

Mother					Father					Any sibling				
Yes[1]	No[2]	D/K[3]	Yes[1]	No[2]	D/K[3]	Yes[1]	No[2]	D/K[3]	N/A[-100]					

Appendix 2.4 **Study No. _____**

Food Allergy or intolerance

6. Has **Mother** ever suffered from symptoms of food allergy or intolerance? Yes[1] | No[2] | D/K[3]
IF 'NO' GO TO Q. 9

7. Did you identify the offending food or component? Yes[1] | No[2]
IF 'NO' GO TO Q. 9

8. If yes, which food caused the problem, what were the major symptoms experienced and how soon after eating/drinking the food did the symptoms appear?

Food	code	Symptom (only 2 major symptoms per food)	code	Temporal relationship	code

9. Has **Father** ever suffered from symptoms of food allergy or intolerance? Yes[1] | No[2] | D/K[3]
IF 'NO' or 'D/K' GO TO Q. 12

10. Did you identify the offending food or component? Yes[1] | No[2]
IF 'NO' GO TO Q. 12

11. If yes, which food caused the problem, what were the major symptoms experienced and how soon after eating/drinking the food did the symptoms appear?

Food	code	Symptom (only 2 major symptoms per food)	code	Temporal relationship	code

12. How many children do you have? _____
IF 'NONE' GO TO Q. 23

13. Has **any child** ever suffered from symptoms of food allergy or intolerance? Yes[1] | No[2] | D/K[3]
IF 'NO' GO TO Q. 23

14. Has **sibling 1** ever suffered from symptoms of food allergy or intolerance? Yes[1] | No[2] | D/K[3]
IF 'NO' GO TO Q. 17

15. Did you identify the offending food or component? Yes[1] | No[2]
IF 'NO' GO TO Q. 17

16. If yes, which food caused the problem, what were the major symptoms experienced and how soon after eating/drinking the food did the symptoms appear?

Food	code	Symptom (only **2** major symptoms per food)	code	Temporal relationship	code

17. Has **sibling 2** ever suffered from symptoms of food allergy or intolerance? Yes[1] | No[2] | D/K[3]
IF 'NO' GO TO Q. 20

18. Did you identify the offending food or component? Yes[1] | No[2]
IF 'NO' GO TO Q. 20

19. If yes, which food caused the problem, what were the major symptoms experienced and how soon after eating/drinking the food did the symptoms appear?

Food	code	Symptom (only **2** major symptoms per food)	code	Temporal relationship	code

20. Has **sibling 3** ever suffered from symptoms of food allergy or intolerance? Yes[1] | No[2] | D/K[3]
IF 'NO' GO TO Q. 23

21. Did you identify the offending food or component? Yes[1] | No[2]
IF 'NO' GO TO Q. 23

22. If yes, which food caused the problem, what were the major symptoms experienced and how soon after eating/drinking the food did the symptoms appear?

Food	code	Symptom (only 2 major symptoms per food)	code	Temporal relationship	code

Pets

23. In house during pregnancy

Cat	Yes[1]		No[2]		
Dog	Yes[1]		No[2]		
Other	Yes[1]		No[2]		What?

24. Regular exposure elsewhere

Cat	Yes[1]		No[2]		
Dog	Yes[1]		No[2]		
Other	Yes[1]		No[2]		What?

Social History

25. Father/Partner's occupation

26. Mother's occupation or usual occupation

27. Mother's highest level of education

School[1]		Further[2]		Higher[3]			
Did not finish school[4]		D/K[5]		Still at school[6]			

28. Father's highest level of education

School[1]		Further[2]		Higher[3]			
Did not finish school[4]		D/K[5]		Still at school[6]			

CONSENT FOR CORD BLOOD

Yes[1]		**No[2]**	

Comments:

20. Has **sibling** ever suffered from symptoms of food allergy or intolerance? Yes[1] | No[2] | D/K[3]
IF 'NO' GO TO Q. 17

21. Did you identify the offending food or component? Yes[1] | No[2]
IF 'NO' GO TO Q. 17

22. If yes, which food caused the problem, what were the major symptoms experienced and how soon after eating/drinking the food did the symptoms appear?

Food	code	Symptom (only 2 major symptoms per food)	code	Temporal relationship	code

20. Has **sibling** ever suffered from symptoms of food allergy or intolerance? Yes[1] | No[2] | D/K[3]
IF 'NO' GO TO Q. 20

21. Did you identify the offending food or component? Yes[1] | No[2]
IF 'NO' GO TO Q. 20

22. If yes, which food caused the problem, what were the major symptoms experienced and how soon after eating/drinking the food did the symptoms appear?

Food	code	Symptom (only 2 major symptoms per food)	code	Temporal relationship	code

Appendix 2.5a **Study No_____**

FAIR Study

Three month Questionnaire

Child's Name & Address	Date of questionnaire / /
	Sex: Male[1] Female[2]
	GP:
	HV:
	Length: ins cms Date D/K
	Weight: lbs oz kgs Date D/K
Child's date of birth:	
Mother's Name	Mother's IW number
Telephone No.	E-mail address

1. Who completed questionnaire?

Mother[1]		Father[2]		Grandparent[3]		Guardian[4]		Other[5]		Who

2. Has your child had the following immunisations?

	1st Immunisation						2nd Immunisation					
Polio	Yes[1]		No[2]		D/K[3]		Yes[1]		No[2]		D/K[3]	
HIB, Diptheria, Tetanus	Yes[1]		No[2]		D/K[3]		Yes[1]		No[2]		D/K[3]	
Whooping Cough	Yes[1]		No[2]		D/K[3]		Yes[1]		No[2]		D/K[3]	
Meningitis C	Yes[1]		No[2]		D/K[3]		Yes[1]		No[2]		D/K[3]	
Other	Yes[1]		No[2]		D/K[3]		What					

3. Has your child ever had wheezing or whistling in the chest in the past three months? Yes[1] No[2] D/K[3]

4. In the last three months, has your child had a dry cough at night, apart from the cough associated with a cold or a chest infection? Yes[1] No[2] D/K[3]

5. Has your child ever had an itchy rash that was coming and going over the last three months? Yes[1] No[2] D/K[3]
IF 'NO' OR D/K GO TO Q. 10

6. If yes, where does your child get the itchy rash?

Place	code	Place	code

7. Have you identified the cause of the itchy rash? Yes[1] No[2] D/K[3]
IF 'NO'OR D/K GO TO Q. 10

8. If yes, what?

Food	Yes[1]		No[2]		
Animals	Yes[1]		No[2]		
House dust mite	Yes[1]		No[2]		
Other	Yes[1]		No[2]		

9. If food

Food	code	Temporal Rel	code	Frequency	code	At what age (Weeks)	Still present			
							Yes[1]		No[2]	
							Yes[1]		No[2]	

10. Has your child ever suffered from vomiting (> 1 tbsp) in the last three months? Yes[1] No[2] D/K[3]
IF 'NO' OR D/K GO TO Q. 14

11. Have you identified the cause of the vomiting? Yes[1] No[2] D/K[3]
IF 'NO' OR D/K GO TO Q. 14

12. If yes, what?

Food	Yes[1]		No[2]	
Other	Yes[1]		No[2]	

13. If food

Food	code	Temporal Rel	code	Frequency	code	At what age (Weeks)	Still present			
							Yes[1]		No[2]	
							Yes[1]		No[2]	

14. Has your child ever suffered from diarrhoea in the last three months? Yes[1] No[2] D/K[3]
IF 'NO' OR D/K GO TO Q. 18

15. Have you identified the cause of the diarrhoea? Yes[1] No[2] D/K[3]
IF 'NO' OR D/K GO TO Q. 18

16. If yes, what?

Food	Yes[1]		No[2]	
Other	Yes[1]		No[2]	

17. If food

Food	code	Temporal Rel	code	Frequency	code	At what age (Weeks)	Still present			
							Yes[1]		No[2]	
							Yes[1]		No[2]	

18. Has your child ever suffered from constipation in the last three months? Yes[1] No[2] D/K[3]
IF 'NO' OR D/K GO TO Q. 22

19. Have you identified the cause of the constipation? Yes[1] No[2] D/K[3]
IF 'NO' OR D/K GO TO Q. 22

20. If yes, what?

Food	Yes[1]		No[2]	
Other	Yes[1]		No[2]	

21. If food

Food	code	Temporal Rel	code	Frequency	code	At what age (Weeks)	Still present			
							Yes[1]		No[2]	
							Yes[1]		No[2]	

22. Has your child ever suffered from abdominal distension in the last three months? | Yes[1] | | No[2] | | D/K[3] | |
IF 'NO' OR D/K GO TO Q. 26

23. Have you identified the cause of the abdominal distension? | Yes[1] | | No[2] | | D/K[3] | |
IF 'NO' OR D/K GO TO Q. 26

24. If yes, what?

Food	Yes[1]		No[2]	
Other	Yes[1]		No[2]	

25. If food

Food	code	Temporal Rel	code	Frequency	code	At what age (Weeks)	Still present			
							Yes[1]		No[2]	
							Yes[1]		No[2]	

26. Has your child ever suffered from colic/tummy ache in the last three months? | Yes[1] | | No[2] | | D/K[3] | |
IF 'NO' OR D/K GO TO Q. 30

27. Have you identified the cause of the colic/tummy ache? | Yes[1] | | No[2] | | D/K[3] | |
IF 'NO' OR D/K GO TO Q. 30

28. If yes, what?

Food	Yes[1]		No[2]	
Other	Yes[1]		No[2]	

29. If food

Food	code	Temporal Rel	code	Frequency	code	At what age (Weeks)	Still present			
							Yes[1]		No[2]	
							Yes[1]		No[2]	

30. Has your child ever suffered from any other food related problems in the last three months? | Yes[1] | | No[2] | | D/K[3] | |
IF 'NO'OR D/K GO TO Q. 33

31. If yes, what was the problem and did you identify the cause?

Problem	code	Cause identified?					
		Yes[1]		No[2]		D/K[3]	
		Yes[1]		No[2]		D/K[3]	

IF CAUSE NOT IDENTIFIED GO TO Q. 33

32. If you identified the cause of the problems, what?

Problem	code	Cause	code	Temp Rel	code	Frequency	code	At what age (Weeks)	Still present			
									Yes[1]		No[2]	
									Yes[1]		No[2]	

Feeding Practices:

33. Which method of feeding are you using **at the moment**?

Breast milk only[1]		Infant formula only[2]		Both[3]	

34. Did your baby have a bottle feed (containing infant formula) **soon after birth** i.e. 1-2 days?
IF 'NO' OR D/K GO TO Q. 36

Yes[1]		No[2]		D/K[3]	

35. If yes, which formula?

36. Since the baby's birth, have you given your baby any water?

Yes[1]		No[2]	

Weaning:

37. Have you given your baby any food or drinks other than breast milk/infant formula in the past three months?
IF 'NO' GO TO Q. 39

Yes[1]		No[2]	

38. If yes, what food/drinks and at what age?

Food/Drink	code	Age (wks)

Solids					
Yes[1]		No[2]		N/A[-100]	

39. Has your baby taken any medication (e.g. gripe water, antibiotics etc.) or used any medicated creams in the last three months?
IF 'NO' GO TO Q. 41

Yes[1]		No[2]	

40. If yes what? (If no tick assume answer to be NO)

Gripe water	Yes[1]		No[2]			
Calpol	Yes[1]		No[2]			
Colief	Yes[1]		No[2]			
Infacol	Yes[1]		No[2]			
Antibiotics	Yes[1]		No[2]			
Other medication	Yes[1]		No[2]		Please specify	

Smoking:

41. Do you normally smoke?
IF 'NO' GO TO Q. 46

Yes[1]		No[2]	

42. If yes, have you smoked during baby's first three months of life?
IF 'NO' GO TO Q. 46

Yes[1]		No[2]	

43. If yes, how many cigarettes have you smoked daily on average during this time?

44. Is this

the same as[1]		more than[2]		less than[3]	

normally **before** your pregnancy?

45. Is this

the same as[1]		more than[2]		less than[3]	

normally **during** your pregnancy?

46. Has your baby regularly been exposed to cigarette smoke?

Yes[1]		No[2]	

47. Is your baby exposed to pets at home?

Cat	Yes[1]		No[2]			
Dog	Yes[1]		No[2]			
Other	Yes[1]		No[2]		What?	

48. Is your baby regularly exposed to pets elsewhere?

Cat	Yes[1]		No[2]			
Dog	Yes[1]		No[2]			
Other	Yes[1]		No[2]		What?	

Appendix 2.5b **Study No. _____**

Breastfeeding only (3 months)

1. Are you currently excluding any foods from your diet? | Yes[1] | | No[2] | |
IF 'NO' GO TO Q. 3

2. If yes, why?

Vegetarian	Yes[1]		No[2]		Eat Fish	Yes[1]		No[2]	
Vegan	Yes[1]		No[2]						
Dislike certain foods	Yes[1]		No[2]		Food				
Due to babies allergy/intolerance	Yes[1]		No[2]		Food				
Due to own allergy/intolerance	Yes[1]		No[2]		Food				
Due to lactation	Yes[1]		No[2]		Food				
Other reason	Yes[1]		No[2]		Food				

3. Have you identified any foods in your diet that affected your baby after breast feeding? | Yes[1] | | No[2] | |
IF 'NO'GO TO Q. 5

4. If yes, what foods and what effect did they have?

Food	code	Effect	code

5. Have you taken any medication (e.g. antibiotics, paracetamol or aspirin) since your baby's birth? | Yes[1] | | No[2] | |
IF 'NO' GO TO Q. 7

6. If yes, what? (If no tick assume answer to be NO)

Antibiotics	Yes[1]		No[2]			
Paracetamol	Yes[1]		No[2]			
Aspirin	Yes[1]		No[2]			
Other medication	Yes[1]		No[2]		Please specify	

7. Has your baby ever had an infant formula (bottle)? | Yes[1] | | No[2] | | D/K[3] | |
IF 'NO' OR D/K END OF QUESTIONNAIRE

8. If yes, which formula?

Comments

e.g. fortified / TPN / tube feed

For Office Use Only

		Food	code
Possible Intolerance / Allergy			
Definite Intolerance / Allergy			
No Intolerance / Allergy			

Appendix 2.5c **Study No. _____**

Formula feeding only (3 months)

1. Have you ever breast fed your baby? IF 'NO' GO TO Q. 10

Yes[1]		No[2]	

2. If Yes, for how long?

1 feed[1]		1 day[4]		1 week[10]		7 weeks[16]	
2 feeds[2]		2 days[5]		2 weeks[11]		8 weeks[17]	
3 feeds[3]		3 days[6]		3 weeks[12]		9 weeks[18]	
		4 days[7]		4 weeks[13]		10 weeks[19]	
		5 days[8]		5 weeks[14]		11 weeks[20]	
		6 days[9]		6 weeks[15]		12 weeks[21]	

3. Why did you stop breast feeding your baby?

Reason	code

If Mum breast feeding > 1 week

4. During the time you were breast feeding, did you exclude any foods from your diet? IF 'NO' 'D/K' OR 'N/A' GO TO Q. 6

Yes[1]		No[2]	
D/K[3]		N/A[-100]	

5. If yes, why?

Vegetarian	Yes[1]		No[2]		Eat Fish	Yes[1]		No[2]	
Vegan	Yes[1]		No[2]						
Dislike certain foods	Yes[1]		No[2]		Food				
Due to baby's allergy/intolerance	Yes[1]		No[2]		Food				
Due to own allergy/intolerance	Yes[1]		No[2]		Food				
Due to lactation	Yes[1]		No[2]		Food				
Other	Yes[1]		No[2]		Food				

6. Have you identified any foods in **your** diet that affected your baby after breast feeding? IF 'NO' 'D/K' OR 'N/A'GO TO Q. 8

Yes[1]		No[2]	
D/K[3]		N/A[4]	

7. If yes, what foods and what effect did they have?

Food	code	Effect	code

8. If breast feeding at all, have you taken any medication (e.g. antibiotics, paracetamol or aspirin) since your baby's birth? Yes[1] No[2]
IF 'NO' GO TO Q. 10

9. If yes, what

Antibiotics	Yes[1]		No[2]			
Paracetamol	Yes[1]		No[2]			
Aspirin	Yes[1]		No[2]			
Other medication	Yes[1]		No[2]		Please specify	

10. When did you first introduce formula bottle feeding? Age ____ days ____ weeks

11. Which formula are you using at present? _____

12. Why have you chosen this formula? (If no tick assume answer to be NO)

	Formula 1				Formula 2				
Treatment of allergy/intolerance	Yes[1]		No[2]		Yes[1]		No[2]		
Prevention of allergy	Yes[1]		No[2]		Yes[1]		No[2]		
Other child was allergic to milk	Yes[1]		No[2]		Yes[1]		No[2]		
One that was given in hospital	Yes[1]		No[2]		Yes[1]		No[2]		
Advised to do so	Yes[1]		No[2]		Yes[1]		No[2]		By whom
Own preference	Yes[1]		No[2]		Yes[1]		No[2]		
Available in Baby Clinic	Yes[1]		No[2]		Yes[1]		No[2]		
Other	Yes[1]		No[2]		Yes[1]		No[2]		

13. Have you ever used any formula other than the one you are using at the moment? Yes[1] No[2]
IF 'NO' END OF QUESTIONNAIRE

14. If yes, what formula and why did you change?

Formula	code	Age when you changed	How long used	Reason for change	code

Comments

e.g. fortified / TPN / tube feed

Appendix 2.5c **Study No. _____**

For Office Use Only

		Food	code
Possible Intolerance / Allergy			
Definite Intolerance / Allergy			
No Intolerance / Allergy			

Appendix 2.5d

Study No. _____

Formula + Breast milk (3 months)

1. Are you currently excluding any foods from your diet? Yes[1] No[2]
   IF 'NO' GO TO Q. 3

2. If yes, why?

Vegetarian	Yes[1]		No[2]		Eat Fish	Yes[1]		No[2]
Vegan	Yes[1]		No[2]					
Dislike certain foods	Yes[1]		No[2]		Food			
Due to baby's allergy/intolerance	Yes[1]		No[2]		Food			
Due to own allergy/intolerance	Yes[1]		No[2]		Food			
Due to lactation	Yes[1]		No[2]		Food			
Other	Yes[1]		No[2]		Food			

3. Have you identified any foods in **your** diet that affected your baby after breast feeding? Yes[1] No[2]
   IF 'NO' GO Q. 5

4. If yes, what foods and what effect did they have?

Food	code	Effect	code

5. Have you taken any medication (e.g. antibiotics, paracetamol or aspirin) since your baby's birth? Yes[1] No[2]
   IF 'NO' GO TO Q. 7

6. If yes, what? (If no tick assume answer to be NO)

Antibiotics	Yes[1]		No[2]			
Paracetamol	Yes[1]		No[2]			
Aspirin	Yes[1]		No[2]			
Other medication	Yes[1]		No[2]		Please specify	

7. When did you introduce bottle feeding? Age (weeks) _____

8. Which formula are you using at present? _____

9. Why have you chosen this formula? (If no tick assume answer to be NO)

	Formula 1				Formula 2				
Treatment of allergy/intolerance	Yes[1]		No[2]		Yes[1]		No[2]		
Prevention of allergy	Yes[1]		No[2]		Yes[1]		No[2]		
Other child was allergic to milk	Yes[1]		No[2]		Yes[1]		No[2]		
One that was given in hospital	Yes[1]		No[2]		Yes[1]		No[2]		
Advised to do so	Yes[1]		No[2]		Yes[1]		No[2]		By whom
Own preference	Yes[1]		No[2]		Yes[1]		No[2]		
Available in Baby Clinic	Yes[1]		No[2]		Yes[1]		No[2]		
Other	Yes[1]		No[2]		Yes[1]		No[2]		

10. Have you ever used any formula other than the one you are using at the moment? Yes[1] | | No[2] | |
IF 'NO' GO TO Q. 12

11. If yes, what formula and why did you change?

Formula	code	Age when you changed	How long used	Reason for change	code

12. Do you feed your baby breast/bottle equally, more breast or more bottle?

Breast > half[1]		Equal[2]		Bottle > half[3]		Breast + top up[4]	

Comments

e.g. fortified / TPN / tube feed

For Office Use Only

		Food	code
Possible Intolerance / Allergy			
Definite Intolerance / Allergy			
No Intolerance / Allergy			

Appendix 2.6

Study No. _____

FAIR Study

Six month Questionnaire

Child's Name & Address	Date of questionnaire / /
	Sex: Male[1] Female[2]
	GP
	HV
	Length: ins cms Date D/K
	Weight: lbs oz kgs Date D/K
Child's date of birth:	
Mother's Name	Mother's IW number
Telephone No.	E-mail address:

Intolerance / Allergy from three month questionnaire

		Food	code
Possible Intolerance / Allergy			
Definite Intolerance / Allergy			
No Intolerance / Allergy			

1. Who completed questionnaire?

Mother[1]	Father[2]	Grandparent[3]	Guardian[4]	Other[5]	Who

2. Has the child had 1st and 2nd immunisations at three months? (3/12 Q)

	1st Imm		2nd Imm	
	Yes[1]	No[2]	Yes[1]	No[2]

3. Has your child had the following immunisations in the last three months?

	1st Immunisation			2nd Immunisation		
	Yes[1]	No[2]	D/K[3]	Yes[1]	No[2]	D/K[3]
Polio						
HIB, Diptheria, Tetanus						
Whooping Cough						
Meningitis C						

	3rd Immunisation			
	Yes[1]	No[2]	D/K[3]	
Polio				
HIB, Diptheria, Tetanus				
Whooping Cough				
Meningitis C				
Other				What

4. Has your child ever had wheezing or whistling in the chest in the past three months? Yes[1] No[2] D/K[3]

5. In the last three months, has your child had a dry cough at night, apart from the cough associated with a cold or a chest infection? Yes[1] No[2] D/K[3]

6. In the last three months, has your child suffered from an itchy, stuffy Or runny nose when they did not have a cold or flu? Yes[1] No[2] D/K[3]

7. Has your child ever suffered from an itchy skin that looks like nettle rash /hives? Yes[1] No[2] D/K[3]

8. Has your child ever had an itchy dry flaky skin/eczema that was coming and going over the last three months? Yes[1] | No[2] | D/K[3]
IF 'NO' OR 'D/K' GO TO Q. 10

9. If yes, where does your child get the itchy dry flaky skin/eczema?

Place	code	Place	code

10 Has your child ever suffered from vomiting (>1 tbsp) in the last three months? Yes[1] | No[2] | D/K[3]

11 Has your child ever suffered from diarrhoea in the last three months? Yes[1] | No[2] | D/K[3]

12 Has your child ever suffered from constipation in the last three months? Yes[1] | No[2] | D/K[3]

13 Has your child ever suffered swelling of the eyes, lips, tongue or throat in the last three months? Yes[1] | No[2] | D/K[3]

14 Has your child ever suffered from colic/tummy ache in the last three months? Yes[1] | No[2] | D/K[3]

15 Has your child suffered from any food related problems in the last three months? Yes[1] | No[2] | D/K[3]

16 If yes, what?

Symptom	code	Food	code	Temp Rel	code	Frequency	code	Age (wks)	Still present
									Yes[1] / No[2]
									Yes[1] / No[2]
									Yes[1] / No[2]
									Yes[1] / No[2]

17 Have you consulted your GP/Paediatrician regarding any of the above symptoms in the last six months?
GP Yes[1] | No[2] | Paediatrician Yes[1] | No[2]
IF 'NO' GO TO Q. 19

18 If yes, what symptoms?

Symptom	code	Symptom	code

19 Which method of feeding are you using **at the moment**?
Breast milk only[1] | Bottle only[2] | Both[3]
IF BREAST ONLY OR BOTTLE ONLY GO TO Q. 21

20 If both, do you feed your baby breast/bottle equally, more breast or more bottle?
Breast >half[1] | Equal[2] | Bottle >half[3] | Breast + top up[4] | Breast + occasional bottle[5]

21 In the last three months, have you given your baby any water? Yes[1] | No[2]

22 When did you first introduce solids into your baby's diet? _____ weeks

23 Have you given your baby any of the following foods and at what age?

Rice or baby rice	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Wheat containing foods (e.g. baby rusk, baby cereals, cereals, pasta, bread, cakes, biscuits)	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Oats or oat cereal	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Non-citrus fruit (e.g. banana)	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Citrus fruit (e.g. orange, orange juice, mandarin, clementine, lemon, lime, tangerine, grapefruit)	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Strawberry	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Vegetables (not tomato or potato)	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Tomato	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Potato	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Dairy foods (e.g. yoghurt, fromage frais, custard, ice cream, butter, margarine, cow's milk in food, cheese)	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Chicken or turkey	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Lamb	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Beef	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Pork	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Fish	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Whole egg	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Pulses (e.g. lentils, peas, baked beans)	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Soya	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Tree nuts – almonds, brazil nuts, pecan nuts, hazel nuts, walnuts etc. (e.g. in chocolate, crunchy nut cornflakes, choc chip cookies, pesto sauce, vegetarian meals)	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Peanuts (e.g. Bombay mix, peanut butter, peanut brittle, peanut cookies, Snickers bar, some vegetarian meals)	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Sesame (e.g. humous, tahini, seed rolls, cereal bars)	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Other food (specify)	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	

24 Which three foods have you introduced first?

Food	code	Food	code	Food	code

25 Have you given your baby any baby cereals, packet foods or jars yet? Yes[1] | | No[2] |

26 Are you consciously avoiding any foods from your baby's diet at present? Yes[1] | | No[2]
IF 'NO' GO TO Q. 28

27 If yes, what?

Food	code	Food	code

28 Have you given your baby any of the following drinks and at what age?

Fruit squash –citrus	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Fruit squash – non-citrus	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Diet fruit squash – citrus	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Diet fruit squash – non-citrus	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Fruit juice – citrus	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Fruit juice – non-citrus	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Fruit juice – prune	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Herbal drinks	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	

Tea/coffee		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Cold flavoured milk drinks		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Fizzy drinks		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Cow's milk		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Flavoured water		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Other drinks (specify)		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	

29 Has your baby taken any medication (e.g. gripe water, antibiotics etc) or used any medicated creams in the last three months? Yes[1] No[2]
IF 'NO' GO TO Q. 31

30 If yes what?

Gripe water	Yes[1]		No[2]			
Calpol	Yes[1]		No[2]			
Colief	Yes[1]		No[2]			
Infacol	Yes[1]		No[2]			
Antibiotics	Yes[1]		No[2]			
Other medication	Yes[1]		No[2]		Please specify	

31 Has your baby had a temperature/fever in the last six months? Yes[1] No[2]

32 If yes, how many times?

1		2		3		4		5		6		>6	

33 What was the reason for this temperature/fever?

Immunisation		Gastro-enteritis		Teething		Chest infection		cold	
Flu		Other		specify				Don't know	

34 Do you normally smoke? Yes[1] No[2]

35 If yes, how many cigarettes do you smoke daily on average?

36 Has your baby regularly been exposed to cigarette smoke? Yes[1] No[2]

37 Is your baby exposed to pets at home?

Cat	Yes[1]		No[2]		
Dog	Yes[1]		No[2]		
Other	Yes[1]		No[2]		What?

38 Is your baby regularly exposed to pets elsewhere?

Cat	Yes[1]		No[2]		
Dog	Yes[1]		No[2]		
Other	Yes[1]		No[2]		What?

IF STILL BREAST FEEDING (Breast only / Breast + Bottle)

39 Mum reverted back to breast feeding only after a period of bottle feeding? Yes[1] No[2]

40 Has your baby ever had an infant formula? Yes[1] No[2] D/K[3]
IF 'NO' OR 'D/K' END OF QUESTIONNAIRE

41 If yes, which formula?
IF BREAST FEEDING ONLY END OF QUESTIONNAIRE

IF BOTTLE FEEDING AT ALL (Get info from 3 month questionnaire)

42 When did you first introduce bottle feeding? _____ Days _____ Weeks

43 When did you stop breast feeding? [ ] Days [ ] Weeks

44 Why did you stop breast feeding your baby?

Reason	code

45 Which bottle feed are you using at present? [ ] [ ]

46 In the last three months have you used any formula other than the one you are using at the moment? Yes[1] [ ] No[2] [ ]
IF 'NO' END OF QUESTIONNAIRE

47 If yes, what formula and why did you change?

Formula	code	Age when you changed	How long used	Reason for change	code

For Office Use Only

		Food	code
Possible Intolerance / Allergy			
Definite Intolerance / Allergy			
No Intolerance / Allergy			

Appendix 2.7

Study No. _____

FAIR Study

Nine month Questionnaire

Child's Name & Address	Date of questionnaire / /
	Sex: Male[1] Female[2]
	GP:
	HV:
	Length: ins cms Date D/K
	Weight: lbs oz kgs Date D/K
Child's date of birth:	
Mother's Name	Mother's IW number
Telephone No.	E-mail address:

Intolerance / Allergy from six month questionnaire

		Food	code
Possible Intolerance / Allergy			
Definite Intolerance / Allergy			
No Intolerance / Allergy			

1. Who completed questionnaire?

Mother[1] Father[2] Grandparent[3] Guardian[4] Other[5] Who

2. Has the child had 1st and 2nd immunisations at three months? (6/12 Q)

1st Imm		2nd Imm	
Y[1]	N[2]	Y[1]	N[2]

3. Has your child had the following immunisations in the last three months?

	1st Immunisation			2nd Immunisation		
Polio	Yes[1]	No[2]	D/K[3]	Yes[1]	No[2]	D/K[3]
HIB, Diptheria, Tetanus	Yes[1]	No[2]	D/K[3]	Yes[1]	No[2]	D/K[3]
Whooping Cough	Yes[1]	No[2]	D/K[3]	Yes[1]	No[2]	D/K[3]
Meningitis C	Yes[1]	No[2]	D/K[3]	Yes[1]	No[2]	D/K[3]

	3rd Immunisation		
Polio	Yes[1]	No[2]	D/K[3]
HIB, Diptheria, Tetanus	Yes[1]	No[2]	D/K[3]
Whooping Cough	Yes[1]	No[2]	D/K[3]
Meningitis C	Yes[1]	No[2]	D/K[3]
Other	Yes[1]	No[2]	D/K[3]

What

4. Declined all immunisations: Yes[1] No[2] N/A[-100] Reason

5. Has your child ever had wheezing or whistling in the chest in the past three months? Yes[1] No[2] D/K[3]

6. In the last three months, has your child had a dry cough at night, apart from the cough associated with a cold or a chest infection? Yes[1] No[2] D/K[3]

7. In the last three months, has your child suffered from an itchy, stuffy Or runny nose when they did not have a cold or flu? Yes[1] No[2] D/K[3]

8. Has your child ever suffered from an itchy skin that looks like nettle rash /hives? Yes[1] No[2] D/K[3]

9. Has your child ever had an itchy dry flaky skin/eczema that was coming and going over the last three months? IF 'NO' OR 'D/K' GO TO Q. 11

Yes[1]		No[2]		D/K[3]	

10 If yes, where does your child get the itchy dry flaky skin/eczema?

Place	code	Place	code

11 Has your child ever suffered from vomiting (>1 tbsp) in the last three months?

Yes[1]		No[2]		D/K[3]	

12 Has your child ever suffered from diarrhoea in the last three months?

Yes[1]		No[2]		D/K[3]	

13 Has your child ever suffered from constipation in the last three months?

Yes[1]		No[2]		D/K[3]	

14 Has your child ever suffered swelling of the eyes, lips, tongue or throat in the last three months?

Yes[1]		No[2]		D/K[3]	

15 Has your child ever suffered from colic/tummy ache in the last three months?

Yes[1]		No[2]		D/K[3]	

16 Has your child suffered from any food related problems in the last three months?

Yes[1]		No[2]		D/K[3]	

17 If yes, what?

Symptom	code	Food	code	Temp Rel	code	Frequency	code	Age (wks)	Still present			
									Yes[1]		No[2]	
									Yes[1]		No[2]	
									Yes[1]		No[2]	
									Yes[1]		No[2]	

18 Have you consulted your GP/Paediatrician regarding any of the above symptoms in the last six months?

GP	Yes[1]		No[2]		Paediatrician	Yes[1]		No[2]	

IF 'NO' GO TO Q. 20

19 If yes, what symptoms?

Symptom	code	Symptom	code

20 Which method of feeding are you using **at the moment**?

Breast milk only[1]		Bottle/Beaker only[2]		Both[3]	

IF BREAST ONLY OR BOTTLE ONLY GO TO Q. 22

21 If both, do you feed your baby breast/bottle equally, more breast or more bottle?

Breast >half[1]		Equal[2]		Bottle >half[3]		Breast + top up[4]		Breast + occasional bottle [5]	

22 In the last three months, have you given your baby any water?

Yes[1]		No[2]	

23 In the last three months have you introduced any of the following foods?

Rice or baby rice		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Wheat containing foods (e.g. baby rusk, baby cereals, cereals, pasta, bread, cakes, biscuits)		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Oats or oat cereal		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Non-citrus fruit (e.g. banana)		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Citrus fruit (e.g. orange, orange juice, mandarin, clementine, lemon, lime, tangerine, grapefruit)		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Strawberry		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Vegetables (not tomato or potato)		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Tomato		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Potato		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Dairy foods (e.g. yoghurt, fromage frais, custard, ice cream, butter, margarine, cow's milk in food, cheese)		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Chicken or turkey		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Lamb		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Beef		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Pork		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Fish		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Whole egg		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Pulses (e.g. lentils, peas, baked beans)		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Soya		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Tree nuts – almonds, brazil nuts, pecan nuts, hazel nuts, walnuts etc. (e.g. in chocolate, crunchy nut cornflakes, choc chip cookies, pesto sauce, vegetarian meals)		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Peanuts (e.g. Bombay mix, peanut butter, peanut brittle, peanut cookies, Snickers bar, some vegetarian meals)		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Sesame (e.g. humous, tahini, seed rolls, cereal bars)		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Other food (specify)		Yes[1]		No[2]		D/K[3]		N/A[-100]	
		Yes[1]		No[2]		D/K[3]		N/A[-100]	
		Yes[1]		No[2]		D/K[3]		N/A[-100]	

24 Are you consciously avoiding any foods from your baby's diet at present? Yes[1] | No[2]
IF 'NO' GO TO Q. 26

25 If yes, what?

Food	code	Food	code

26 In the last three months have you given your baby any of the following drinks?

Fruit squash		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Fruit juice		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Tea/coffee		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Fizzy drinks		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Cow's milk / flavoured milk drinks		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Flavoured water		Yes[1]		No[2]		D/K[3]		N/A[-100]	
Other drinks (specify)		Yes[1]		No[2]		D/K[3]		N/A[-100]	

27 Has your baby taken any medication (e.g. gripe water, antibiotics etc) or used any medicated creams in the last three months? Yes[1] | No[2]
IF 'NO' GO TO Q. 29

28 If yes what?

Gripe water	Yes[1]		No[2]			
Calpol	Yes[1]		No[2]			
Colief	Yes[1]		No[2]			
Infacol	Yes[1]		No[2]			
Antibiotics	Yes[1]		No[2]			
Neurofen	Yes[1]		No[2]			
Other medication	Yes[1]		No[2]		Please specify	

29 Do you normally smoke? Yes[1] | No[2]

30 If yes, how many cigarettes do you smoke daily on average?

31 Has your baby regularly been exposed to cigarette smoke? Yes[1] | No[2]

32 Is your baby exposed to pets at home?

Cat	Yes[1]	No[2]	
Dog	Yes[1]	No[2]	
Other	Yes[1]	No[2]	What?

33 Is your baby regularly exposed to pets elsewhere?

Cat	Yes[1]	No[2]	
Dog	Yes[1]	No[2]	
Other	Yes[1]	No[2]	What?

IF BOTTLE FEEDING AT ALL (Get info from 3/6 month questionnaire)

34 When did you first introduce bottle feeding? _____ Days _____ Weeks

35 When did you stop breast feeding? _____ Days _____ Weeks

36 Why did you stop breast feeding your baby?

Reason	code

37 Which bottle/beaker feed are you using at present?

38 In the last three months have you used any formula other than the one you are using at the moment? Yes[1] | No[2]
IF 'NO' END OF QUESTIONNAIRE

39 If yes, what formula and why did you change?

Formula	code	Age when you changed	How long used	Reason for change	code

For Office Use Only

		Food	code
Possible Intolerance / Allergy			
Definite Intolerance / Allergy			
No Intolerance / Allergy			

Appendix 2.8 **Study No. _____**

FAIR Study

Twelve month Questionnaire

Child's Name & Address	Date of questionnaire / /
	Sex: Male[1] Female[2]
	GP
	HV
	Height: ins cms
	Weight: lbs oz kgs
Child's date of birth:	
Mother's Name	Mother's IW number
Telephone No.	E-mail address

1. Have you, your partner or children suffered with the following

	Mother	Father	Siblings					
			M	F	M	F	M	F
Asthma								
Hayfever								
Eczema								
Urticaria								
Food Allergy								

2. Parental smoking

Mother	Yes[1]	No[2]
Father/Partner	Yes[1]	No[2]

3. Is your baby regularly exposed to pets?

Cat	Yes[1]	No[2]	
Dog	Yes[1]	No[2]	
Other	Yes[1]	No[2]	What?

4.

Birth weight										
Type of delivery	NVD		EmCS		ElCS		Forceps		Ventouse	
Breast fed	days		weeks		months					
Weaning age	weeks		months							

5. Has your child ever had wheeze/whistling in the chest in the last 3 months? Yes[1] No[2]
IF 'NO' GO TO Q. 15

6. If yes, how many times in the last year? 0[1] 1-3[2] 4-12[3] >12[4]

7. Did it cause sleep disturbance? 0[1] <1 night a weeek[2] >1 night a week[3]

8. Did your child require hospitalisation for this at any time? Yes[1] No[2]

9. Has your child ever had wheeze/whistling with a chest infection or cold? Yes[1] No[2]

10 Has your child ever had wheeze/whistling when he/she did not have a chest infection or cold? Yes[1] No[2]

Appendix 2.8 **Study No. _____**

11 Has your child ever had asthma — Yes[1] | No[2]

12 Has your child ever had treatment for wheeze/asthma? — Yes[1] | No[2]

13 Have you identified a cause for the wheeze or asthma? — Yes[1] | No[2]
IF 'NO' GO TO Q. 15

14 If yes, what?

Pollen[1]		Dust[2]		Smoke[3]		Animal[4]		Infections[5]	
Food[6] (specify)									
Other[7] (specify)									

15 Has your child ever had a dry cough at night apart from that associated with a cold or flu in the last 3 months? — Yes[1] | No[2]
IF 'NO' GO TO Q. 21

16 If yes, does he/she usually have a cough only with a cold or flu? — Yes[1] | No[2]

17 Does he/she usually have a cough without a cold or flu? — Yes[1] | No[2]

18 How many episodes has he/she had in the last 12 months? — 0[1] | 1-3[2] | 4-6[3] | 7 or more[4]

19 Have you identified a cause for the cough? — Yes[1] | No[2]
IF 'NO' GO TO Q. 21

20 If yes what?

Pollen[1]		Dust[2]		Smoke[3]		Animal[4]		Infections[5]	
Food[6] (specify)									
Other[7] (specify)									

21 Has your child ever had a dry scaly rash coming and going (for more than 6 months)? — Yes[1] | No[2]
IF 'NO' GO TO Q. 28

22 If yes, has your child ever been diagnosed with eczema? — Yes[1] | No[2]

23 Has your child ever been treated for rash/eczema — Yes[1] | No[2]
IF 'NO' GO TO Q. 25

24 If yes, with what?

25 Where is the rash/eczema?

Face[1]		Trunk[2]		Arms[3]		Legs[4]		Folds of skin[5]	
Other[6] (specify)									

26 Have you identified a cause for the eczema? — Yes[1] | No[2]
IF 'NO' GO TO Q. 28

27 If yes, what?

Pollen[1]		Dust[2]		Smoke[3]		Animal[4]		Infections[5]	
Food[6] (specify)									
Other[7] (specify)									

28 Has your child had a runny or stuffy nose in the last 3 months? Yes[1] | | No[2] | |
IF 'NO' GO TO Q. 34

29 If yes, how often? <1/month | | 1-3/month | | >1/week | |

30 Have you identified a cause for this? Yes[1] | | No[2] | |
IF 'NO' GO TO Q 32

31 If yes, what?

Pollen[1]		Dust[2]		Smoke[3]		Animal[4]		Infections[5]			
Food[6] (specify)											
Other[7] (specify)											

32 Has your child ever been treated for this? Yes[1] | | No[2] | |

33 If yes, with what? | | | | | |

34 Has your child had diarrhoea in the last 3 months? Yes[1] | | No[2] | |
IF 'NO' GO TO Q 38

35 If yes, how often? <1/month | | 1-3/month | | >1/week | |

36 Have you identified a cause for this? Yes[1] | | No[2] | |

37 If yes, what?

Infection[1]		Drug[2]		Food[3] (specify)							
						Other[4] (specify)					

38 Has your child had vomiting in the last 3 months? Yes[1] | | No[2] | |
IF 'NO' GO TO Q 42

39 If yes, how often? <1/month | | 1-3/month | | >1/week | |

40 Have you identified a cause for this? Yes[1] | | No[2] | |

41 If yes, what?

Infection[1]		Drug[2]		Food[3] (specify)							
						Other[4] (specify)					

42 Has your child had food related problems in the last 3 months? Yes[1] | | No[2] | |
IF 'NO' GO TO Q. 46

43 If yes, what?

Symptom	code	Food	code	Temp Rel	code	Frequency	code

44 Have you avoided any of these foods from your baby's diet? Yes[1] | | No[2] | |
IF 'NO' GO TO Q. 46

45 If yes what?

Food	code	Reason	code	Improvement in symptoms				Diagnosis confirmed			
				Yes[1]		No[2]		Yes[1]		No[2]	
				Yes[1]		No[2]		Yes[1]		No[2]	
				Yes[1]		No[2]		Yes[1]		No[2]	
				Yes[1]		No[2]		Yes[1]		No[2]	

46 Has your child had any of the following in the last 3 months?

		Yes[1]	No[2]	No. of Episodes
Urticaria				
Swelling of:	Lip			
	Lip and face			
	Tongue/throat			

47 Have you identified a cause for the above? Yes[1] No[2]

48 If yes, what?

Drug[1]		Insect sting[2]		Food[3] (specify)		
				Other[4] (specify)		

49 Has your child required any medication in the last 3 months? Yes[1] No[2]

50 If yes, what

	Yes[1]	No[2]						
Lotions / creams / ointments								
Inhalers								
Eye drops								
Suspensions								
Other								

Appendix 2.8 **Study No. _____**

Medical Examination

Eyes	redness[1]		swollen eyelids[2]		other[3]		

Skin

dry[1]		erythema[2]		excoriation[3]		lichenification[4]		vesicles[5]		other[6]		

Nose

rhinorrhoea[1]		crusting[2]		congestion/blockage[3]		polyps[4]		other[5]		

Respiratory System

chest deformity[1]		wheeze[2]		crackles[3]		other[4]		

Other

Skin Prick Tests

Aeroallergens			Size	Food Allergens			Size
HDM				Milk			
Grass				Wheat			
Cat				Egg			
Dog				Fish			
Cladosp				Sesame			
Alternaria				Other			
Other							

Other Investigations

Food Challenge

Appendix 2.9 **Study No. _____**

FAIR Study

Two Year Questionnaire

Child's Name & Address	Date of questionnaire / /
	Sex: Male[1] Female[2]
	GP
	HV
	Height: ins cms
	Weight: lbs oz kgs
Child's date of birth:	
Mother's Name	Mother's IW number
Telephone No.	E-mail address

1. Do you, your partner or children suffer with or have you, your partner or children suffered with the following

	Mother	Father	Sibling1		Sibling2		Sibling3		Sibling4		Sibling5	
			M[1]	F[2]	M[1]	F[2]	M[1]	F[2]	M[1]	F[2]	M[1]	F[2]
	Y[1]/N[2]	Y[1]/N[2]	Y[1]/N[2]	Y[1]/N[2]	Y[1]/N[2]	Y[1]/N[2]	Y[1]/N[2]	Y[1]/N[2]	Y[1]/N[2]	Y[1]/N[2]	Y[1]/N[2]	Y[1]/N[2]
Asthma												
Nocturnal/recurrent cough												
Hayfever												
Eczema												
Urticaria												
Food Allergy												

2. Parental **smoking** Smoke during pregnancy Yes[1] No[2]

3. Does anyone in the house smoke now?

				In house		How many
Mother	Yes[1]	No[2]	N/A	Yes[1]	No[2]	/day
Father/Partner	Yes[1]	No[2]	N/A	Yes[1]	No[2]	/day
Other	Yes[1]	No[2]	N/A	Yes[1]	No[2]	/day

4. Do any of the above smoke outside the house Yes[1] No[2] N/A

5. **Pets** in the house in the last year

Cat	Yes[1]	No[2]	
Dog	Yes[1]	No[2]	
Other	Yes[1]	No[2]	What?

6. Baby regularly exposed to pets elsewhere in the last year

Cat	Yes[1]	No[2]	
Dog	Yes[1]	No[2]	
Other	Yes[1]	No[2]	What?

7. Has your child been immunised to

DPT	Yes[1]		No[2]		
DT (without pertussis)	Yes[1]		No[2]		
Polio	Yes[1]		No[2]		
Hib	Yes[1]		No[2]		
Meningococcal Group C	Yes[1]		No[2]		
BCG	Yes[1]		No[2]		
MMR	Yes[1]		No[2]		
Other	Yes[1]		No[2]	What?	

Appendix 2.9 **Study No. _____**

8. Has your child ever had wheeze/whistling in the chest at any time in the past? Yes[1] No[2]
IF 'NO' GO TO Q. 20

9. Any wheeze/whistling in the last 12 months? Yes[1] No[2]

10 If yes, how many times in the last year? 0[1] 1-3[2] 4-12[3] >12[4]

11 Average sleep disturbance it caused in 12 months? 0[1] <1 night a weeek[2] >1 night a week[3]

12 Did your child require hospitalisation for this at any time? Yes[1] No[2]

13 Has your child ever had wheeze/whistling with a chest infection or cold? Yes[1] No[2]

14 Has your child ever had wheeze/whistling when he/she did not have a chest infection or cold? Yes[1] No[2]

15 Has your child ever been diagnosed with asthma? Yes[1] No[2]

16 Has your child ever had treatment for wheeze/asthma? Yes[1] No[2]

17 If yes, what?

18 Have you identified a cause for the wheeze or asthma? Yes[1] No[2]
IF 'NO' GO TO Q. 20

19 If yes, what?

Pollen[1]		Dust[2]		Smoke[3]		Animal[4]		Infections[5]	
Food[6] (specify)									
Other[7] (specify)									

20 Has your child ever had a dry cough at night apart from that associated with a cold or chest infection? Yes[1] No[2]
IF 'NO' GO TO Q. 28

21 Has your child ever had a dry cough at night in the last 12 months? Yes[1] No[2]

22 If yes, does he/she usually have a cough only with a cold or chest infection? Yes[1] No[2]

23 Does he/she usually have a cough without a cold or chest infection? Yes[1] No[2]

24 How many episodes has he/she had in the last 12 months? 0[1] 1-3[2] 4-12[3] >12[4]

25 Average sleep disturbance it caused in 12 months 0[1] <1 night a week[2] >1 night a week[3]

26 Have you identified a cause for the cough? Yes[1] No[2]
IF 'NO' GO TO Q. 28

27 If yes what?

Pollen[1]		Dust[2]		Smoke[3]		Animal[4]		Infections[5]	
Food[6] (specify)									
Other[7] (specify)									

28 Has your child ever had a dry itchy rash coming and going (for at least 6 months)? Yes[1] No[2]
IF 'NO' GO TO Q. 38

29 At what age did it first occur? days | weeks | months

30 Has your child had a dry itchy rash at any time in the last 12 months? Yes[1] No[2]

31 In the last 12 months on average has your child been kept awake by this itchy rash? 0[1] | <1 night/week[2] | > 1 night/week[3]

32 If yes, has your child ever been diagnosed with eczema? Yes[1] No[2]

33 Has your child ever been treated for rash/eczema Yes[1] No[2]
IF 'NO' GO TO Q. 38

34 If yes, with what?

35 Where is the rash/eczema?
Face[1] | Trunk[2] | Arms[3] | Legs[4] | Folds of skin[5]
Other[6] (specify)

36 Have you identified a cause for the eczema? Yes[1] No[2]
IF 'NO' GO TO Q. 38

37 If yes, what?
Pollen[1] | Dust[2] | Smoke[3] | Animal[4] | Infections[5]
Food[6] (specify)
Other[7] (specify)

38 Has your child had a problem with sneezing or a runny or blocked nose in the last 12 months? Yes[1] No[2]
IF 'NO' GO TO Q. 44

39 If yes, how often? <1/month[1] | 1-3/month[2] | >1/week[3]

40 Have you identified a cause for this? Yes[1] No[2]
IF 'NO' GO TO Q 44

41 If yes, what?
Pollen[1] | Dust[2] | Smoke[3] | Animal[4] | Infections[5]
Food[6] (specify)
Other[7] (specify)

42 Has your child ever been treated for this? Yes[1] No[2]

43 If yes, with what?

44 Has your child had diarrhoea in the last 12 months? Yes[1] No[2]
IF 'NO' GO TO Q 48

45 If yes, how often? <1/month[1] | 1-3/month[2] | >1/week[3]

46 Have you identified a cause for this? | Yes[1] | | No[2] | |

47 If yes, what?

Infection[1]		Drug[2]		Food[3] (specify)		
				Other[4] (specify)		

48 Has your child had vomiting in the last 12 months? | Yes[1] | | No[2] | |
IF 'NO' GO TO Q 52

49 If yes, how often? | <1/month[1] | | 1-3/month[2] | | >1/week[3] | |

50 Have you identified a cause for this? | Yes[1] | | No[2] | |

51 If yes, what?

Infection[1]		Drug[2]		Food[3] (specify)		
				Other[4] (specify)		

52 Has your child had food related problems in the last 12 months? | Yes[1] | | No[2] | |
IF 'NO' GO TO Q. 56

53 If yes, what?

Symptom	code	Food	code	Temp Rel	code	Frequency	code

54 Have you avoided any of these foods from your baby's diet? | Yes[1] | | No[2] | |
IF 'NO' GO TO Q. 56

55 If yes what?

Food	code	Reason	code	Improvement in symptoms				Diagnosis confirmed			
				Yes[1]		No[2]		Yes[1]		No[2]	
				Yes[1]		No[2]		Yes[1]		No[2]	
				Yes[1]		No[2]		Yes[1]		No[2]	
				Yes[1]		No[2]		Yes[1]		No[2]	

56 Has your child had any of the following in the last 12 months?

		Yes[1]	No[2]	No. of Episodes
Urticaria				
Swelling of:	Lip			
	Eyes			
	Lip and face			
	Tongue/throat			
Other rash				
Collapse				

57 Have you identified a cause for the above? | Yes[1] | | No[2] | |

58 If yes, what?

Drug[1]		Insect sting[2]		Food[3] (specify)			
				Other[4] (specify)			

59 Has your child required any medication in the last 12 months? Yes[1] | | No[2] |

60 If yes, what

	Yes[1]	No[2]					
Lotions / creams / ointments							
Inhalers							
Eye drops							
Suspensions							
Other							

61 Are you consciously avoiding any foods from your baby's diet at present? Yes[1] | | No[2] |

62 If yes, what?

Food	code	Food	code

63 Did you avoid peanuts during pregnancy? Yes[1] | No[2] | N/A[-100]

64 If yes, for what reason?

65 The government issued advice in 1998 about eating peanuts whilst pregnant and breastfeeding. Do you remember hearing about that at the time? Yes[1] | No[2] | Don't remember[3]

66 Did any of the following people speak to you or give you information about eating peanuts and peanut containing foods **during your pregnancy**?

	N/A[-100]					
GP	Yes[1]		No[2]		Don't remember[3]	
Midwife	Yes[1]		No[2]		Don't remember[3]	
Health Visitor	Yes[1]		No[2]		Don't remember[3]	
Dietitian	Yes[1]		No[2]		Don't remember[3]	
Other	Yes[1]		No[2]		Don't remember[3]	
Media	Yes[1]		No[2]		Don't remember[3]	

IF 'NO' OR 'DON'T REMEMBER' GO TO Q. 69

67 Did you change your diet on the basis of this advice? Yes[1] | | No[2] | | Don't remember[3]

68 If you changed your diet did you

Stop eating peanuts completely?[1]	
Stop eating obvious peanuts but continue eating foods that 'may contain peanut?[2]	
Increase your consumption of peanut?[3]	
Don't remember[4]	

69 Breast fed | days | weeks | months

IF NOT BREAST FED END OF QUESTIONNAIRE

70 Did any of the following people speak to you or give you information about eating peanuts and peanut containing foods **whilst breastfeeding**?

	N/A[-100]					
GP	Yes[1]		No[2]		Don't remember[3]	
Midwife	Yes[1]		No[2]		Don't remember[3]	
Health Visitor	Yes[1]		No[2]		Don't remember[3]	
Dietitian	Yes[1]		No[2]		Don't remember[3]	
Other	Yes[1]		No[2]		Don't remember[3]	
Media	Yes[1]		No[2]		Don't remember[3]	

IF 'NO' OR 'DON'T REMEMBER' END OF QUESTIONNAIRE

71 Did you change your diet on the basis of this advice? Yes[1] No[2] Don't remember[3]

72 If you changed your diet did you

Stop eating peanuts completely?[1]	
Stop eating obvious peanuts but continue eating foods that 'may contain peanut?[2]	
Increase your consumption of peanut?[3]	
Don't remember[4]	

		Food	code
Possible Intolerance / Allergy			
Definite Intolerance / Allergy			
No Intolerance / Allergy			

Appendix 2.9 **Study No.** _____

Medical Examination (Not done[10])

Eyes

redness[1]		swollen eyelids[2]		other[3]		normal[9]		

Skin

dry[1]		erythema[2]		excoriation[3]		lichenification[4]		vesicles[5]		other[6]		normal[9]	
Eczema[17]													

Nose

rhinorrhoea[1]		crusting[2]		congestion/blockage[3]		polyps[4]		other[5]		normal[9]	

Respiratory System

chest deformity[1]		wheeze[2]		crackles[3]		other[4]		normal[9]		

Other

Skin Prick Tests Not done[-103]

Food allergens	Size	Positive[1]	Negative[2]	Aeroallergens	Size	Positive[1]	Negative[2]
Histamine				HDM			
Saline				Cat			
Milk				Grass			
Egg				Other			
Wheat							
Fish							
Peanut							
Sesame							
Other							

Food Challenge

Appendix 2.10 Example of School information sheet

Isle of Wight Healthcare NHS
NHS Trust

The David Hide Asthma & Allergy Research Centre
St. Mary's Hospital
Newport
Isle of Wight
PO30 5TP

Direct Tel. No. (01983) 534178

Food Allergy and Intolerance Research (FAIR) Study
Information Sheet to Students and Parents/Guardians of children in Year 10

Dear Parent(s)/Guardian(s)/Student

You are invited to take part in an important research study. Before you decide, it is essential for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is **anything that is not clear** or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?
Currently we don't have any good scientific information on the number of children affected by food allergy and food intolerance. In addition, food allergy and food intolerance is perceived to be on the increase in the Western world. We have been successful in obtaining a research grant from the government's Food Standards Agency to find out exactly how common is food allergy and intolerance amongst English children. We are looking at pre-school children as well as children in Year 1, Year 6 and Year 10 of school.

Part of the study is to establish how common food allergy and intolerance is amongst 15 year olds. To gain an accurate picture of how frequently these problems occur, it is really important that we have information on as many children as possible. Scientifically it would be more valid if we could include all 15 year olds on the Island.

Why has my child been chosen?
The study involves all children on the Isle of Wight who will be 15 years old in the period between September 2002 and August 2003. We are approaching all the children via their schools and your school has kindly agreed to forward this information to you on our behalf. Your name and address has **not** been disclosed to us at this stage but if you decide to take part, you can give us this information by completing the enclosed questionnaire.

Does my child have to take part?
It is up to you to decide whether or not to take part. If you decide to take part we suggest you keep this information sheet. We will also ask you to complete and sign the enclosed consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. Your decision not to take part or withdraw from the study will not in any way influence other medical care you receive.

How is the study conducted?
Our study is a whole population epidemiological study. This means that we need to look at a great many people to see if they have food allergy. We are looking at 4 groups of children born in different years who are resident on the Isle of Wight during the study period. The first group is a newborn cohort who will be followed from birth to three years of age. The second and third cohorts are all the 6 and 11 year olds on the Island and the fourth cohort **(your child is in this cohort)** is all the 15 year olds on the Island. We are interested in finding out how common food allergy/food intolerance is perceived to be and how common it is when we assess it using food challenges. We are also interested in finding out what proportion of the children are sensitised to some of the most common foods associated with food allergy.

What will happen if we decide to take part?
If you decide to take part in the study we would ask you to undertake the following:

Appendix 2.10 Example of

School information sheet

Part (i) To complete a simple one-page questionnaire asking about any problems your child may have with any food. It is important for us to have a comprehensive picture of as many children as possible. Hence we would be grateful if you could complete the questionnaire even if the answers to all the questions are no.

Part (ii) For your child to have a skin prick test to 6 food allergens (milk, egg, wheat, peanut, fish, and sesame) and 3 air allergens (house dust mite, grass and cat allergens). Although we are mainly concerned with food allergy, skin prick testing to inhalant allergens will help us in profiling your child's allergies more accurately.
Skin Prick testing is a painless procedure that is carried out routinely at the Allergy Centre on babies, children and adults of all ages. The nurses and the doctors of the Centre are very experienced in skin testing, having carried out thousands of these tests over recent years.
The test involves drawing on the arm and placing on it several drops of allergen. The top layer of skin is then very gently pricked through the liquid allowing a tiny amount in to the skin. If there is a positive reaction a small itchy wheal will appear (looks like a red circle) after 10 minutes. This will disappear fairly soon after the test (10-15minutes).

We would like to carry out this test on **all** children if possible regardless of whether they have a history of any food allergy. This is because we need to know what number have the food allergy and we can only determine this if we test everyone. However, you have the option of completing the questionnaire only and refusing the skin prick test if you wish to do so.

To cause minimum inconvenience our team of doctors and nurses would like to carry out the skin testing at your child's school. This would take 20 minutes and the school is happy for us to do this during school time at the school. If you would prefer this test to be performed at the Allergy Centre, we could offer this service instead. If you have indicated that you would like to know the results of your child's skin test, this will be handed to them on the day.

Part (iii) Those pupils who have positive skin test to foods that they have never previously eaten, plus pupils reporting food related problems will be invited to the Allergy Centre for further investigations. Based on studies in other countries we expect only 20% of children to fall into this category. If your child is in this group, again you have the option of doing part (i) alone or parts (i) and (ii) and decline to undertake part (iii). A separate information sheet and consent form will be given to you if this part is applicable to your child.

What are the benefits of taking part?
This study is described as a non-therapeutic epidemiological study. Most children participating in the study will be healthy volunteers. Some of the children have asthma and allergies and some may have other conditions. The study does not include any treatment for any condition. Although you may find it useful to know whether your child is sensitised to any foods or inhalants, the main reason for conducting this study is to help us understand the scale of food allergy amongst children living in England.

What are the possible disadvantages and risks of taking part?
There are no disadvantages or risks in taking part in this study. The only issue is the inconvenience of completing a questionnaire and a possible temporary minor discomfort some children may experience with skin prick testing.

Will my taking part in this study be kept confidential?
All information, which is collected about your child during the course of the research, will be kept strictly confidential. You will not be individually identified in any reports or publications resulting from the study. Your GP will be informed that you are participating in this study.

We do hope you will agree to your child taking part in this really important study which will help us better understand food allergy.
If you have any questions please ring The David Hide Asthma and Allergy Research Centre – 534178 - and speak to one of the study team who are:
Dr. Brett Pereira (Clinical Research Fellow) Jane Grundy (Research Nurse) Bernie Mealy (Research Midwife) Carina Venter (Research Dietitian) Monica Fenn (Research Nurse) Gillian Glasbey (Study Coordinator) Dr. Tara Dean (Project Lead)

Isle of Wight Healthcare NHS
NHS Trust

The David Hide Asthma & Allergy Research Centre
St. Mary's Hospital
Newport
Isle of Wight
PO30 5TG

Direct Tel. No. (01983) 534178

Food Allergy and Intolerance Research (FAIR)

Consent Form

Please delete as appropriate

We have read the Study Information Sheet — Yes / No

We have been given information on who to contact if we want to ask more questions about this study — Yes / No

We understand that we are free to withdraw from the study:

- At any time
- Without having to give a reason for withdrawing — Yes / No

I agree to complete a questionnaire about my child's reaction to food — Yes / No

I will be happy for my child to have a skin prick test at school — Yes / No
OR
I will be happy for my child to have a skin prick test at the Allergy Centre — Yes / No

I would be willing for my child to participate further in the study if necessary — Yes / No

I also give consent for my GP Dr .....
to be informed of our participation in the study. — Yes / No

The undersigned certify that the Information Sheet has been read and understood by the parent/guardian

Signature Parent/Guardian Date

Signature Student's name Date

Study No. _____(RS)

Food Allergy and Intolerance Research (FAIR) Study Questionnaire

Before completing this form please read the information sheet which should explain some of the questions

Please complete this form by ticking the boxes or writing in the appropriate parts and return it with the consent form to the David Hide Asthma and Allergy Centre in the enclosed pre-paid envelope. Please answer every question even if the answer is no. If you have any queries, please phone the FAIR Study team on 534178

Name of Child						
Home Address						
Contact Telephone No.						
Child's Date of Birth		Sex	Male		Female	
Child's School						
Child's GP						

1. Does your child **currently** have a problem with any of the following foods? (Please tick as appropriate)

Milk	Yes		No			
Egg	Yes		No			
Peanut	Yes		No			
Tree nut (e.g. almond, brazil)	Yes		No			
Wheat	Yes		No			
Fish	Yes		No			
Sesame	Yes		No			
Other	Yes		No		Please specify	

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

Food	Problem

3. Is your child avoiding any of the above foods from his/her diet? Yes ☐ No ☐

4. If yes, please state which foods

5. Would you be willing for your child to be skin tested to milk, egg, peanut, wheat, fish, sesame, house dust mite, grass and cat? Yes ☐ No ☐

6. Would you be happy to be invited for further investigations if necessary? Yes ☐ No ☐

7. Would you like to know the results of your child's skin test? Yes ☐ No ☐

Thank you for taking the time to complete this questionnaire. Please return it to the David Hide Asthma & Allergy Research Centre in the prepaid envelope provided as soon as possible

Appendix 2.13 Completed skin prick test form

FAIR STUDY

Result of Skin Prick Test

Name _____ Date of Birth 1 / 01 / 88

Study No 1685 Date of Test 14 / 05 / 03

		Mean wheal diameter	
Histamine	○ 8·5 X 7	7·75.	
Saline	—		
Milk	○ 3X2	2·5 mm	neg.
Egg	○ 2X1·5.	1·75 mm	neg
Wheat	○ 7X4.	5·5 mm	+
Fish	○ 3X2·5	2·75 mm	neg
Peanut	○ 14X10.	12 mm	+
Sesame	○ 8·5X4.	6·25 mm	+
House Dust Mite	○ 8X6.	7 mm	+
Cat	○ 3·5X3	3·25 mm	+
Grass	—	0	neg
Tomatoe	—	0 m	neg
Kiwi.	—	0 m	neg.

asthmatic, hayfever, atopic family.

* Did take Piriton @ 9pm last night.

Peanut allergy since childhood; angio oedema, ↑ wheeze. Has epipen.
Eats all the rest w/o problem. Has HDM/pet/pollen advice.

Isle of Wight Healthcare NHS
NHS Trust

The David Hide Asthma & Allergy Research Centre
St. Mary's Hospital
Newport
Isle of Wight
PO30 5TG

Direct Tel. No. (01983) 534178

Food Allergy and Intolerance Research (FAIR)

Consent For Food Challenge

Method of Challenge:	Open Challenge		DBPCFC				
Route:	Oral		Labial		Topical		

Food(s): _____
_____
_____

The challenge procedure has been explained to me and I have read the appropriate information sheet. I hereby consent to undergoing a food challenge:

Patient Details:

Name:_____

Date of Birth: _____ IW Number: _____

I also give consent for my GP .....
to be informed of our participation in the study. Yes / No

Patient/Parent Name (in block letters) Signature Date

Investigator Name Signature Date

Study No. _____

The David Hide Asthma and Allergy Research Centre
Isle of Wight

Patient information prior to the one-day open food challenge

1. Certain medications must be stopped:

	Avoid for _____ before challenge
Pirition (Chlorpheniramine), *Vallergan, Phenergan*	48 hours
Ketotifen , Zirtek (Ceterizine), *Clarityn* (Loratadine)	72 hours
Hismanal (Astemizol)	1 month

(If not possible to avoid completely, tailor the antihistamines down to the lowest effective dose)

On the day of challenge, do not take or use:

- Anti-cholinergics (Ipatropium bromide - *Atrovent)*
- B-agonist bronchodilators *(Ventolin and Bricanyl)*
- Cromolyn (*Intal or Nalcrom*)
- Nasal sprays and oral decongestants
- Steroids - discuss the use of all steroids with the doctor/nurse/dietitian responsible for the challenge.

2. The challenge should be done on an almost empty stomach, so your child should eat only a light breakfast before you come in.

3. What will happen during the day?
   You will sign a consent form for the challenge.
   A doctor and nurse will see your child before the challenge. They will also monitor any changes in your child's condition during the challenge.

   Your child's blood pressure, pulse rate, respiration and peak flow will be monitored if and when appropriate.

   We start the challenge by wiping the inside of the lip with the suspected allergen (e.g. milk/egg/soya) whilst observing your child closely. If no reaction occurs your child will be asked to undergo an oral food challenge test, which involves eating or drinking a very small quantity of the suspected food or drink in increasing amounts. This could be milk hidden in another fluid, cake or biscuits for an egg challenge or flapjacks for a nut challenge. If your child is a fussy eater, discuss this with the dietitian.

   The challenge may take several hours so be prepared to spend most of the day at the hospital.

   If your child has a reaction at any stage, the challenge will be stopped and treatment given.

   Before you go home the Doctor will ensure that your child is well.

   There is tea and coffee available and we can provide a sandwich lunch or you can obtain lunch from the canteen. You are welcome to bring along any foods/drinks your child likes and would normally have for when your child gets hungry/thirsty. No food will be allowed for the first 2 hours of the challenge.

Although there are toys available to entertain young children, it is a good idea to bring some activities or toys along.

4. On discharge, your child should remain quiet for the remainder of the day as strenuous exertion could induce a delayed reaction.

5. Should you experience a delayed reaction, please inform the ward. These reactions are extremely unlikely to be severe, but if you have any concerns out of office hours, contact your Children's Ward. The Dietitian and/or Doctor will be in contact with you regularly during the week following the challenge.

6. For any further information, please do no hesitate the contact the Dietitian, Carina Venter, on 01983 - 534193.

Appendix 2.16

FAIR Study

General challenge information on one-day food challenge procedures for open food challenges and double blind placebo controlled food challenges:
Paediatric Day Case Unit, St. Mary's Hospital, Isle of Wight

1. Challenges will be conducted by the doctor, nurse and/or dietititan

2. All challenges will start at 09h30. Patients are only allowed a light breakfast or 1 bottle feed early morning.

3. **The offending food** must be avoided for at least 2 weeks prior to the challenge. The dietitian involved will advise patients accordingly.

4. **The following medications must be stopped/adjusted:**

Antihistamines

Pirition (Chlorpheniramine), *Vallergan, Phenergan*	48 hours before challenge
Ketotifen ,Zirtek (Ceterizine), *Clarityn* (Loratadine)	72 hours before challenge
Hismanal (Astemizol)	1 month before challenge

(Antihistamines may occasionally only be tailored down to the lowest effective dose)

On the day of challenge, the patient should not take or use the following unless indicated by the study physician:

- Anti-cholinergics (Ipratropium bromide - *Atrovent)*
- B-agonist bronchodilators *(Ventolin and Bricanyl)*
- Cromolyn (*Intal or Nalcrom*)
- Nasal sprays or oral congestants

Steroids (oral, topical and inhaled) – should be stopped or tailored down to ensure sufficient bronchial stability, as agreed with the doctor. This dosage must be maintained for a fortnight before the challenge.

5. Ensure patient is well e.g. rhinitis without fever or a cough without fever.

6. Get written consent.

7. Take baseline observations: blood pressure, pulse rate, respiration and peak flow and repeat when appropriate. The doctor or nurse will perform all physical examinations.

8. Confirm anaphylaxis kit and resuscitation equipment (team) are ready.

9. If any reaction occurs such as erythema, mouth/lip swelling, itching or vomiting at any stage of the challenge, STOP the challenge and consult the doctor.

10. Record the outcome of the challenge on symptom chart.

Open or Double Blind Placebo Controlled Food Challenge Procedure

Challenge procedure for each challenge provided as summarised in Appendices 2.17 and 2.21.

11. Keep patient on hospital site for 2 hours after the challenge or agree on an appropriate length of time with the overseeing doctor.

12. Patients should be informed that some reactions might be delayed up to 2-3 days later. If this happens, it should be reported.

13. If the challenge is positive, please ensure:
    The patient has received the necessary information about avoidance.
    The appropriate medication gets prescribed.
    Further appointments for challenges are arranged.
    The GP is informed in case of severe reactions.

* as discussed according to the patient's history

Appendix 2.17 One-day open food challenge procedures

Cow's Milk

For infants < 6 months: Use any cow's milk formula

All other children: Use skimmed cow's milk

Place 1 drop of cow's milk on lower oral mucosa of the patient. 10 minutes observation

If no reaction, proceed to:

0.5 ml cow's milk to be drunk	15 minutes observation
1 ml cow's milk to be drunk	15 minutes observation
2 ml cow's milk to be drunk	15 minutes observation
5 ml cow's milk to be drunk	15 minutes observation
10 ml cow's milk to be drunk	15 minutes observation
15 ml cow's milk to be drunk	15 minutes observation
25 ml cow's milk to be drunk	15 minutes observation
40 ml cow's milk to be drunk	2 hours observation

100 – 200 ml cow's milk to be drunk (can use cow's milk formula for children < 1 year)
or 100 – 200 ml of yoghurt 2 hours observation

Egg

Use 40 g cooked egg (10 g dried product)

Rub the lower mucosa of the lip with cooked egg.	10 minutes observation

If no reaction, proceed to:

1 g egg to be eaten	15 minutes observation
2 g egg be eaten	15 minutes observation
5 g egg to be eaten	15 minutes observation
10 g to be eaten	15 minutes observation
22 g egg to be eaten	2 hours observation

1 egg to be eaten
(for children < 1year = 1 medium egg; children >1 year 1 large egg; children > 12 years 1 extra large egg) 2 hours observation

Please note: Boil 3 eggs for the challenge. This will give the opportunity to mix the egg with either salad cream, egg free mayonnaise, tomato sauce or the child's favourite food if he/she does not want to eat the boiled egg.

Appendix 2.17 One-day open food challenge procedures

Wheat: Weetabix

Use ½ Weetabix for challenge (9.4 g dried product)

Place 1 drop of Weetabix mixed with water on lower lip	10 minutes observation
If no reaction, proceed to:	
¼ teaspoon of Weetabix to be eaten	15 minutes observation
½ teaspoon of Weetabix to be eaten	15 minutes observation
1 teaspoon of Weetabix to be eaten	15 minutes observation
2 teaspoons of Weetabix to be eaten	15 minutes observation
5 teaspoons of Weetabix to be eaten	2 hours observation
If possible, 1 Weetabix to be eaten	2 hours observation

Wheat: Pasta

Use 30 g cooked pasta (10 g raw) for challenge (9 g dried product)

Place 1 drop of wheat flour mixed with water on lower lip	10 minutes observation
If no reaction, proceed to:	
1 g pasta to be eaten	15 minutes observation
2 g pasta to be eaten	15 minutes observation
3 g pasta to be eaten	15 minutes observation
5 g pasta to be eaten	15 minutes observation
8 g pasta to be eaten	2 hours observation
10 g pasta to be eaten	2 hours observation
If possible, 1 slice of bread or 80g pasta or 1 Weetabix to be eaten	2 hours observation

Appendix 2.17 One-day open food challenge procedures

Tomato

Use 150 g of tomato for challenge. (9.45 g dried product)

Rub the lower mucosa of the patient with tomato.	10 minutes observation
If no reaction, proceed to:	
1 g of tomato to be eaten	15 minutes observation
2 g of tomato to be eaten	15 minutes observation
5 g of tomato to be eaten	15 minutes observation
10 g of tomato to be eaten	15 minutes observation
15 g of tomato to be eaten	15 minutes observation
45 g of tomato to be eaten	15 minutes observation
70 g of tomato to be eaten	2 hours observation

If possible, at the end of the challenge, the child should consume:

- < 2 years:	30 g tomato	
- 2-3 years:	30–60 g tomato	
- 3- 5 years:	60-80 g tomato	
- > 5 years:	100–120 g tomato	2 hours observation

Corn

Use 10 g corn or maize flour for challenge (8.8 g of maize/corn)

Place 1 drop of corn flour mixed with water on lower lip	10 minutes observation
If no reaction, proceed to:	
1 g corn flour made into a porridge or sauce to be eaten	15 minutes observation
2 g corn flour made into a porridge or sauce to be eaten	15 minutes observation
3 g corn flour made into a porridge or sauce to be eaten	15 minutes observation
4 g corn flour made into a porridge or sauce to be eaten	2 hours observation
If possible, 5-10 g corn flour made into a porridge or sauce to be eaten	2 hours observation

Appendix 2.17 One-day open food challenge procedures

Fish

Use 60 g poached fish for challenge. (13 g dried product)

Rub the lower mucosa of the patient with the fish.	10 minutes observation
If no reaction, proceed to:	
1 g of poached fish to be eaten	15 minutes observation
2 g of poached fish to be eaten	15 minutes observation
5 g of poached fish be eaten	15 minutes observation
10 g of poached fish to be eaten	15 minutes observation
15 g of poached fish to be eaten	15 minutes observation
27 g of poached fish to be eaten	2 hours observation

100 g poached fish to be consumed openly or

< 3 years	1-2 fish fingers	
3-5 years	2-3 fish fingers	
> 5 years	3–4 fish fingers	2 hours observation

Strawberry Challenge

Use 100 g of Strawberry for challenge.

Strawberry can be mashed or pureed for ease of measurement. (10.5 g of dried products)

Place 1 drop of strawberry on lower oral mucosa of the patient.	10 minutes observation
If no reaction, proceed to:	
½ teaspoon of strawberry to be eaten	15 minutes observation
1 teaspoon of strawberry to be eaten	15 minutes observation
1 teaspoon of strawberry to be eaten	15 minutes observation
2 teaspoons of strawberry to be eaten	15 minutes observation
3 teaspoons of strawberry to be eaten	15 minutes observation
4 teaspoons of strawberry to be eaten	2 hours observation

If possible, the child should consume:
1 portion:

- < 2 years:	40–80 g strawberries	
- 2-3 years:	80–100 g strawberries	
- > 3- 5 years:	100 g strawberries	2 hours observation

Appendix 2.17 One-day open food challenge procedures

Citrus

Use 100 ml orange juice for challenge. (10.8 g solids)	
Rub the lower mucosa of the patient with orange juice.	10 minutes observation
If no reaction, proceed to:	
1 ml of orange juice to be drunk	15 minutes observation
2 ml of orange juice to be drunk	15 minutes observation
5 ml of orange juice to be drunk	15 minutes observation
10 ml of orange juice to be drunk	15 minutes observation
25 ml of orange juice to be drunk	15 minutes observation
47 ml of orange juice to be drunk	2 hours observation
If possible, 60 - 100 ml of orange juice to be drunk	2 hours observation

Soya Milk

For infants < 2 years: Use any soya milk formula	
All other children: Use unflavoured soya milk	
Use 100 ml of soya milk for challenge (10.3 g of dried product)	
Place 1 drop of soya milk on lower oral mucosa of the patient	10 minutes observation
If no reaction, proceed to:	
0.5 ml soya milk to be drunk	15 minutes observation
1 ml soya milk to be drunk	15 minutes observation
2 ml soya milk to be drunk	15 minutes observation
5 ml soya milk to be drunk	15 minutes observation
10 ml soya milk to be drunk	15 minutes observation
15 ml soya milk to be drunk	15 minutes observation
25 ml soya milk to be drunk	15 minutes observation
40 ml soya milk to be drunk	2 hours observation
If possible, 100 – 200 ml soya milk to be drunk: - soya milk formula or soya yoghurt for children < 2 years	
- soya milk or soya yoghurt for children > 2 year	2 hours observation

Appendix 2.17 One-day open food challenge procedures

Citric acid: Lemon juice

Place 1 drop of lemon juice on lower lip of patient.	10 minutes observation
If no reaction, proceed to:	
0.5 ml lemon juice to be taken	15 minutes observation
1 ml lemon juice to be taken	15 minutes observation
5 ml lemon juice to be taken	30 minutes observation

Peanut: Flapjack

Rub the lower mucosa of the lip with a peanut (not salted)	10 minutes observation
If no reaction – proceed to:	
1/32 of flapjack to be eaten (250 mg peanut or ¼ peanut)	15 minutes observation
1/16 of a flapjack to be eaten	15 minutes observation
1/8 of a flapjack to be eaten	15 minutes observation
¼ of a flapjack to be eaten	15 minutes observation
½ of a flapjack to be eaten	15 minutes observation (Child has consumed 8 g of peanut)

At the end of the challenge: The child should consume another 10 peanuts OR 1 peanut flapjack OR 1 slice of bread with peanut butter openly

Peanut: unsalted peanuts or chocolate covered peanuts

Rub the lower mucosa of the lip with a peanut (not salted)	10 minutes observation
Child needs to eat 10 peanuts in total (8 g peanut)	
If no reaction – proceed to:	
½ peanut to be eaten	15 minutes observation
1 peanut to be eaten	15 minutes observation
2 peanuts to be eaten	15 minutes observation
3 peanuts to be eaten	15 minutes observation
3 ½ peanuts to be eaten	15 minutes observation
(Child has consumed 8 g of peanut)	

At the end of the challenge: The child should consume another 10 peanuts OR 1 peanut flapjack OR 1 slice of bread with peanut butter openly.

Appendix 2.17 One-day open food challenge procedures

Peanut: Peanut flour
Use 8 g of peanut flour for the challenge

Rub the lower mucosa of the lip with a peanut (not salted)	10 minutes observation
If no reaction – proceed to:	
500 mg of peanut flour to be eaten	15 minutes observation
1 g of peanut flour to be eaten	15 minutes observation
1.5 g of peanut flour to be eaten	15 minutes observation
2 g of peanut flour to be eaten	15 minutes observation
3 g of peanut flour to be eaten	15 minutes observation
(Child has consumed 8 g of peanut)	

At the end of the challenge: The child should consume another 10 peanuts OR 1 peanut flapjack OR 1 slice of bread with peanut butter openly.

Banana
Use 80 g of banana for challenge. (9.45 g dried product)

Rub the lower mucosa of the patient with banana.	10 minutes observation
If no reaction, proceed to:	
1 g of banana to be eaten	15 minutes observation
2 g of banana to be eaten	15 minutes observation
5 g of banana to be eaten	15 minutes observation
10 g of banana to be eaten	15 minutes observation
15 g of banana to be eaten	15 minutes observation
47 g of banana to be eaten	15 minutes observation

If possible, at the end of the challenge, the child should consume:

- < 2 years:	30 g banana	
- 2-3 years:	30–60 g banana	
- 3- 5 years:	60-80 g banana	
- > 5 years:	100–120 g banana	2 hours observation

Appendix 2.17 One-day open food challenge procedures

Almond: unsalted almonds or chocolate covered almonds

Child needs to eat 8-10 g of almonds in total

Rub the lower mucosa of the lip with an almond (not salted)	10 minutes observation
If no reaction – proceed to:	
500 mg almond to be eaten	15 minutes observation
1 g almond to be eaten	15 minutes observation
2 g almond to be eaten	15 minutes observation
3 g almond to be eaten	15 minutes observation
3.5 g almond to be eaten	15 minutes observation

At the end of the challenge: The child should consume another 10 g almond or an amount equal to a normal portion for that child

Icing (containing a mixture of artificial colourings)
Use 10 g of icing for the challenge

1 g of icing to be eaten	15 minutes^{+} observation
2 g of icing to be eaten	15 minutes^{+} observation
3 g of icing to be eaten	15 minutes^{+} observation
4 g of icing to be eaten	15 minutes^{+} observation

At the end of the challenge: The child should consume another biscuit with icing spread on it (2-5 g).

Appendix 2.17 One-day open food challenge procedures

Kiwi

Use 100 g of kiwi for challenge. (8 g dried product)

Rub the lower mucosa of the patient with melon.	10 minutes observation
If no reaction, proceed to:	
1 g of kiwi to be eaten	15 minutes observation
2 g of kiwi to be eaten	15 minutes observation
5 g of kiwi to be eaten	15 minutes observation
10 g of kiwi to be eaten	15 minutes observation
15 g of kiwi to be eaten	15 minutes observation
25 g of kiwi to be eaten	15 minutes observation
40 g of kiwi to be eaten	2 hours observation
If possible, 60 - 100 g of kiwi to be eaten	2 hours observation

Cheese

Use 60g of cheese for challenge. (36 g solids)

Rub the lower mucosa of the patient with cheese (when applicable).	10 minutes observation
If no reaction, proceed to:	
1 g cheese to be eaten	15 minutes observation
2 g cheese to be eaten	15 minutes observation
5 g cheese to be eaten	15 minutes observation
10 g cheese to be eaten	15 minutes observation
15 g cheese to be eaten	15 minutes observation
27 g cheese to be eaten	2 hours observation
If possible, the child should consume another 30 – 60 g cheese	2 hours observation

Appendix 2.17 One-day open food challenge procedures

Melon Challenge

Use 100 g of melon for challenge. (8 g dried product)

Rub the lower mucosa of the patient with melon.	10 minutes observation

If no reaction, proceed to:

1 g of melon to be eaten	15 minutes observation
2 g of melon to be eaten	15 minutes observation
5 g of melon to be eaten	15 minutes observation
10 g of melon to be eaten	15 minutes observation
15 g of melon to be eaten	15 minutes observation
25 g of melon to be eaten	15 minutes observation
40 g of melon to be eaten	2 hours observation
If possible, 60 - 100 g of melon to be eaten	2 hours observation

Hazelnut

Child needs to eat 8- 10 g of hazelnuts in total

Rub the lower mucosa of the lip with a hazelnut (not salted)	10 minutes observation

Rub the lower lip mucosa with a hazelnut:

If no reaction – proceed to:

500 mg hazelnut to be eaten	15 minutes observation
1 g hazelnut to be eaten	15 minutes observation
2 g hazelnut to be eaten	15 minutes observation
3 g hazelnut to be eaten	15 minutes observation
3.5 g hazelnut be eaten	15 minutes observation (Child has consumed 8 g of hazelnut)

At the end of the challenge: The child should consume another 10 g hazelnut or an amount equal to a normal portion for that child

Appendix 2.17 One-day open food challenge procedures

Raisin Challenge

Use 25 g of raisins for challenge. (12 g dried product)

Rub the lower mucosa of the patient with a raisin.	10 minutes observation
If no reaction, proceed to:	
1 g of raisin to be eaten	15 minutes* observation
2 g of raisin to be eaten	15 minutes observation
5 g of raisin to be eaten	15 minutes observation
10 g of raisin to be eaten	15 minutes observation
20 g of raisin to be eaten	15 minutes observation
30 g of raisin to be eaten	15 minutes observation
32 g of raisin to be eaten	15 minutes observation

If possible, at the end of the challenge, the child should consume:

- < 2 years: 30 g raisin
- 2-3 years: 30-60 g raisin
- 3- 5 years: 60-80 g raisin
- > 5 years: 100–120 g raisin — 2 hours observation

Prawn

Use 35 g cooked prawns for challenge. (10.5 g dried product) hidden in fish cake

Rub the lower mucosa of the patient with a prawn.	10 minutes observation
If no reaction, proceed to:	
1 g of prawn or placebo to be eaten	15 minutes* observation
2 g of prawn or placebo to be eaten	15 minutes observation
3 g of prawn or placebo be eaten	15 minutes observation
5 g of prawn or placebo to be eaten	15 minutes observation
10 g of prawn or placebo to be eaten	15 minutes observation
14 g of prawn or placebo to be eaten	2 hours observation
At the end of both challenges: 100 g prawns to be consumed openly or	2 hours observation

Appendix 2.17 One-day open food challenge procedures

Ribena

Give the patient 1 glass of Ribena for challenge as reported by the history.
2-4 hours observation

Orange squash

Give the patient 1 glass of Orange squash for challenge as reported by the history.
2-4 hours observation

Salicylate

Give the patient 250 ml of the combination drink containing: strawberry, orange and plum juice.
2-4 hours observation

NOTE: The observation period in between dosages and after the challenges will vary according to the patient history.

Appendix 2.18

General information prior to the one-week open food challenge procedures

The David Hide Asthma and Allergy Research Centre, Isle of Wight
Food Allergy and Intolerance Research (FAIR) Study

1. Your child should avoid the offending for at least two weeks before the challenge.

2. Certain medications must be stopped:

	Avoid for _____ before challenge
Pirition (Chlorpheniramine), *Vallergan, Phenergan*	48 hours
Ketotifen , Zirtek (Ceterizine), *Clarityn* (Loratadine)	72 hours
Hismanal (Astemizol)	1 month

(If not possible to avoid completely, tailor the antihistamines down to the lowest effective dose)

These medication also not be taken during the week of the challenge or could be discussed with the study doctor:

- See above list
- Anti-cholinergics (Ipatropium bromide - *Atrovent)*
- B-agonist bronchodilators *(Ventolin and Bricanyl)*
- Cromolyn (*Intal or Nalcrom*)
- Nasal sprays
- Steroids - discuss the use of all steroids with the doctor/nurse/dietitian responsible for the challenge.

3. What will happen during the initial consultation?
   You will sign a consent form for the challenge.
   A doctor and nurse will see your child before the challenge. They will also monitor any changes in your child's condition during the 7-day challenge when reported by you.

   Your child's blood pressure, pulse rate, respiration and peak flow will be monitored if and when appropriate.

   FOOD CHALLENGE PROVIDED: See appendix 2.19

4. Apart from the foods on the above list, we would like you to continue the food (milk, egg, wheat etc) that we are using during the food challenge diet as discussed with the dietitian.

5. Coud you please also complete the food diary provided to you.

5. At the end of the open challenge we would like you to send the food diary back to us in the pre-paid envelope provided.

If your child has a reaction at any stage, stop the challenge and please get in contact with us on 01983 534178. Treatment will be arranged.

Brett Pereira Carina Venter
Jane Grundy Bernie Mealy
Gill Glasbey Monica Fenn

Appendix 2.19 **One-week open food challenge procedures**

Milk challenge

For children < 1 years:

For the 7 day challenge, we would like you to provide the **equivalent of 20 oz of cow's milk formula per day** to your child on a daily basis. You can use the formula to make custard or use it on cereal.

For children 1 – 15 years:

For the 7 day challenge, we would like you to provide the following foods to your child on a daily basis:

2-3 portions of cow's milk or cow's milk products per day:

The following foods are all equal to 1 portion of milk:

- 8 fl oz of cow's milk infant formula
- 8 fl oz of cow's milk
- 8 oz of custard
- 1 yoghurt or fromage frais
- 1 oz cheese

Chocolate challenge

Based on the history given: For the 7-day chocolate challenge, we would like you to give your child one chocolate bar per day as provided to you.

Citrus challenge

For children < 1 year:

For the 7 day challenge, we would like you to provide the **equivalent of 1 citrus fruit portion** to your child on a daily basis.

This amounts to:
1 small satsuma
½ orange
100 ml orange juice

For children over 1 years (1- 2 ½ years):

For the 7 day challenge, we would like you to provide the **equivalent of 1 citrus fruit portion** to your child on a daily basis.

This amounts to:

1-2 small satsumas
½ -1 orange
100 – 200 ml orange juice

Soya challenge

For children < 1 years:

For the 7 day challenge, we would like you to provide the **equivalent of 20 oz of soya milk formula per day** to your child on a daily basis. You can use the formula to make custard or use it on cereal.

For children over 1 years (1- 2 ½ years):

For the 7 day challenge, we would like you to provide your child with the **equivalent of 20 oz of soya milk per day:**

The following foods are all equal to 1 oz of milk:

- 1 oz of soya milk infant formula
- 1 oz of soya milk (up to a maximum of 5 oz mixed in with food) not suitable as a main source of milk intake in children younger than 2 years
- 1 oz of custard made with soya milk e.g. Bird's original custard
- ¼ soya yoghurt
- 1 oz soya cheese e.g. "Cheezly" available from Sainsbury's and Tesco's.

Wheat challenge

For the 7-day challenge, we would like you to provide the following amounts of wheat containing foods to your child:

Age of child	
6 months to 2 years	2-3 portions
2 - 3 years	4 portions
6 years	4-5 portions
11 and 15 years	4-6 portions

You could give ½ portions of a larger variety of wheat containing foods as well, i.e. To provide 3 portions to a one year old child, you could give 6 x ½ portions.

The following foods are all equal to 1-wheat portion:

- 1 slice of bread
- 3 tablespoons of cereal (not rice cereals or corn cereals)
- 1 Weetabix or Shredded Wheat
- 1 biscuit
- 1 slice of cake
- 1 tablespoon pasta

Additives

For the 7-day additive challenge, we would like you to give your child 1 x 250 ml drink (containing a variety of artificial colours and sodium benzoate) per day as provided to you.

Appendix 2.20

The David Hide Asthma and Allergy Research Centre, Isle of Wight
FAIR Study

Patient information sheet prior to the one-day double blind placebo controlled food challenge

1. Certain medications must be stopped:

	Avoid for _____ before challenge
Piriton (Chlorpheniramine), *Vallergan, Phenergan*	48 hours
Ketotifen , Zirtek (Ceterizine), *Clarityn* (Loratadine)	72 hours
Hismanal (Astemizol)	1 month

(If not possible to avoid completely, tailor the antihistamines down to the lowest effective dose)

On the day of challenge, do not take or use:

- Anti-cholinergics (Ipatropium bromide – *Atrovent)*
- B-agonist bronchodilators *(Ventolin and Bricanyl)*
- Cromolyn (*Intal or Nalcrom*)
- Nasal sprays or oral decongestants
- Steroids – discuss the use of all steroids with the doctor/nurse/dietitian responsible for the challenge.

2. The challenge should be done on an almost empty stomach, so your child should eat only a light breakfast before you come in.

3. What will happen during the day?
   You will sign a consent form for the challenge.
   A doctor and nurse will see your child before the challenge. They will also monitor any changes in your child's condition during the challenge.

   Your child's blood pressure, pulse rate, respiration and peak flow will be monitored if and when appropriate.

   Your child will receive two sets of food or drink on the day of challenge. One will contain the suspected allergen (e.g. cow's milk) and the other placebo (dummy substance). The challenge begins by wiping the inside of the lip with either the suspected allergen or a placebo whilst observing your child closely. If no reaction occurs, your child will be asked to undergo an oral food challenge test which involves eating or drinking increasing amounts of the food or drink containing the suspected food or placebo. This could be milk hidden in another fluid, cake or biscuits for an egg challenge or flapjacks for a nut challenge. If your child is a fussy eater, discuss this with the dietitian.

   The first challenge, which could contain either the suspected allergen or the placebo will be performed in the morning and the next challenge (allergen or placebo) follows at a later date as discussed with the study doctor. The challenge may take several hours so be prepared to spend most of the day at the hospital.

   Neither the doctor nor nurse involved in the study knows which food or drink contains the active or placebo.

If your child has a reaction at any stage, the challenge will be stopped and treatment given.

You and your child may have to remain a further hour or two at the hospital after the completion of the challenge, whether negative or positive.

There are tea and coffee available and we will provide you with a sandwich or you could obtain lunch from the canteen. Only bring food that your child has eaten safely before. No food will be allowed for the first 2 hours of the challenge.

Although there are toys available to entertain young children, it is a good idea to bring some activities or toys along.

4. Should you experience a delayed reaction, please inform the ward. These reactions are extremely unlikely to be severe, but if you have any concerns out of office hours, contact Children's Ward`

5. For any further information, please do no hesitate the contact the Dietitian, Carina Venter, on 01983 - 534193.

Appendix 2.21 One-day double blind placebo controlled food challenge procedures

Double Blind Placebo Controlled Milk challenge

Active: 10 g milk powder per 100 ml current formula or milk substitute

Placebo: 10 g dextrose/Caloreen per 100 ml of the current infant formula or milk substitute

Place 1 drop of liquid (Active or Placebo) on lower oral mucosa of the patient.
10 minute observation

If no reaction, proceed to:

0.5 ml liquid to be drunk	15 minutes observation
1 ml liquid to be drunk	15 minutes observation
2 ml liquid to be drunk	15 minutes observation
5 ml liquid to be drunk	15 minutes observation
10ml liquid to be drunk	15 minutes observation
25 liquid to be drunk	15 minutes observation
40ml liquid to be drunk	2 hours observation

At the end of both the active and placebo challenge:
100 – 200 ml cow's milk to be drunk (can use cow's milk formula for children < 1 year) or 100 – 200 ml of yoghurt 2 hours observation

Double Blind Placebo Controlled Egg challenge

Use 40 g cooked egg hidden in custard, egg pasta, apple puree

Liquidise a small amount of the challenge food.

Place 1 drop of liquid (Active or Placebo) on lower oral mucosa of the patient.

10 minute observation

If no reaction, proceed to:

1 g egg to be eaten	15 minutes observation
2 g egg be eaten	15 minutes observation
5 g egg to be eaten	15 minutes observation
10 g to be eaten	15 minutes observation
22 g egg to be eaten	2 hours observation

At the end of both the active and placebo challenge, the following should be eaten openly:
1 egg to be eaten (for children < 1year = 1 medium egg)
(for children >1 year 1 large egg)
2 hours observation

Appendix 2.21 One-day double blind placebo controlled food challenge procedures

Double Blind Placebo Controlled Kiwi challenge:

Use 100 g of kiwi for challenge. (8 g dried product)

1 g of kiwi to be eaten	15 minutes observation
2 g of kiwi to be eaten	15 minutes observation
5 g of kiwi to be eaten	15 minutes observation
10 g of kiwi to be eaten	15 minutes observation
15 g of kiwi to be eaten	15 minutes observation
25 g of kiwi to be eaten	15 minutes observation
40 g of kiwi to be eaten	2 hours observation

After the active and placebo challenges have been performed, in case of a negative challenge:

If possible, 60 - 100 g of kiwi to be eaten	2 hours observation

Double blind placebo controlled prawn challenge

Use 35 g cooked prawns for challenge. (10.5 g dried product) hidden in fish cake

Rub the lower mucosa of the patient with a prawn.	10 minutes observation

If no reaction, proceed to:

1 g of prawn or placebo to be eaten	15 minutes observation
2 g of prawn or placebo to be eaten	15 minutes observation
3 g of prawn or placebo be eaten	15 minutes observation
5 g of prawn or placebo to be eaten	15 minutes observation
10 g of prawn or placebo to be eaten	15 minutes observation
14 g of prawn or placebo to be eaten	2 hours observation

At the end of both challenges:

100 g prawns to be consumed openly	2 hours observation

Appendix 2.21 One-day double blind placebo controlled food challenge procedures

Double blind placebo controlled Sesame challenge

Child needs to eat 8- 10 g of sesame in total. Use sesame hidden in chicken curry.

500 mg sesame or placebo to be eaten	15 minutes observation
1 g sesame or placebo to be eaten	15 minutes observation
2 g sesame or placebo to be eaten	15 minutes observation
3 g sesame or placebo to be eaten	15 minutes observation
3.5 g sesame or placebo to be eaten	15 minutes observation

At the end of the challenge: The child should consume 2 bars of the sesame snap.
2 hours observation

Double Blind Placebo Controlled Soya Milk challenge

Active: Soya milk (100 ml) hidden in suitable vehicle/placebo
For infants < 2 years : Use any soya milk formula
All other children : Use unflavoured soya milk

Placebo: Any other tolerated milk (100 ml) hidden in suitable vehicle/placebo

Place 1 drop of liquid (Active or Placebo) on lower oral mucosa of the patient.
10 minute observation

If no reaction, proceed to:

0.5 ml liquid to be drunk	15 minutes observation
1 ml liquid to be drunk	15 minutes observation
2 ml liquid to be drunk	15 minutes observation
5 ml liquid to be drunk	15 minutes observation
10ml liquid to be drunk	15 minutes observation
25 liquid to be drunk	15 minutes observation
40ml liquid to be drunk	2 hours observation

At end of both active and placebo: 100–200 ml soya milk to be drunk openly
- soya milk formula or soya yoghurt for children < 2 years
- soya milk or soya yoghurt for children > 2 years

2 hours observation

Appendix 2.21 One-day double blind placebo controlled food challenge procedures

Double Blind Placebo Controlled Wheat challenge

Use 10 g dried pasta for challenge (33 g cooked)
Active: pasta made from wheat

Placebo: Wheat free pasta

Rub the lower mucosa of the patient with pasta shell.	10 minutes observation

If no reaction, proceed to:

1 g pasta to be eaten	15 minutes observation
2 g pasta to be eaten	15 minutes observation
3 g pasta to be eaten	15 minutes observation
5 g pasta to be eaten	15 minutes observation
8 g pasta to be eaten	15 minutes observation
14 g pasta to be eaten	2 hours observation

At the end of both the active and placebo challenge, the following should be eaten openly:
1 portion of wheat containing pasta (60–100 g) or 1 Weetabix to be eaten
2 hours observation

NOTE: The observation period in between dosages and after the challenges will vary according to the patient history.

Appendix 2.22

The David Hide Asthma and Allergy Research Centre

Isle of Wight

General information on the one-week double blind placebo controlled food challenge

1. Your child should avoid the offending food for at least two weeks before the challenge.

2. Certain medications must be stopped:

	Avoid for _____ before challenge
Pirition (Chlorpheniramine), *Vallergan, Phenergan*	48 hours
Ketotifen , Zirtek (Ceterizine), *Clarityn* (Loratadine)	72 hours
Hismanal (Astemizol)	1 month

(If not possible to avoid completely, tailor the antihistamines down to the lowest effective dose)

These medication also not be taken during the week of the challenge or could be discussed with the study doctor:

- See above list
- Anti-cholinergics (Ipatropium bromide - *Atrovent)*
- B-agonist bronchodilators *(Ventolin and Bricanyl)*
- Cromolyn (*Intal or Nalcrom*)
- Nasal sprays or oral decongestants
- Steroids - discuss the use of all steroids with the doctor/nurse/dietitian responsible for the challenge.

3. What will happen during the initial consultation?
   You will sign a consent form for the challenge.
   A doctor or nurse will see your child before the challenge. They will also monitor any changes in your child's condition during the 7-day challenge when reported by you.

   Your child's blood pressure, pulse rate, respiration and peak flow will be monitored if and when appropriate.

   Your child will receive two sets of food or drink during the two phases of the 7-day challenge. One will contain the suspected allergen (e.g. cow's milk) and the other placebo (dummy substance). This could be milk hidden in another fluid, cake or

biscuits for an egg challenge or flapjacks for a nut challenge. If your child is a fussy eater, discuss this with the dietitian.

The first challenge, which could contain either the suspected allergen or the placebo will be performed during the first week and the next challenge (allergen or placebo) one week after the first challenge. In others words, we have a one week washout period between the two challenges. If your child develops symptoms at any point in time, we will wait for the symptoms to subside before we start the next challenge.

Neither you, the doctor, nurse or dietitian involved in the study knows which food or drink contains the active or placebo.

At the end of the challenge we would like you to send the food diary back to us in the pre-paid envelope provided.

Information regarding the challenge food provided is available in Appendix 20 for each of the challenges.

If your child has a reaction at any stage, please get in contact with us on 01983-534178 and the challenge will be stopped. Treatment will be arranged.

Brett Pereira

Carina Venter

Jane Grundy

Bernie Mealy

Gill Glasbey

Appendix 2.23 One-week double blind placebo controlled food challenge procedures

7 day DBPCFC: Milk

Infants: Please provide your child with 2 x 8 oz bottles of "milk" per day as provided to you.

Older children: Please provide your child with 2 x tubs of ice cream per day as provided to you.

7 day DBPCFC: Wheat

Infants: Please provide your child with 1 slice of cake or 1 biscuit and 1 dish of pasta as provided to you per day.

Older children: Please provide your child with 1 slice of cake, 2 biscuits and 1 dish of pasta per day.

(PLEASE NOTE: Portions of food provided was adjusted for each age group)

7 day DBPCFC: Chocolate

Please provide your child with 1 x tub of ice cream per day as provided to you.

(PLEASE NOTE: Ice cream contained either chocolate or carob).

7 day DBPCFC: Additives

Please provide your child with 1 x 8 oz bottles of "fruit juice" per day as provided to you.

(PLEASE NOTE: The active drink contained a mixture fruit juices with added azo-dyes and sodium benzoate and the placebo drink of natural fruit juices only.

Appendix 2.24 **Study No. _____**

1.

THE DAVID HIDE ASTHMA & ALLERGY RESEARCH CENTRE

Pre-Challenge Information

DOB	
IW No	

Food reported

Skin Test done | SPT[1] | | P-P[2] | | Both[3] | | None[4] |

SPT/P-P test result as on challenge form

Date	Control/Food	Size	SPT/P-P
	Histamine		SPT

Symptom 1 reported

Date reported | Age symptom developed | Y | M | D |

How soon after food eaten

How much food eaten

Any other factors involved? | Yes[1] | | No[2] | | N/A[100] |

If yes, what?

Symptom 2 reported

Date reported | Age symptom developed | Y | M | D |

How soon after food eaten

How much food eaten

Any other factors involved? | Yes[1] | | No[2] | | N/A[100] |

If yes, what?

Appendix 2.24 **Study No. _____**

Symptom 3 reported

Date reported | Age symptom developed (Y M D)

How soon after food eaten

How much food eaten

Any other factors involved? Yes[1] | No[2] | N/A[-100]

If yes, what?

Date exclusion started | Patient seen by Dietitian Yes[1] | No[2]

If yes, date Dietitian seen

Advice given Yes[1] | No[2]

Next questionnaire: _____

Appendix 2.25 Study No. _____

THE DAVID HIDE ASTHMA & ALLERGY RESEARCH CENTRE
Children's Day Ward, St. Mary's Hospital

FOOD CHALLENGE FORM

1 DAY CHALLENGE PROCEDURE

Food to be challenged: | | **Date:** | |

Type of Challenge | Open | | Double blind Placebo controlled | |

To be completed only when code is broken | Active | | Placebo | |

Patient's Name & Address	DOB	
	Age at challenge	yr mth
	IW No	
	Weight at challenge	

Other relevant allergies/illness (asthma etc) Yes[1] | | No[2] |

If yes

Relevant medication taken in last 3 days Yes[1] | | No[2] |

If yes

Supervising Doctor | B. Pereira[1] | | Other[2] | | Name

Supervising Nurse

J. Grundy[1]		B. Mealy[2]		M. Fenn[3]	
Other[4]		Name		None[5]	

Supervising Dietitian | C. Venter[1] | | C. Gant[2] | | None[3] |

Overall Result of Challenge

Negative[1]		Positive[2]		Not completed[3]		Reason

Reactions | Yes[1] | | No[2] | | N/A[-100] | | If yes

Medication given | Yes[1] | | No[2] | | N/A[-100] | | If yes

Medication		Dose

Doctor's signature _____ Date _____

Parents acceptance of challenge outcome

Open:	Yes[1]		No[2]		N/A[3]		D/K[4]	

If Yes / No, Reason

DBPCFC:	Yes[1]		No[2]		N/A[3]		D/K[4]	

If Yes / No, Reason

At end of DBPCFC:

Parents preference

Open[1]		DBPCFC[2]		No Preference[3]		D/K[4]	

If preference, Reason

Appendix 2.25 Study No. _____

FOOD CHALLENGE CLINICAL MANIFESTATION
For 1 Day Challenge

Method of Challenge:

Labial[1]		Oral[2]		Topical[3]	

Name		No.	
DOB		Weight	

Time								
T								
P								
R								
BP								
Peak flow								
Erythmatous rash								
Eczema								
Pruritis								
Urticaria								
Angio-oedema								
Rash								
Sneezing/Itching								
Nasal congestion								
Rhinorrhoea								
Laryngeal								
Wheezing								
Abdo pain								
Nausea								
Vomiting								
Diarrhoea								
Pallor								
Headache								
Other								

Change in behaviour, mood, activity – describe:

Other – describe:

Appendix 2.25 Study No. _____

Time given	Vehicle/ Food	Dose	Time evaluated	Reaction (additional notes on reverse)

Appendix 2.26 Food Challenge Symptom Score Chart

SKIN
Erythematous Rash - % area involved
(attach Scorad index)

Pruritis
0 = Absent
1 = Mild – occasional scratching
2 = Moderate – scratching continuously for > 2 min at a time
3 = Severe – hard continuous scratching – excoriations

Urticaria
0 = Absent
1 = Mild - < 3 hives
2 = Moderate - <10 hives but > 3
3 = Severe – generalised involvement

Angioedema
0 = absent
1 = 1 area affected (e.g. lips)
2 = 2 areas affected (e.g. lips and tongue)
3 = 3 or more areas affected (e.g. lips, tongue, throat, eyes)

Rash
0 = Absent
1 = Few areas of faint erythema
2 = Moderate – areas of erythema, macular and raised rash
3 = Severe – generalised marked erythema (>50%), extensive raised lesions (25%), vasculation and/or piloerection)

UPPER RESPIRATORY
Sneezing
0 = Absent
1 = Mild – rare bursts
2 = Moderate – bursts <10, intermittent rubbing of nose, and/or eyes
3 = Severe – continuous rubbing of nose and/or eyes, periocular swelling and long bursts of sneezing

Nasal Congestion
0 = Absent
1 = Mild – some hindrance to breathing
2 = Moderate – nostrils feel blocked, breathes through mouth most of time
3 = Severe – nostrils occluded

Rhinorrhoea
0 = Absent
1 = Mild – occasional sniffing
2 = Moderate – frequent sniffing, requires tissues
3 = Severe nose runs freely despite sniffing and tissues

Laryngeal
0 = Absent
2 = Mild – occasional sniffing
4 = Moderate – hoarseness, frequent dry cough
6 = Severe – Inspiratory stridor

LOWER RESPIRATORY
Wheezing
0 = Absent
2 = Mild – expiratory wheezing to ausculation
4 = Moderate – dyspnoea, inspiratory and expiratory wheezing

6 = Severe – dyspnoea, use of accessory muscles, audible wheezing

GASTROINTESTINAL
Subjective:
Nausea
0 = Absent
1 = Mild – frequent c/o nausea + decreased activity
2 = Moderate – frequent c/o of nausea > 30 min + decreased activity + pallor
3 = Severe – patient in bed, notably distressed

Abdo pain
0 = Absent
1 = Mild – frequent c/o abdo pain + decreased activity
2 = Moderate – frequent c/o of abdo pain > 30 min + decreased activity + pallor
3 = Severe – patient in bed, notably distressed

Objective
Vomiting
0 = Absent
1 = Mild – 1 episode of emesis
2 = Moderate – 2-3 episodes of emesis
3 = Severe - > 3 episodes of emesis

Diarrhoea
0 = Absent
1 = Mild – 1 episode of diarrhoea
2 = Moderate – 2-3 episodes of diarrhoea
3 = Severe - > 3 episodes of diarrhoea

Pallor
0 = Absent
1 = Mild
2 = Moderate
3 = Severe

Headache
0 = Absent
1 = Mild - c/o headache
2 = Moderate – frequent c/o headache > 30 min
3 = Severe – patient in obvious distress, crying

Appendix 2.27 **Patient's Name** **Study No. _____**

THE DAVID HIDE ASTHMA & ALLERGY RESEARCH CENTRE
Challenge Outcome – 1 day challenge

Date:	

Labial Yes[1] ☐ No[2] ☐

Symptom 1 experienced ☐

	Minutes	Seconds
Time from rub to symptoms		

Symptom 2 experienced ☐

	Minutes	Seconds
Time from rub to symptoms		

Symptom 3 experienced ☐

	Minutes	Seconds
Time from rub to symptoms		

Medication Given Yes[1] ☐ No[2] ☐ What

Oral Yes[1] ☐ No[2] ☐

Symptom 1 experienced ☐

Last dose

Total dose

	Hours	Minutes	Seconds
Time from first dose to symptoms			
Time from last dose to symptoms			

Symptom 2 experienced ☐

Last dose

Total dose

	Hours	Minutes	Seconds
Time from first dose to symptoms			
Time from last dose to symptoms			

Symptom 3 experienced

Last dose

Total dose

	Hours	Minutes	Seconds
Time from first dose to symptoms			
Time from last dose to symptoms			

Medication given Yes No What

Topical Yes[1] No[2]

Symptom 1 experienced

Dose used

	Days	Hours	Minutes	Seconds
Time from application to symptoms				

Symptom 2 experienced

Dose used

	Days	Hours	Minutes	Seconds
Time from application to symptoms				

Symptom 3 experienced

Dose used

	Days	Hours	Minutes	Seconds
Time from application to symptoms				

Medication given Yes[1] No-[2] What

Hours	Minutes

Challenge Duration (from labial – going home)

Any problems experienced with administering food during challenge

Appendix 2.27 **Patient's Name** **Study No. _____**

Could you keep to time intervals as recommended by challenge protocol? Yes[1] | | No[2] | |

If No, why?

1		
2		
3		
4		

Were any vehicles used? Yes[1] | | No[2] | |

If yes, how many vehicles were used?

	Vehicle	Reason	code
1			
2			
3			
4			
5			
6			

How many doses were used? (from 1st dose (not labial) till end of Part A)

1		2		3		4		5		6		7		8		9		10	

How many doses on challenge protocol?

1		2		3		4		5		6		7		8		9		10	

Reasons for change in dosages:

Total Amount Taken:

	Amount Taken	Recommended
Part A		
Part B		

Did parents accept challenge outcome?	Yes[1]		No[2]		D/K[3]		*N/A[-100]	

If No, Reason

* If need to proceed to prolonged challenge or if first part of DBPCFC

Next Questionnaire: _____

4.

THE DAVID HIDE ASTHMA & ALLERGY RESEARCH CENTRE
DBPCFC
Challenge Outcome – 1 day challenge

Overall Result of Challenge	Positive[1]		Negative[2]		Uncertain[3]	
	Not completed[4]		Reason			

Staff Involved	BP[1]		CV[2]		JG[3]		BM[4]		MF[5]	
	Other[6]								None[7]	

ACTIVE

Challenge Food		

Date:	Weight:

Challenge Result	Positive[1]		Negative[2]		Uncertain[3]	
	Not completed[4]		Reason			

Labial Yes[1] ☐ No[2] ☐

Symptom 1 experienced		

	Minutes	Seconds
Time from rub to symptoms		

Symptom 2 experienced		

	Minutes	Seconds
Time from rub to symptoms		

Symptom 3 experienced		

	Minutes	Seconds
Time from rub to symptoms		

Medication Given Yes[1] ☐ No[2] ☐ What

Oral Yes[1] ☐ No[2] ☐

Symptom 1 experienced		

Last dose	

Total dose	

	Hours	Minutes	Seconds
Time from first dose to symptoms			
Time from last dose to symptoms			

Symptom 2 experienced

Last dose

Total dose

	Hours	Minutes	Seconds
Time from first dose to symptoms			
Time from last dose to symptoms			

Symptom 3 experienced

Last dose

Total dose

	Hours	Minutes	Seconds
Time from first dose to symptoms			
Time from last dose to symptoms			

Medication given Yes ☐ No ☐ What

Topical Yes[1] ☐ No[2] ☐

Symptom experienced

Dose used

	Days	Hours	Minutes	Seconds
Time from application to symptoms				

Medication given Yes[1] ☐ No-[2] ☐ What

Hours	Minutes

Challenge Duration (from labial – going home)
(time taken for active + placebo challenge)

Any problems experienced with administering food during challenge

Could you keep to time intervals as recommended by challenge protocol? | Yes[1] | | No[2] | |

If No, why?

1		
2		
3		
4		

Were any vehicles used? | Yes[1] | | No[2] | |

If yes, how many vehicles were used?

	Vehicle	Reason	code
1			
2			
3			
4			
5			
6			

How many doses were used? (from 1st dose (not labial) till end of Part A)

1		2		3		4		5		6		7		8		9		10	

How many doses on challenge protocol?

1		2		3		4		5		6		7		8		9		10	

Reasons for change in dosages:

Total Amount Taken:

	Amount Taken	Recommended
Part A		
Part B		

Active Challenge Delayed	Yes[1]		No[2]	

Reason(s)		

PLACEBO

Placebo used				
		Date:		

Reaction to Placebo | Yes[1] | | No[2] |

If yes, what?

Placebo Challenge Delayed	Yes[1]		No[2]	

Reason(s)		

Challenge performed at

Home[1]		Children's ward[2]		Other[3]		Specify

Symptoms/No symptoms reported by

Mum[1]		Dr.[2]		Nurse[3]		Other[4]		Specify

Symptoms/No symptoms verified by doctor | Yes[1] | | No[2] |

If yes,	B. Pereira[1]		Paed Dr. [2]		A/E Dr.[3]	
	GP[4]		Other[5]			

Parents acceptance of challenge outcome

DBPCFC: | Yes[1] | | No[2] | | N/A[3] | | D/K[4] |

If Yes / No, Reason | |

Parents preference

Open[1]		DBPCFC[2]		No preference[3]	

Reason	

Next questionnaire _____

Appendix 2.29 Study No. _____

THE DAVID HIDE ASTHMA & ALLERGY RESEARCH CENTRE
Children's Day Ward, St. Mary's Hospital

FOOD CHALLENGE FORM

1 WEEK CHALLENGE PROCEDURE

Food to be challenged: | **Date:**

Type of Challenge | Open | Double blind Placebo controlled |
To be completed only when code is broken | Active | Placebo

Patient's Name & Address

DOB

Age at challenge yr mth

IW No

Weight at challenge

Other relevant confirmed allergies/illness (asthma etc) Yes[1] No[2]
If yes,

Relevant medication taken in last 3 days Yes[1] No[2]
If yes,

Supervising Doctor | B. Pereira[1] | Other[2] | Name

Supervising Nurse

J. Grundy[1]	B. Mealy[2]	M. Fenn[3]
Other[4]	Name	None[5]

Supervising Dietitian | C. Venter[1] | C. Gant[2] | None[3]

Overall Result of Challenge

Negative[1]	Positive[2]	Not completed[3]	Reason

Reactions | Yes[1] | No[2] | N/A[-100] | If yes

Medication given | Yes[1] | No[2] | N/A[-100] | If yes

Medication	Dose

Doctor's signature _____ Date _____

Parents acceptance of challenge outcome

Open:	Yes[1]		No[2]		N/A[3]		D/K[4]	

If Yes / No, Reason

DBPCFC:	Yes[1]		No[2]		N/A[3]		D/K[4]	

If Yes / No, Reason

At end of DBPCFC (both Active and Placebo):

Parents preference

Open[1]		BDPCFC[2]		No Preference[3]		D/K[4]	

If preference, Reason

Appendix 2.29 **Study No. _____**

For 1 week challenge

Date:								
Time								
T								
P								
R								
BP								
Peak flow								
Erythmatous rash								
Eczema								
Pruritis								
Urticaria								
Angio-oedema								
Rash								
Sneezing/Itching								
Nasal congestion								
Rhinorrhoea								
Laryngeal								
Wheezing								
Abdo pain								
Nausea								
Vomiting								
Diarrhoea								
Pallor								
Headache								
Other								
Change in behaviour, mood, activity – describe:								
Other – describe:								

Appendix 2.29 **Study No. _____**

Date	Time given	Vehicle	Dose	Time evaluated	Reaction (additional notes on reverse)

Appendix 2.30 **Date** _____ **Study No.** _____

Food Diary at Home

Patient's Name & Address

DOB	
Age	
Consultant	
IW No	
Weight	

Day 1		
Recommended food intake	Amount of food given	Reason why recommended intake has not been eaten

Any symptoms experienced	Mild	Moderate	Severe
1			
2			
3			

Day 2		
Recommended food intake	Amount of food given	Reason why recommended intake has not been eaten

Any symptoms experienced	Mild	Moderate	Severe
1			
2			
3			

Day 3		
Recommended food intake	Amount of food given	Reason why recommended intake has not been eaten

Any symptoms experienced	Mild	Moderate	Severe
1			
2			
3			

Day 4		
Recommended food intake	Amount of food given	Reason why recommended intake has not been eaten

Any symptoms experienced	Mild	Moderate	Severe
1			
2			
3			

Day 5		
Recommended food intake	Amount of food given	Reason why recommended intake has not been eaten

Any symptoms experienced	Mild	Moderate	Severe
1			
2			
3			

Day 6		
Recommended food intake	Amount of food given	Reason why recommended intake has not been eaten

Any symptoms experienced	Mild	Moderate	Severe
1			
2			
3			

Day 7		
Recommended food intake	Amount of food given	Reason why recommended intake has not been eaten

Any symptoms experienced	Mild	Moderate	Severe
1			
2			
3			

3.

THE DAVID HIDE ASTHMA & ALLERGY RESEARCH CENTRE
OPEN CHALLENGE
Challenge Outcome – 1 week challenge

Challenge food		

Date:	Weight:

Challenge Result

Positive[1]		Negative[2]		Uncertain[3]	
Not completed[3]		Reason			

Staff Involved

BP[1]		CV[2]		JG[3]		BM[4]		MF[5]	
Other[6]								None[7]	

Oral

Yes[1]		No[2]	

Symptom 1 experienced

Day(s) 1 2 3 4 5 6 7

Symptom 2 experienced

Day(s) 1 2 3 4 5 6 7

Symptom 3 experienced

Day(s) 1 2 3 4 5 6 7

Symptom 4 experienced

Day(s) 1 2 3 4 5 6 7

Challenge Duration Days Recommended

Reasons for change

Any problems with administering food during challenge

Appendix 2.31 **Patient's Name** **Study No. _____**

Was any vehicle used? | Yes[1] | | No[2] | |

If yes, how many vehicles were used

	Vehicle	Reason	code
1			
2			
3			
4			
5			
6			

Doses used:

Day	Recommended dose	Dose given	Reason (if dose given different from recommended dose)	code
1				
2				
3				
4				
5				
6				
7				

Challenge delayed	Yes[1]		No[2]	

Reason(s)		

Challenge performed at

Home[1]		Children's ward[2]		Other[3]		Specify

Symptoms/No symptoms reported by

Mum[1]		Dr.[2]		Nurse[3]		Other[4]		Specify

Symptoms/No symptoms verified by doctor | Yes[1] | | No[2] | |

If yes,	B. Pereira[1]		Paed Dr. [2]		A/E Dr.[3]	
	GP[4]		Other[5]			

Parents acceptance of challenge outcome

Open:	Yes		No		N/A		D/K	

If Yes / No, Reason

Next questionnaire: _____

5.

THE DAVID HIDE ASTHMA & ALLERGY RESEARCH CENTRE
DBPCFC
Challenge Outcome – 1 week challenge

Overall Result of Challenge	Positive[1]		Negative[2]		Uncertain[3]	
	Not completed[4]		Reason			

Staff Involved	BP[1]		CV[2]		JG[3]		BM[4]		MF[5]	
	Other[6]								None[7]	

ACTIVE

Challenge food		

Date:	Weight:

Challenge Result	Positive[1]		Negative[2]		Uncertain[3]	
	Not completed[3]		Reason			

Staff Involved	BP[1]		CV[2]		JG[3]		BM[4]		MF[5]		Other[6]

Oral Yes[1] ☐ No[2] ☐

Symptom 1 experienced ☐

Day(s) 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐

Symptom 2 experienced ☐

Day(s) 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐

Symptom 3 experienced ☐

Day(s) 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐

Symptom 4 experienced ☐

Day(s) 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐

Challenge Duration Days ☐ Recommended ☐

Reasons for change ☐

Any problems with administering food during challenge

Was any vehicle used? Yes[1] | | No[2] | |

If yes, how many vehicles were used

	Vehicle	Reason	code
1			
2			
3			
4			
5			
6			

Doses used:

Day	Recommended dose	Dose given	Reason (if dose given different from recommended dose)	code
1				
2				
3				
4				
5				
6				
7				

Active Challenge Delayed	Yes[1]		No[2]	

Reason(s)		

PLACEBO

Placebo used				
		Date:		

Reaction to Placebo Yes[1] | | No[2] | |

If yes, what?

Placebo Challenge Delayed	Yes[1]		No[2]	

Reason(s)		

Challenge performed at

Home[1]		Children's ward[2]		Other[3]		Specify

Symptoms/No symptoms reported by

Mum[1]		Dr.[2]		Nurse[3]		Other[4]		Specify

Symptoms/No symptoms verified by doctor	Yes[1]		No[2]	

If yes,	B. Pereira[1]		Paed Dr.[2]		A/E Dr.[3]	
	GP[4]		Other[5]			

Parents acceptance of challenge outcome

DBPCFC:	Yes[1]		No[2]		N/A[3]		D/K[4]	

If Yes / No, Reason	

Parents preference

Open[1]		DBPCFC[2]		No preference[3]	

Reason	

Next questionnaire: _____

Appendix 2.33

CRIB SHEET (Challenge)

Food and drinks given to baby causing symptoms

Milk and Dairy (S)	42	Citrus fruit/juice	54
Meat (S)	43	Non-citrus fruit/juice	55
Poultry (S)	44	Strawberry	56
Fish (S)	45	Additives	57
Pulses (S)	46	Soya	58
Wheat	47	Peanuts	59
Rice	48	Tree nuts (S)	60
Oats	49	Egg	61
Corn	50	Shellfish	62
Vegetables (not tomato or potato) (S)	51	Sesame	63
Tomato/Tomato sauce	52	Spicy food	64
Potato	53	Other food (S)	65
		Other drinks (S)	66
		Don't know (S)	67

Symptoms / Reasons / Cause

Asthma	1	Collapse / anaphylaxis	21
Runny, itchy nose / Rhinitis	2	Failure to thrive	22
Distended stomach / bloated / flatulence	3	Rhinoconjunctivitis (runny, swollen nose/eyes)	23
Colic	4	Cough	24
Abdominal pain /stomach ache	5	Otitis media	25
Colic and abdominal pain /stomach ache	6	Hyperactivity	26
Nausea	7	None	27
Vomiting	8	Itch	28
Diarrhoea	9	Other (Specify)	29
Constipation	10	Positive on Skin Prick Test	30
Blood in stools	11	Generally unwell	31
Wheeze / whistling / SOB	12	Sleeping disturbed	32
Eczema	13	SPT result <3mm with symptom of allergic disease	33
Urticaria / nettle rash	14		
Rash	15		
Lip swelling	16		
Mouth, eye and/or facial swelling / angioedema	17		
Mouth ulcers	18		
Excessive crying	19		
Sleepiness	20		

Temporal Relationship

< 2 hours	1	2-12 hours	2	>12 hours	3	Never had food before	4	Don't know	5

Reasons for not keeping to time intervals/dosages/duration

Baby falling asleep	1	Baby not taking enough of challenge food	6
Baby full/had enough	2	Challenge discontinued	7
Refused challenge food	3	Other	8
Teething (refused food)	4	Baby wanted more food at once	9
Positive challenge	5		

Reasons for vehicle

Food specified by history	1	Mum's choice of challenge food	6
To make challenge food more palatable	2	Mum wanted to try food	7
To mask challenge food - SB	3	Baby not taking enough of challenge food	8
To mask challenge food - DBPCFC	4	Food by challenge protocol	9
Placebo	5		

Appendix 2.33

Factors Involved

Emotional stress	1	Season	5
Exercise	2	Cross Reaction	6
Alcohol	3	Other	7
Illness/infection	4		

Appendix 3.1 **Food Frequency Questionnaire** **Study No.** _____

Please complete this form when you are 36 WEEKS PREGNANT by ticking the appropriate boxes and send back to the David Hide Asthma and Allergy Centre in the enclosed pre-paid envelope. Please answer every question. If you have any queries, please phone the Dietitian: Carina Venter on 534193

Name & Address	Date questionnaire completed / /
Hospital Number	
Date of Birth	

Tel No: (Home)	Other contact:
(Work)	
(Mobile)	

1. How are you planning to feed your baby?

Breast[1]		Bottle[2]		Undecided[3]		Both[4]	

2. Please tick all of the following statements that are applicable to you:

I am following a normal diet	Yes[1]		No[2]	
I am following a vegetarian diet	Yes[1]		No[2]	
I am following a vegan diet	Yes[1]		No[2]	
I am excluding raw eggs, unpasteurised soft cheese, liver etc. due to my pregnancy	Yes[1]		No[2]	
I am excluding peanuts due to my pregnancy	Yes[1]		No[2]	
I am following a special diet due to medical reasons (please state medical condition)	Yes[1]		No[2]	
I am excluding certain foods due to personal choice (please list foods)	Yes[1]		No[2]	

3. Have you taken any medication during pregnancy e.g. antibiotics, aspirin, paracetamol etc. Yes[1] No[2]
IF 'NO' GO TO Q. 5

4. If yes, what?

5. Have you taken any of the following supplements during this pregnancy?

	Yes[1]	No[2]	
Multivitamin			
Multi mineral			
Calcium			
Iron			
Folic acid			
Other			What?

6. On average, how often have you eaten these foods during pregnancy?

	Never[1]	Rarely (1-2 per month or less)[2]	Occasionally (1-3 per week)[3]	4 times per week or more[4]	Uncertain[5]
Milk and milk products (e.g. custard, yoghurt, ice cream, chocolate, butter, margarines, cheese – pizza, cheese sauce, lasagne, cheezy biscuits)					
Egg (e.g. omelettes, flans, meringues, cakes, cookies, batter mixes, egg pasta, quorn, mayonnaise, quiches)					
Wheat (e.g. bread, cereals, pasta, pizza, cakes, pies, pastry)					
White fish (e.g. tuna, fish cakes, battered fish,fish fingers)					
Shellfish (e.g. crab, prawns, shrimps, lobster, crayfish)					
Oily fish (e.g. mackerel, salmon, sardines, pilchards, herring, kipper, white bait, trout, crab, FRESH tuna)					
Peanuts (e.g. Bombay mix, peanut butter, peanut brittle, peanut cookies, sate, some vegetarian meals)					
Tree nuts - almonds, brazil nuts, pecan nuts, hazel nuts, walnuts etc. (e.g. in chocolate, crunchy nut cornflakes, stuffing mix, sweet mincemeat, choc chip cookies, almond slice, marzipan, pesto sauce. vegetarian meals, Greek desserts like bakklava)					
Seeds e.g. sesame, poppy, sunflower (on bread rolls, tahini paste)					
Citrus fruits (eg orange, tangerine, grapefruit, lemon, lime)					

7. How many helpings/portions of fruit and vegetables do you eat **daily**? (1 portion is: 1 fruit, 1 bowl of salad, 2-3 tablespoons of vegetables, 1 bowl of fruit salad, large slice of melon or other large fruit, a handful of dried fruit or a cupful of berries or grapes)

1 portion[1]		2 portions[2]		3 portions[3]		4 portions[4]		5 portions[5]		More than 5 portions[6]	
Less than 1 portion[7]											

8. Have you deliberately excluded soya from your diet during pregnancy? Yes[1] ☐ No[2] ☐

9. Have you deliberately excluded any additives from your diet during pregnancy? Yes[1] ☐ No[2] ☐

10. Do you normally smoke? Yes[1] ☐ No[2] ☐
IF 'NO' GO TO Q.12

11. If yes:
Have you cut down during this pregnancy? Yes[1] ☐ No[2] ☐
Have you stopped smoking during this pregnancy? Yes[1] ☐ No[2] ☐
How many cigarettes do you smoke daily on average? ☐

12. **Have you regularly been exposed to cigarette smoke elsewhere?**

At home	Yes[1]	☐	No[2]	☐		
At work	Yes[1]	☐	No[2]	☐	N/A[3]	☐

Comments

Thank you for taking the time to complete this questionnaire.

Isle of Wight Healthcare NHS
NHS Trust

A study to validate a Food Frequency Questionnaire used in pregnancy

The David Hide Asthma and Allergy Research Centre, St. Mary's Hospital, Newport, Isle of Wight

PARTICIPANTS INFORMATION SHEET (This information was provided to the participants as an illustrated booklet)

We are currently conducting a large scale study looking at how common food allergy and intolerance is in children on the Isle of Wight. We have previously asked the mothers of the infants in this study to complete a food frequency questionnaire during pregnancy. This questionnaire looked at the diet they were following during pregnancy, which foods they were avoiding, which supplements they were taking and also how often they have eaten certain foods.

We would like you to help us to validate this questionnaire by completing an initial questionnaire about yourself, food diaries and the same questionnaire that the study mothers completed, when you are 36 weeks pregnant.

Please take time to read the following information carefully and discuss it with anyone you wish to.

Please ask us if there is anything that is not clear or if you would like more information.

Thank you for reading this.

What do we need from you?
We need you to indicate information about yourself on the recruitment questionnaire which includes your age, level of education, history of asthma, eczema, hay fever or food allergy and previous pregnancies.
We would like you to complete a 7-day food diary on four occasions, at 16, 20, 28 and 32 weeks of pregnancy. This should not take much of your time as we only need you to write down what you eat during the specific day. We are not interested in how much you eat, except for fruit and vegetables. We would also like you to write down on each diary the name of any vitamin or mineral supplement you might be taking and whether you are avoiding any particular foods.
In addition, we would like you to complete a one page food frequency questionnaire when you are 36 weeks pregnant.

The dietitian or nurse recruiting will be able to go through an example of both the food diaries and food frequency questionnaire with you.

Why have you been chosen?
We need a certain number of pregnant women to help us with our validation study and will approach all women at the ante-natal clinic until we have reached our target number.

Appendix 3.2 Participant information sheet: Validation study

Do you have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part we suggest you keep this information sheet and you will be asked to sign a consent form. You are free to withdraw at any time and without giving a reason. Your decision not to participate or to withdraw from the study will not in any way influence other medical care you
receive.

What will happen if you decide to agree to the study?
We will complete a recruitment questionnaire with you if you are happy to participate in the study on the day of recruitment.
We will ask you to complete 7-day food diaries at four occasions.
The dietitian or nurse will complete the days and dates on which we would like you to write down your daily food intake on the diary.
At 36 weeks of pregnancy, we would like you to complete our food frequency questionnaire. This questionnaire will be posted to you nearer the time. You are welcome to contact the dietitian if you have any queries.

The purpose of the questionnaire and food diaries is by no means to evaluate your food intake during pregnancy. We only compare the data on the food diaries with the data on the food frequency questionnaires and we do not wish you to change your eating habits in any way.

What are the benefits of taking part?
You will play a valuable role in helping us to validate our food frequency questionnaire. Once validated, it will provide us with the means of assessing whether food intake during pregnancy may play a role in the development of food allergy in the child, using our large groups of pregnant women previously recruited.

What are the possible disadvantages and risks of taking part?
There are no disadvantages or risk in taking part in this study other than the inconvenience of completing the diaries and food frequency questionnaire.

Will my taking part in this study be kept confidential?
All information, which is collected about you during the course of the research will be kept strictly confidential. You will not be individually identified in any reports or publications resulting from the study.

What will happen to the results of the research study?
We hope to publish the findings of the study in suitable clinical journals. We will also summarise our findings in a brief report and would be happy to share this with all those who participate in the study.

Who is organising and funding the research?
The study is funded by the Food Standards Agency. The Food Standards Agency is an independent food safety watchdog set up by an Act of Parliament in 2000 to protect the public's health and consumer interests in relation to food. Although the FSA is a Government agency, it works at 'arm's length' from Government because it doesn't report to a specific minister and is free to publish any advice it issues.

Who has reviewed the study?
The Food Standards Agency's Appraisal Panel has reviewed the study. In addition the study has been reviewed by the Isle of Wight, Portsmouth and South East Hampshire Research Ethics Committee.

Appendix 3.2 Participant information sheet: Validation study

Dr. Tara Dean (Project Lead)

How can I get more information on this study before I decide whether to take part or not?

If you have any questions concerning this study or require additional information, please contact Carina Venter the Research Dietitian:

01983 534178

The David Hide Asthma and Allergy Research Centre
St. Mary's Hospital
Newport
Isle of Wight
PO30 5TG

Consumers for Ethics in Research (CERES) publish a leaflet entitled 'Medical Research and You'. This leaflet gives more information about medical research and looks at some questions you may want to ask. A copy may be obtained from CERES, PO Box 1365, London, N16 0BW.

Thank you for taking the time to read this information booklet.

Study No. _____

Appendix 3.3 **Recruitment form**

Isle of Wight Healthcare NHS
NHS Trust

Testing the validity and reliability of a food frequency questionnaire used in pregnancy.

Date of Questionnaire

Participant's Name and Address

DOB:

IW number:

Expected date of delivery:

Telephone number: (h) (mobile)

1) How many children do you have?

2) Have you ever had asthma? Yes[1] No[2]

3) Have you ever suffered from hay fever? Yes[1] No[2]

4) Have you ever had an itchy rash that was coming and going for at least 6 months? Yes[1] No[2]

Study No. _____

Appendix 3.3 **Recruitment form**

5) Have you ever had wheezing or whistling in the chest at any time in the past?

Yes[1]	No[2]

6) Have you ever suffered from an itchy, stuffy or runny nose and/or swollen itchy eyes when you did not have a cold?

Yes[1]	No[2]

7) Have you ever suffered from food allergy or intolerance?

Yes[1]	No[2]

If yes, which foods? _____ ☐

_____ ☐

8) Please indicate your highest level of education:
Please tick:

School[1]		Further[2]		Higher[3]	
Did not finish school[4]		D/K[5]		Still at school[6]	

THANK YOU FOR YOUR TIME

7– Day Food diary

Isle of Wight Healthcare NHS
NHS Trust

Date to be completed: Week beginning 11/10/2004 – 16th week

Name: _____

Date of Birth: 1975-06-

Guidelines

Please record the following on the food diary:

1) **All foods and beverages taken—quantity not required**

2) **Please write down the Brand name of a product where possible**

EXAMPLE

Breakfast
Kellogg's Crunchy nut cornflakes with milk
Toast (white/wholemeal/granary), butter and marmalade
Tea with milk

Midday meal
Heinz Cream of Tomato soup
Ham and cheese sandwich (white/wholemeal/granary bread)
1 apple
Danone BioYoghurt (strawberry flavour)
Tea with milk and sugar
Kit Kat chocolate bar

Evening meal
1 glass of pure orange juice
Spaghetti with Dolmio Bolognaise sauce
Carrots and cabbage
Minghella Rum and Raisin Ice Cream
Banana

In-between meal snacks
Fruesli bar, orange squash
Walkers cheese and onion crisps and diet coke
Apple
Bournville chocolate
McDonalds doughnut and strawberry milk shake
Lemon and poppy seed cake, coffee with milk
Hot chocolate and rich tea biscuit

PLEASE COMPLETE THE FOLLOWING :

At present:

1. Are you avoiding any nuts or seeds from your diet?

Peanuts (e.g. Bombay mix, peanut butter, peanut brittle, Snickers, pesto sauce, sate, some vegetarian meals, peanut cookies, crunchy nut cornflakes)	Yes	(No)	D/K
Other nuts i.e. almonds, hazelnut, brazil, walnut, cashew, pistachio, macadamia, pecan (e.g. in chocolate, crunchy nut cornflakes, stuffing mix, sweet mincemeat, choc chip cookies, bakewell tart, marzipan pesto sauce, vegetarian meals, Greek deseerts like bakklava)	Yes	(No)	D/K
Seeds e.g. sunflower, poppy, sesame, pumpkin seeds (e.g. On bread rolls, tahini paste)	Yes	(No)	D/K

If so, why _____

~~If "No" to above please go to Q. 4~~

2. Are you avoiding any foods with hidden nuts (e.g. do you check ingredients labels)? Yes (No)

3. Are you avoiding any foods which "may contain traces of nuts" Yes (No)

4. In the last four weeks have you eaten any:

Peanuts (as above)	(Yes)	No	D/K
Other nuts (as above)	(Yes)	No	D/K
Seeds (as above)	Yes	(No)	D/K

5. Are you avoiding other foods from my diet at present: (Yes) No

If yes, please indicate which foods you are avoiding:

Salmon, raw fish
Soft cheeses (Brie, Camembert)
Caffeine

If yes, why Can contain toxins that are harmful in pregnancy

6. Are you taking any nutritional supplements (e.g. vitamins, minerals, oils, herbs) at present?
(Yes) No

If yes, please indicate which ones?

Folic acid
Multivitamins
Iron

7. Are you currently smoking? Yes (No)

If yes, how many per day? _____ Inside Outside

Study No. _____

MONDAY

DAILY FOOD AND DRINK INTAKE

Breakfast

Sainsbury's Weetabix with milk and sugar
Toast (white) with butter
Water (glass)

Midday meal

Cheese and tomato sandwich (white)
1 Apple
Water (glass)

Evening meal

Lamb stew, mixed vegetables and rice.
1 Glass of lime juice
Haagendaz Banoffi Ice cream

PLEASE RECORD: In between meal snacks e.g. biscuits, sweets, chocolate, fruit
Beverages taken if not already stated

Yoghurt (Sainsbury's Greek style)
Cheese and biscuits
Glass of water.

DO YOU TAKE MILK IN COFFEE: YES/NO **TEA: YES/NO**

TUESDAY

DAILY FOOD AND DRINK INTAKE

Breakfast

Toast (white) with butter
Banana
Glass of water.

Midday meal

Ham and tomato baguette
Walkers salt and vinegar crisps.
Glass of water.

Evening meal

Chickenbreast with boiled potatoes
Mixed Salad
Glass of water

PLEASE RECORD: In between meal snacks e.g. biscuits, sweets, chocolate, fruit
Beverages taken if not already stated

Chocolate biscuits (McVite's)
Sainsbury's greek style Yoghurt
Pop Corn.
Glass of orange juice (Tropicana)

DO YOU TAKE MILK IN COFFEE: YES/NO **TEA:** YES/NO

Study No. _____

WEDNESDAY

DAILY FOOD AND DRINK INTAKE

Breakfast

Sainsbury's Weetabix with milk and sugar.
Strawberry milkshake

Midday meal

Glass of orange juice
Roast chicken sandwich (wholemeal)
Vegetable quiche

Evening meal

Roast lamb, pumpkin and potatoes.
Glass of water.

PLEASE RECORD: In between meal snacks e.g. biscuits, sweets, chocolate, fruit
Beverages taken if not already stated

Grapes
Danone strawberry Yoghurt
Glass of water

DO YOU TAKE MILK IN COFFEE: YES/NO **TEA:** YES/NO

THURSDAY

DAILY FOOD AND DRINK INTAKE

Breakfast

Kellogs cornflakes with milk and sugar.
Orange juice

Midday meal

Apple
Ham and tomato roll
Bottle of water

Evening meal

Chicken stir fry with fried rice.
Danone Biogyogurt (strawberry)
Water.

PLEASE RECORD: In between meal snacks e.g. biscuits, sweets, chocolate, fruit
Beverages taken if not already stated

Water
Walkers cheese and onion crisps.

DO YOU TAKE MILK IN COFFEE: YES/NO **TEA: YES/NO**

Study No. _____

FRIDAY

DAILY FOOD AND DRINK INTAKE

Breakfast

Toast with butter (white)
Sainsbury's natural Greek style yoghurt with honey
Water.

Midday meal

Roast chicken sandwich
Banana
Water.

Evening meal

Pasta with olive oil and cheese.
Roll (white) with butter.
Orange juice

PLEASE RECORD: In between meal snacks e.g. biscuits, sweets, chocolate, fruit
Beverages taken if not already stated

Cadbury's Turkish Delight.
Water
McVite's chocolate biscuit.

DO YOU TAKE MILK IN COFFEE: YES/NO **TEA: YES/NO**

Study No. _____

SATURDAY

DAILY FOOD AND DRINK INTAKE

Breakfast

Sainsbury's weetabix with milk and sugar
Water.
Danone strawberry yoghurt.

Midday meal

Toasted cheese and tomato sandwich (white)
Water.
Apple.

Evening meal

Lamb curry, potatoes and rice.
Water.

PLEASE RECORD: In between meal snacks e.g. biscuits, sweets, chocolate, fruit
Beverages taken if not already stated

Haagendaz Banoffi ice cream.
Cheese and biscuits.

DO YOU TAKE MILK IN COFFEE: YES/NO TEA: YES/NO

Study No. _____

SUNDAY

DAILY FOOD AND DRINK INTAKE

Breakfast

Toast (white) with butter.
Sainsbury's greek style yeghurt.
Orange juice.

Midday meal

Baguette (white) with salami, cheese and tomato.
Canned pineapples (Somerfield)
Water.

Evening meal

Tomato and basil soup
Toast with butter (white)
Plum.
Water.

PLEASE RECORD: In between meal snacks e.g. biscuits, sweets, chocolate, fruit
Beverages taken if not already stated

Apple
Water.

DO YOU TAKE MILK IN COFFEE: YES/NO **TEA: YES/NO**

Appendix 3.5: Participant information sheet: Reliability study: This information was provided as a booklet to the participants

Isle of Wight Healthcare NHS
NHS Trust

A study to determine the reliability of a Food Frequency Questionnaire used in pregnancy

The David Hide Asthma and Allergy Research Centre, St. Mary's Hospital, Newport, Isle of Wight

PARTICIPANTS INFORMATION SHEET (This information was provided to the participants as an illustrated booklet)

We are currently conducting a large scale study looking at how common food allergy and intolerance is in children on the Isle of Wight. We have previously asked the mothers of the infants in this study to complete a food frequency questionnaire during pregnancy. This questionnaire looked at the diet they were following during pregnancy, which foods they were avoiding, which supplements they were taking and also how often they have eaten certain foods.

We would like you to help us to test the reliability of this questionnaire by completing the same questionnaire that the study mothers completed, when you are 30 weeks pregnant and again at 36 weeks.

Please take time to read the following information carefully and discuss it with anyone you wish to.

Please ask us if there is anything that is not clear or if you would like more information.

Thank you for reading this.

What do we need from you?
We need you to indicate information about yourself on the recruitment questionnaire which includes your age, level of education, history of asthma, eczema, hay fever or food allergy and previous pregnancies.
We would like you to complete two food frequency questionnaires one month apart, at 30 and 36 weeks of pregnancy. This should not take much of your time.
We would also ask you the name of any vitamin or mineral supplement you might be taking and whether you are avoiding any particular foods. We are not interested in how much you eat, except for fruit and vegetables.

The dietitian or nurse recruiting will be able to go through an example of the food frequency questionnaire with you.

Why have you been chosen?
We need a certain number of pregnant women to help us with our reliability study and will approach all women at the ante-natal clinic until we have reached our target number.

Appendix 3.5: Participant information sheet: Reliability study: This information was provided as a booklet to the participants

Do you have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part we suggest you keep this information sheet and you will be asked to sign a consent form. You are free to withdraw at any time and without giving a reason. Your decision not to participate or to withdraw from the study will not in any way influence other medical care you
receive.

What will happen if you decide to agree to the study?
We will complete a recruitment questionnaire with you if you are happy to participate in the study on the day of recruitment.
We will ask you to complete a food frequency questionnaire on two occasions. The dietitian or nurse will indicate the dates on which we would like you to complete the questionnaires. The food frequency questionnaires will be given to you on the day of recruitment or posted to you nearer the time. We may even ask you to complete the first questionnaire on the day of recruitment.

You are welcome to contact the dietitian if you have any queries.

The purpose of the food diaries is by no means to evaluate your food intake during pregnancy. We only compare the data on the two food frequency questionnaires to test the reliability of the questionnaire and we do not wish you to change your eating habits in any way.

What are the benefits of taking part?
You will play a valuable role in helping us to test the reliability of our food frequency questionnaire. Once established, it will provide us with the means of assessing whether food intake during pregnancy may play a role in the development of food allergy in the child, using our large group of pregnant women previously recruited.

What are the possible disadvantages and risks of taking part?
There are no disadvantages or risk in taking part in this study other than the inconvenience of completing the food frequency questionnaires.

Will my taking part in this study be kept confidential?
All information, which is collected about you during the course of the research will be kept strictly confidential. You will not be individually identified in any reports or publications resulting from the study.

What will happen to the results of the research study?
We hope to publish the findings of the study in suitable clinical journals. We will also summarise our findings in a brief report and would be happy to share this with all those who participate in the study.

Who is organising and funding the research?
The study is funded by the Food Standards Agency. The Food Standards Agency is an independent food safety watchdog set up by an Act of Parliament in 2000 to protect the public's health and consumer interests in relation to food. Although the FSA is a Government agency, it works at 'arm's length' from Government because it doesn't report to a specific minister and is free to publish any advice it issues.

Appendix 3.5: Participant information sheet: Reliability study: This information was provided as a booklet to the participants

Who has reviewed the study?
The Food Standards Agency's Appraisal Panel has reviewed the study. In addition the study has been reviewed by the Isle of Wight, Portsmouth and South East Hampshire Research Ethics Committee.
Dr. Tara Dean (Project Lead)

How can I get more information on this study before I decide whether to take part or not?

If you have any questions concerning this study or require additional information, please contact Carina Venter the Research Dietitian:

01983 534178

The David Hide Asthma and Allergy Research Centre
St. Mary's Hospital
Newport
Isle of Wight
PO30 5TG

Consumers for Ethics in Research (CERES) publish a leaflet entitled 'Medical Research and You'. This leaflet gives more information about medical research and looks at some questions you may want to ask. A copy may be obtained from CERES, PO Box 1365, London, N16 0BW.

Thank you for taking the time to read this information booklet.

Appendix 3.6 Suggested Food Frequency Questionnaire

1. Please tick all of the following statements that are applicable to you:

I am following a normal diet	Yes[1]		No[2]	
I am excluding peanuts due to my pregnancy	Yes[1]		No[2]	
I am following a special diet due to medical reasons (please state medical condition)	Yes[1]		No[2]	
I am excluding certain foods due to personal choice	Yes[1]		No[2]	

2. Have you taken any of the following supplements during this pregnancy?

	Yes[1]	No[2]	
Multivitamin			
Multi mineral			
Calcium			
Iron			
Other			What?

3. On average, how often have you eaten these foods during pregnancy?

	Never[1]	Moderate (1-2 per month up to 1-3 per week)[2]	Frequently[3]	Uncertain[4]
Milk and milk products (e.g. custard, yoghurt, ice cream, chocolate, butter, margarines, cheese – pizza, cheese sauce, lasagne, cheezy biscuits)				
Wheat (e.g. bread, cereals, pasta, pizza, cakes, pies, pastry)				
White fish (e.g. tuna, fish cakes, battered fish,fish fingers)				
Shellfish (e.g. crab, prawns, shrimps, lobster, crayfish)				
Oily fish (e.g. mackerel, salmon, sardines, pilchards, herring, kipper, white bait, trout, crab, FRESH tuna)				
Peanuts (e.g. Bombay mix, peanut butter, peanut brittle, peanut cookies, sate, some vegetarian meals)				

4. How many helpings/portions of fruit and vegetables do you eat **daily**? (1 portion is: 1 fruit, 1 bowl of salad, 2-3 tablespoons of vegetables, 1 bowl of fruit salad, large slice of melon or other large fruit, a handful of dried fruit or a cupful of berries or grapes)

< 5 portions[1]		≥5 portions[2]	

5. Have you deliberately excluded soya from your diet during pregnancy? Yes[1] ☐ No[2] ☐

6. Have you deliberately excluded any additives from your diet during pregnancy? Yes[1] ☐ No[2] ☐

7. Do you normally smoke? Yes[1] ☐ No[2] ☐

Thank you for taking the time to complete this questionnaire

Ethical approval

ISLE OF WIGHT HEALTH AUTHORITY

LOCAL RESEARCH ETHICS COMMITTEE

Chairman: Mrs Denise Grannum

DC/sjb

28 March 2001

Dr T Dean
Director
RDSU
St Mary's Hospital
Newport
Isle of Wight

Dear Tara

PROTOCOL NO 9/01 – CHILDHOOD PREVALENCE/INCIDENCE OF FOOD ALLERGY

Thank you for your above submission.

The Committee considered your protocol on Friday 23 March 2001 and asked for the following amendments to be made:-

Page 7 item 20 – written consent from the child will be required.

Page 9 item 28 – should be yes and an explanation attached.

Page 11 item 31 should be yes.

A parent and child consent form should be included.

Information sheet – fourth paragraph – should read your not you.

Approval was given for the study to proceed once the amendments have been received by the Administrator of the Ethics Committee.

Yours sincerely

Denise J Grannum

DENISE GRANNUM
Chairman
G:\LRDC\PROT901.doc

RECEIVED 30 MAR 20

ISLE OF WIGHT HEALTH AUTHORITY

LOCAL RESEARCH ETHICS COMMITTEE

Chairman: Mrs Denise Grannum

DC/sjb

19 April 2001

Dr T Dean
Director
RDSU
St Mary's Hospital
Newport
Isle of Wight

Dear Tara

PROTOCOL NO 9/01 – CHILDHOOD PREVALENCE/INCIDENCE OF FOOD ALLERGY

Thank you for your letter of 18 April regarding the amendments to the above submission.

The Chairman considered your amendments and has agreed that approval can now be given for the project to go ahead.

We wish you every success with your study and would ask you to inform us of the outcome in the future.

If, for any reason, you cannot undertake your study, please inform the Committee, quoting the protocol number and the date of approval.

As the Isle of Wight and Portsmouth Health Authorities have now merged the Local Research Ethics Committee's office is now based in Portsmouth. If you should need to contact the LREC administrator her name is Sandra Jenkinson, Isle of Wight Portsmouth and South East Hants Health Authority, Finchdean House, Milton Road, Portsmouth, PO3 6DP Tel: 023 9283 8340.

Yours sincerely

S J Butchers

pp DENISE GRANNUM
Chairman

G:\LRDC\PROT901a doc

IOW Portsmouth and SE Hampshire
Local Research Ethics Committee
Finchdean House
St Mary's Hospital
Milton Road
Portsmouth
Hampshire
PO3 6DP

Tel: 023 9283 5139
Fax: 023 9285 5312

Our Ref: **04/Q1701/18**
Your Ref:

PRIVATE AND CONFIDENTIAL
Dr Tara Dean
The David Hide Asthma and Allergy Research Centre
St Mary's Hospital
Newport
Isle of Wight
PO30 5TG

24 May 2004

Dear Dr Dean

Full title of study: Validation of a self-administered food frequency questionnaire (FFQ) designed to determine the frequency of food consumption during pregnancy
REC reference number: 04/Q1701/18
Protocol number: 1

The Research Ethics Committee reviewed the above application at the meeting held on 21 May 2004.

Ethical opinion

The Committee notes that all issues from the previous correspondence have been addressed.

The members of the Committee present gave a favourable ethical opinion to the above research on the basis described in the application form, protocol and supporting documentation.

The favourable opinion applies to the following research site:

Site: Isle of Wight NHS Trust
Principal Investigator: Dr Tara Dean

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The documents reviewed and approved at the meeting were:

Document Type: Application
Version: 3
Dated: 26/03/2004
Date Received: 29/03/2004

Document Type: Investigator CV
Version: Dr T Dean
Dated: 29/03/2004
Date Received: 29/03/2004

Document Type: Protocol
Version: 1
Dated: 24/03/2004
Date Received: 29/03/2004

Document Type: Covering Letter
Version:
Dated: 25/03/2004
Date Received: 29/03/2004

Document Type: Summary/Synopsis
Version: 1
Dated: 24/03/2004
Date Received: 29/03/2004

Document Type: Letter from Sponsor
Version: Foods Standards Agency
Dated: 03/09/2001
Date Received: 29/03/2004

Document Type: Copy of Questionnaire
Version: 1
Dated: 24/03/2004
Date Received: 29/03/2004

Document Type: Participant Information Sheet
Version: 1
Dated: 24/03/2004
Date Received: 29/03/2004

Document Type: Participant Consent Form
Version: 1
Dated: 24/03/2004
Date Received: 29/03/2004

Document Type: Response to Request for Further Information
Version:
Dated: 07/05/2004
Date Received: 11/05/2004

Document Type: Other
Version: 1
Dated: 24/03/2004
Date Received: 29/03/2004

Management approval

The study may not commence until final management approval has been confirmed by the organisation hosting the research.

All researchers and research collaborators who will be participating in the research must obtain management approval from the relevant host organisation before commencing any research procedures. Where a substantive contract is not held with the host organisation, it may be necessary for an honorary contract to be issued before approval for the research can be given.

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached

sheet.

Notification of other bodies

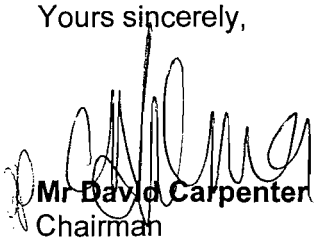
We shall notify the research sponsor, Isle of Wight NHS Trust that the study has a favourable ethical opinion.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

REC reference number: 04/Q1701/18	**Please quote this number on all correspondence**

Yours sincerely,



Mr David Carpenter
Chairman

Email: claire.fleming@ports.nhs.uk

Enc/s
R&D

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