The prevalence of food allergy and weaning practices in a birth cohort of UK infants

The Prevalence of Infant Food Allergy (PIFA) Study

T07046

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Abbreviations

DBPCFC	Double-blind, placebo-controlled food challenge
EAACI	European Academy of Allergy and Clinical Immunology
FSA	Food Standards Agency
ISAAC	International study of asthma and allergy in childhood
IQR	Interquartile range
LCPUFA	Long chain polyunsaturated fatty acid
NCT	National Childbirth Trust
SD	Standard deviation
SpIgE	Specific Immunoglobulin E
SPT	Skin prick testing
WTCRF	Wellcome Trust Clinical Research Facility

1. Executive Summary

Food allergy is a relatively frequent problem in infancy that is associated with considerable morbidity for the child and burden to the family. There is currently no cure for food allergy. The condition necessitates vigilance by the family to avoid the relevant allergen and they need to be prepared to treat an anaphylactic reaction. The reasons why an infant develops a food allergy are unclear, partly because the number of participants in previous studies have been too small to provide definitive evidence. It has been suggested that maternal ingestion of allergenic foods during pregnancy, or their early introduction during infancy, is responsible for food allergy but the evidence is conflicting. More recent evidence has suggested that the route of exposure to the food allergen may be as or more important than the timing.

To explore the aetiology of food allergy in infancy, the pan-European EuroPrevall Project was funded by the European Union Framework 6 Programme. A United Kingdom cohort was added to the EuroPrevall birth cohort with funding from the UK Foods Standards Agency (FSA). The aims of the FSA funded, UK study were to recruit a UK EuroPrevall birth cohort by recruiting mothers to be during pregnancy (Objective 1), assess the infants' health by questionnaire at 12 and 24 months (Objective 5) and explore and evaluate the prevalence and pattern of food allergies in infants in the UK (Objective 3). Uniquely in the UK birth cohort, mothers kept a prospective diary of their infants' diet for 12 months (Objective 2) to provide an opportunity to assess whether specific nutritional factors (Objective 4) or specific complementary feeding patterns (Objective 6) are associated with the development of food allergy.

During the study, a total of 1192 pregnant women (delivering 1203 infants as 11 women had twins), were recruited into the study between September 2005 and September 2007 in collaboration with the Winchester and Eastleigh midwives (Objective 1). The recruitment target was revised from 1500 to 1200 recruits per birth cohort centre with the addition of further EuroPrevall sites which increased the total number of infants recruited across Europe and reduced the number needed from each country. A total of 1197 infants satisfied the inclusion criteria for the UK cohort with baseline (i.e. 'at the point of recruitment') data being available for 1170. In total, 12274 infants were born into the EuroPrevall Birth Cohort across all the European sites up to July 2009. A total of 733 were assessed at 12 months and 823 at 24 months. Given this follow up rate, 823 has been used as the denominator for the rest of the study findings. The UK mothers were representative of the recruitment area in terms of geography, age, education and ethnicity although they tended to be older and better educated than the average for the UK population. Infant food diaries were returned by the majority of mothers (Objective 2). A total of 594 completed diaries until 24 weeks of age with 241 completing them for the whole first year. Mothers who had left education later tended to complete the food diaries for a longer period of their child's infancy than those who left education earlier.

A total of 173 parents contacted the study team during the study with concerns about food related symptoms arising in their infant, and a further 61 were identified from the 12 and 24 month questionnaires (Objective 3). This has given a high rate of 28.4% (95% confidence interval (CI) 25.4 – 31.6%) for parent perceived food allergy. Only 135 of these infants were thought to possibly have food allergy on the basis of the study triage system and were therefore invited for clinical assessment. That is a physician perceived prevalence rate of (16.4%, CI 13.9 – 19.1%). Of these, 74 were provisionally diagnosed as having a food allergy because they had specific immunoglobulin E (allergy antibody) SpIgE to food of at least 0.35kU_A/l, and/or a positive skin prick test (wheal of at least 3mm) and/or a convincing clinical history of food allergy. That corresponds to 9.0% (CI 7.1 – 11.2%) of the whole cohort being provisionally diagnosed as having a food allergy. In

many of these 74 infants, a double-blind, placebo-controlled food challenge ruled out allergy giving a confirmed cumulative prevalence of food allergy among the entire cohort of 5.0% (CI 3.6 – 6.7%). This is comparable with the current literature and represents a considerable health burden for UK families. The common foods causing a reaction were cows' milk (prevalence of 3.0%), egg (prevalence of 2.6%), peanut (prevalence of 0.7%), soy (prevalence of 0.4%), wheat (prevalence of 0.2%) and fish (prevalence of 0.1%).

To meet objective 4, the available *quantitative* food diary data was analysed from birth until symptoms developed. A total of 31 of the food allergic infants had associated food diaries providing adequate quantitative data and these were analysed along with diaries from 62 age-matched control infants (Objective 4) who had no symptoms of food allergy. There were no significant differences in any of the pre-specified nutrients between the groups.

A total of 733 (63%) and 823 (70%) participants were assessed at 12 and 24 months respectively (Objective 5). The 12 month questionnaire data indicate that 90% of infants received at least some breast milk, but the median duration of breast feeding was only 5 months (inter-quartile range 2.1 to 8.0 months).

Since some mothers kept food diaries but did not give quantities consumed, more diaries were available for food diary pattern analysis than for quantitative analysis. Consequently, 39 of the infants diagnosed with a food allergy had food diaries giving details of *food intake patterns* from birth and these were analysed along with the diaries of 78 age-matched infants who did not have a food allergy (Objective 6). There were no significant differences in breastfeeding initiation or duration, duration of exclusive breastfeeding, age at first infant formula, age at first cows' milk protein, age at first egg, or age at first wheat introduction between the groups (food allergic infants versus control infants). However allergic infants were introduced to solids earlier than their controls (p=0.049). Principal Component Analysis identified four feeding patterns that were found to be significantly different between symptomatic and control infants. Factors that were protective for food allergy were concurrent feeding of breast milk whilst solids were introduced (p=0.044), concurrent feeding of breast milk and formula (p=0.008), diversity of diet (p=0.02) and following the infant feeding guidelines (p=0.027). The infant guidelines food pattern was characterised by high component scores for fresh fruit, dried fruit and fish and low scores for crisps, commercial baby foods given daily and potato products.

Outside the scope of T07046, by contributing to the European EuroPrevall Project, it will be possible for the UK birth cohort prevalence and experience of food allergy in the first 2 years of life to be compared with the rest of Europe. This may highlight important nutritional, cultural and climatic influences on the pathogenesis of food allergy. This is only possible with the critical mass of participants that the EuroPrevall birth cohort has successfully recruited and followed. This also provides the potential to make important clinical advances in diagnostic testing for food allergy and our understanding of the genetics of food allergy.

In summary, food allergy is an unmet need in early childhood. At present we do not understand why some infants develop this problem and we are unable to cure them. The Europrevall study aims to improve our understanding these issues. The results from the first two years of the lives of the 1197 infants in UK part of the Europrevall birth are covered in this report. Nearly a third had parent perceived food allergy during this time. Only a third of these infants had symptoms or allergy test results that satisfied our criteria for physician perceived food allergy. These infants underwent the gold standard test for food allergy, a double-blind, placebo-controlled food challenge. This confirmed food allergy in one in twenty infants. The commonest foods giving rise to reactions were cow's milk, egg, peanut, soy, wheat and fish. Using daily food diary data from the first year of life

that is unique to the UK cohort, no significant differences in the level of micro- or macro-nutrients between those infant with or without food allergy. An analysis of the pattern of weaning, using these diaries, showed that allergic infants were introduced to solids earlier, were less likely to be receiving breast milk while starting a cow's milk formula or starting solids, followed a less diverse diet and did not follow the infant feeding guidelines. In the near future we will be looking at the combined results from all the 9 European Europrevall birth cohorts.

2. Background

2.1 Food allergy as a major problem for families of UK infants

Food allergy is a major problem for infants and their families in the UK and it frequently presents in early life. Food allergy results from a hypersensitivity reaction mediated by an aberrant immunological reaction to an otherwise harmless food. Immediate IgE-mediated food allergy results in symptoms within minutes. Typically these include angioedema (swelling), urticaria (a "nettle sting" like rash), rhinoconjunctivitis (itchy, runny eyes and nose) and vomiting. More severe reactions can present as anaphylaxis with difficulty in breathing (eg stridor or wheeze) or cardiovascular collapse due to hypotension. Fatal cases of food-induced anaphylaxis are still seen in the UK (Pumphrey and Gowland 2007). The second form of food allergy presents as a more delayed non-IgE mediated reaction. Typically symptoms start at least 4 hours post contact with the food with vomiting, abdominal pain, diarrhoea and eczema predominating. The pathogenesis of food allergy will be discussed in the next section.

At present there is no cure for food allergy, although some infants outgrow it. Management is therefore dependent on avoidance and being prepared to treat any allergic reactions. Avoidance is challenging as food products are frequently not labelled in such a way to make the presence of an allergen obvious, examples are loose foods or food from restaurants. This is further complicated by the lack of education of health professionals in teaching families how to avoid specific allergens. To be adequately prepared to manage an allergic reaction, many families need to carry medication such as antihistamine and adrenaline or auto-inhalers with them. It is well established from research carried out that many do not do this. The need to avoid trigger foods, to carry rescue medication and the anxieties associated with the potential for further allergic reactions represents a considerable burden for children with food allergy and their families Additionally, food allergy has a significant socioeconomic impact on affected families. Food allergy in infancy is therefore an important health problem for the UK.

2.2 Prevalence of food allergy in childhood

The prevalence of food allergy in children is difficult to establish with certainty, mainly because of the challenges in correctly defining it (Objective 3). Many studies have simply documented reported food allergy (Rona et al. 2007). A recent meta-analysis by the EuroPrevall project has concluded that although there is significant variation in the prevalence of self-reported food allergy in different populations, the prevalence of self reported food allergy is over 10% (as shown in Table 2.1) (Rona et al. 2007). In an attempt to refine and improve the diagnosis of food allergy, some investigators have utilised a definition that includes symptoms in association with the food and sensitisation as defined by a positive skin prick test or serum specific IgE. With this definition, the prevalence of food allergy is around 3% (Rona et al. 2007) with the important allergens in infancy being milk, egg and peanuts (Table 2.2). With some infants growing out of their food allergy (ie they are able to eat the food allergen without any clinical symptoms as they get older) and the rate of false positive results with specific IgE and skin prick testing, the only definitive test for food allergy is an oral food challenge. The early symptoms are often subjective and therefore a double blind placebo controlled food challenge is the gold standard test (Venter et al. 2007). The meta-analysis by the EuroPrevall group suggests that the prevalence of food allergy to any food based on challenge is about 3% (Rona et al. 2007) (Table 2.3). A characteristic of all of these analyses is the variation between prevalences quoted by the different authors used in the meta-analysis. The reason for

this is unclear, but it is likely to represent real differences in the prevalence of food allergy in different countries. This strongly suggests that a child's experience growing up in different countries may heavily influence the chances that they will develop a food allergy. It is therefore, very important that the rates of food allergy are compared between countries and interpreted in terms of potential risk factors to which children are exposed. To date, this is being impeded by the lack of homogeneity in the protocols used to assess food allergy.

Table 2.1. Prevalence (%) of self-reported food allergy to any food in the population stratified for children 0 to 4 years and 5 to 16 years. Figures from Rona *et al* (2007).

Study	Year	Country	Prevalence of self-reported food allergy
0-4 years			
Eggesbo	1999	Norway	36%
Kristjansson	1999	Sweden	6%
Kaczmarski	1999	Poland	10%
Osterballe	2005	Denmark	15%
Kristjansson	1999	Iceland	5%
5-16 years			
Bockel-Geelkerken	1992	Netherlands	12%
Brugman	1998	Netherlands	8%
Penard-Morand	2005	France	2%
Rance	2005	France	7%
Perreira	2005	United Kingdom	12%
Kanny	2001	France	4%
Aardoom	1997	Holland	4%
Roehr	2004	Germany	38%
Combined			**12%**

Table 2.2. Prevalence (%) of symptomatic and sensitized (by SPT≥3mm or spIgE >0.35kU/l) people in the population to any food, cows' milk, egg, peanut, stratified by age. Figures from Rona *et al* ((2007).

Study	Year	Country	Prevalence of symptoms and sensitisation to food
Any food			
0-4 years			
Kristjansson	1999	Iceland	2.0%
Kristjansson	1999	Sweden	2.0%
Kaczmarski	1999	Poland	4.3%
5-16 years			
Roehr	2004	Germany	4.5%
Adults			
Zuberbier	2004	Germany	2.1%
Bjornsson	1996	Sweden	4.4%
Woods	2002	Australia	2.3%
Combined			**3.0%**
Peanut			
0-4 years			
Kristjansson	1999	Sweden	0.2%
Kristjansson	1999	Iceland	0.2%
Dalal	2002	Israel	0.0%
Tariq	1996	United Kingdom	0.7%
5-16 years			
Perreira	2005	United Kingdom	0.9%
Roehr	2004	Germany	1.0%
Kagan	2003	Canada	1.5%
Adults			
Zuberbier	2004	Germany	2.4%
Combined			**0.7%**
Egg			
0-4 years			
Dalal	2002	Israel	0.4%
Arshad	2001	United Kingdom	2.4%
Kristjansson	1999	Iceland	1.2%
Kristjansson	1999	Sweden	1.5%
5-16 years			
Roehr	2004	Germany	0.6%
Adults			
Zuberbier	2004	Germany	0.8%
Combined			**0.9%**
Milk			
0-4 years			
Kristjansson	1999	Iceland	0.6%
Kristjansson	1999	Sweden	0.4%
Garcia Ara	2003	Spain	1.9%
Dalal	2002	Israel	0.3%
Host	1990	Denmark	2.0%
5-16 years			
Roehr	2004	Germany	0.1%
Adults			
Woods	2002	Australia	0.1%
Zuberbier	2004	Germany	0.1%
Combined			**0.6%**

Table 2.3. Prevalence (%) in the population based on food challenge provocation tests to any food, and separately to fish, milk, and egg, stratified by age. Reproduced from Rona *et al* (2007).

Any food

Study	Year	Country	Prevalence of challenge proven food allergy
0-4 years			
Osterballe	2005	Denmark	2.5%
5-16 years			
Perreira	2005	United Kingdom	2.0%
Roehr	2004	Germany	4.0%
Adults			
Osterballe	2005	Denmark	12.0%
Zuberbier	2004	Germany	3.5%
Young	1994	United Kingdom	2.0%
Janssen	1994	Holland	2.0%
Combined			**3.0%**

Fish

0-4 years			
Kristjansson	2005	Iceland	1.0%
Kristjansson	2005	Sweden	0.2%
Osterballe	2005	Denmark	0.1%
Adults			
Osterballe	2005	Denmark	0.1%
Combined			**0.2%**

Milk

0-4 years			
Host	1990	Denmark	2.2%
Osterballe	2005	Denmark	0.6%
Madrigal	1996	Mexico	1.7%
Schrander	1992		2.2%
Altintas	1995	Turkey	1.5%
5-16 years			
Roehr	2004	Germany	0.2%
Adults			
Osterballe	2005	Denmark	0.3%
Janssen	1994	Holland	0.1%
Combined			**0.9%**

Egg

0-4 years			
Madrigal	1996	Mexico	0.6%
Osterballe	2005	Denmark	1.6%
5-16 years			
Roehr	2004	Germany	0.2%
Adults			
Osterballe	2005	Denmark	0.1%
Combined			**0.3%**

2.3 Pathogenesis of food allergy in childhood

Food allergy results from an misdirected immunological response to a harmless food protein (Sicherer 2002). It is either IgE mediated or non IgE mediated depending on the type of hypersensitivity responses involved (Johansson et al. 2004).

IgE is an immunoglobulin normally present at very low levels in the plasma of non-allergic individuals, but levels are raised in patients suffering from allergic conditions such as asthma, atopic dermatitis and anaphylaxis. Production of allergen specific IgE is due to class switching of B-cells to produce this immunoglobulin isotype in preference to immunoglobulin subtypes. B cells undergo class switching and affinity maturation when they become activated for the first time through a sequence involving antigen presenting cells and T cells. This is termed sensitisation. IgE has a very short life in plasma (half-life less than 1 day) but can remain fixed to mast cells in tissues for weeks or months, waiting to come into contact with the specific allergen to which it is directed. When food allergens penetrate mucosal barriers and reach food specific IgE antibodies bound to mast cells or basophils, this causes the mast cell to degranulate, releasing vasoactive and chemotactic mediators. These induce vasodilation, vascular leakage, smooth muscle contraction and mucus secretion, which result in the immediate symptoms associated with a food allergic reaction.

Non-IgE mediated food allergy occurs via a T-cell mediated mechanism where T cells that have been activated to food allergens release cytokines which initiate an inflammatory response causing the delayed symptoms associated with non-IgE mediated food allergy.

The pathogenesis of childhood food allergy is unclear. It is a two part process with firstly sensitisation and then the development of clinical allergy. Many children are sensitised to a food protein meaning that they have specific IgE or T-cells that can react to food proteins. Many of these sensitised children though do not manifest clinical allergy to these foods. It is unclear what governs whether a child is merely sensitised or is clinically allergic but there are suggestions that there is a considerable genetic influence and that early exposure to food allergens may be important. Food allergy seems to cluster with other atopic diseases in individuals. Many infants with eczema have associated food allergy (Eigenmann et al. 1998). Additionally, a number of studies have shown that food allergy is a risk factor for the later development of other atopic diseases such as asthma (Tariq et al. 2000). There has been considerable interest in understanding the genetic basis of atopic disease. For common diseases such as asthma, many genes have been implicated although they do not replicate across all populations (Ober and Hoffjan 2006). Understanding of the genetics of food allergy is still very much in its infancy (Cochrane et al. 2009). The infant gut has to deal with a large number of novel foreign proteins and serious reactions to safe food allergens must be avoided while the infant actively responds to pathogens such as viruses and bacteria. Whether contact with a foreign protein results in immunological tolerance or SpIgE production is thought to depend on how it is handled in the gut and presented to the immune system. Most common food allergens are not readily altered by the digestive factors of low pH or proteolytic enzyme activity and so are presented to the immune system in a well conserved structure. The timing and quantity seem to be important. Peanut is introduced into the infant diet in Israel unlike in the UK, unlike the UK they have very little peanut allergy tolerance (Du Toit et al. 2008). This has lead to the concept of high zone tolerance to food (Du Toit et al. 2008) with exposure of the immune system to high doses of allergen in the first few years on an infant's life leading to immune tolerance of potential allergens. (www.leapstudy.org.uk). The route seems to be critical with a suggestion that exposure to a food allergen via the skin is more likely to lead to sensitisation (Lack et al. 2003). Timing of first exposure to potential allergenic food proteins is also thought to be important. Many groups have

suggested exclusive breast feeding for at least 6 months with concurrent introduction of the allergenic foods as a way of preventing the development of food allergy (Poole et al. 2006)(Snijders et al. 2008). Evidence is mounting though to suggest that delayed introduction of allergenic foods may actually promote the development of allergy. For example, there is ten-fold more peanut allergy in Jewish children in the UK compared to those in Israel (Du Toit et al 2008). These differences cannot be explained by demographic differences the UK. We are, therefore, in need of more data to understand the relationship between weaning and the onset of food allergy particularly with respect to the pattern of introduction of foods and coexisting breast feeding.

2.4 Weaning practices in the UK and across Europe and food allergy development

There is a lack of evidence on the effect of weaning (more correctly termed complementary feeding) (Sritharan and Morgan 2003) in relation to the later development of food allergy. In spite of this, delaying the introduction of solids into an infant's diet has been widely advocated as an allergy prevention measure. The question of when to introduce solids, and whether the introduction of allergenic foods should be delayed, is an area of confusion. Observations have led to the concept of the "window of vulnerability" in early infancy as the optimal period where atopic 'priming' occurs, consequently implementation of feeding guidelines to prevent food allergy has occurred despite the lack of a significant evidence base to support them. Furthermore, many national guidelines continue to be modified despite the absence of any controlled data to demonstrate either evidence for effect or harm of previous guidelines (Greer et al. 2008). Therefore, there is a need to examine the relationship between solid food introduction and the later development of food allergy.

Given the current recommendations in many countries to delay the introduction of all complementary foods until 6 months, and for much longer delays for specific allergenic foods, it is surprising that the evidence of the effects of delaying the introduction of allergenic foods into the infant diet is extremely limited. There has been little research looking solely at the relationship between solid food introduction and the later development of allergic disease. Fergusson and Horwood looked at both the timing and rate of introduction of solids into an infant diet with the later development of eczema (Fergusson and Horwood 1994) and found that introduction before 3 months age and the number of foods introduced was associated with an increased incidence of eczema. Other studies have looked at the relationship between timing of complementary feeding and allergy development but differences in methodology makes it difficult to establish a relationship either way (Tarini et al. 2006). A recent systematic review which considered studies of complementary feeding before 4 months of age could find little data linking early solid feeding and allergic conditions outside that demonstrated by Fergusson and called for additional trials to look at the relationship between the introduction of solids and allergic risk (Tarini et al. 2006).

More recently, infant feeding data collected as part of birth cohort studies have been analysed to investigate the relationship between solid food introduction and the later development of atopy (Filipiak et al. 2007; Snijders, et al. 2008; Zutavern et al. 2004; Zutavern et al. 2008). No study found any benefit on allergic outcome by delaying the introduction of solids and two found an association between the delayed introduction of milk (Snijders, et al. 2008) and egg allergy (Filipiak, et al. 2007; Zutavern, et al. 2008) and increased incidence of eczema and atopic sensitisation. More recently it has been suggested that children exposed to cereal grains after 4 but before 6 months of age (as

opposed to after 6 months of age) are protected from the development of wheat-specific IgE. However, all studies collected feeding data retrospectively which makes the findings vulnerable to both recall bias (which is when a respondent's answer to a question is affected by their memory) and reverse causality (where the association seen is due to the presence of symptoms, not the cause of those symptoms)

In summary, further research is needed to establish what affect the timing of the introduction of solids in general and allergenic foods in particular into the infant diet has on allergic disease and how concurrent breast feeding might influence any relationship.

2.5 The EuroPrevall Project

T07046 is part of a multi-disciplinary trans-sectorial project entitled EuroPrevall which is a multidisciplinary project involving 53 partners with an EU contribution of 14.5 Million Euros (9.6 Million Sterling). http://www.europrevall.org.
The overall objective of this project is to deliver the information and tools necessary for policy makers, regulators and the food industry to effectively manage food allergies across Europe and hence deliver an improved quality of life to food allergic consumers. This will be achieved by integrating information and tools related to:

1. Characterising patterns and prevalence of food allergies across Europe in infants [involving birth cohorts in 9 centres], children and adults [using cross-sectional surveys in 10 centres].
2. Using samples and information from the surveys to identify risk factors (environmental, microbial, genetic) and novel predictor models (biochemical or genetic) for food allergy would facilitate implementation of preventive measures e.g., during pregnancy.
3. Developing serological methods capable of improving the quality of food allergy diagnosis and hence reducing need for confirmatory food challenge tests.
4. Investigating how the food matrix affects the allergenicity of foods, including developing new reference materials for food challenges which are truly blind and based on "real" food matrices.
5. Developing and applying instruments to determine the impact of food allergies on the quality of life and its economic cost for sufferers and their families

T07046 is one of the 9 birth cohorts which are part of the EuroPrevall work that aims to characterise the patterns and prevalence of food allergies across Europe (Keil et al. 2009). The details of the other centres of the EuroPrevall birth cohort are shown in table 2.1. Six of the centres were funded by the EuroPrevall project but 3 centres (Netherlands, Italy and the United Kingdom) were funded nationally to maximise the statistical power of the birth cohort work, and to incorporate different geographical characteristics. The Food Standards Agency funded the UK cohort to support the EuroPrevall project and also obtain additional data specific to a UK birth cohort, specifically details of how infants are fed in the first year of life.

Involvement in this European project will also allow the UK experience to be compared with the rest of Europe looking at how the cultural and climatic variation within a continent impacts on the prevalence of food allergy. These influences will particularly focus on cultural differences in dietary habits during pregnancy and infancy. Additionally, it will be possible to assess the quality of life and economic burden of food allergy in the UK compared to the rest of Europe.

Table 2.1. Details of EuroPrevall birth cohort study centres

Country	Centre	Principal Investigator
Germany	Charite Hospital, Berlin	Dr Kirsten Byer
Greece	National and Kapodistrian University of Athens	Dr Paraskevi Xepapadaki
Iceland	Landspitali University Hospital Institute for Medical Laboratory Sciences, Reykjavik	Dr Sigurveig Sigurdardottir
Lithuania	Vilnius Hospital, Vilnius	Dr Ruta Dubakiene
Poland	Medical University of Lodz	Dr Marik Kowalski
Spain	University Hospital La Paz, Madrid	Dr Cristina Pascual
The Netherlands	Emma Children's Hospital, Amsterdam	Dr Aline Sprikkelman
Italy	Macedonio Melloni Hospital, Milan	Dr Alessandro Fiocchi
United Kingdom	Southampton General Hospital	Dr Graham Roberts

3. Aims and objectives of the FSA-funded T07046 project

The overall aim of T07046 was to evaluate the prevalence and pattern of food allergies in infants in the UK as part of the EuroPrevall multi-centre birth cohort study using that study protocol (Objectives 1, 3 and 5). In addition, the FSA incorporated additional objectives into the study's scope of work to maximise the information gleaned from the birth cohort established as part of EuroPrevall. These additional objectives related to collecting prospective dietary intake data from the infants who were part of T07046 (objective 2). Initially these data were collected to establish general infant feeding practices for the cohort, and also to investigate whether the development of food allergy was related to nutritional differences in the infant diet. (Objective 4 subtasks 1 and 2) but once further uses for the data were identified then additional objectives were added into the Scope of Work. Objective 6 looking at how complementary feeding practises may be associated with the development of food allergy was added to the scope of work in 2007, and Objective 4 subtask 3 looking at the nutritional adequacy of a milk exclusion diet was added in 2010).

Objective 1 (EuroPrevall-wide objectives)
Recruitment of Study volunteers
Subtask1 Application for ethical approval
Subtask 2 Questionnaires developed and diagnostic criteria agreed
Subtask 3 Enrolment of Volunteers

Objective 2 - Collection of dietary intake information

Objective 3 - (EuroPrevall-wide objective)
Clinical evaluation of allergic sensitisation (including DBPCFC)

Objective 4 - Analysis of dietary intake information
Subtask 1 Processing of dietary intake data from the whole birth cohort
Subtask 2 Analysis of detailed diet data from those infants diagnosed with food allergy and their controls
Subtask 3 Additional analysis of infant dietary data to investigate the nutritional adequacy of a milk exclusion diet

Objective 5 - (EuroPrevall-wide objective)
Administration of telephone questionnaires at 1 and 2 years of age

Objective 6 - To identify specific complementary feeding patterns associated with the development of food allergy by 1 and 2 years of age, by Principal Component Analysis

Objective 7 - Final Report

4. Study Methodology

4.1. Birth Cohort methodology

T07046 has a longitudinal prospective cohort design starting from birth. Pregnant women booked with the Winchester and Eastleigh midwives were approached to participate in the study. This was done at both antenatal appointments and antenatal classes. This was supported by study flyers placed in the women's booking paperwork as well as advertisements to general practitioners and the National Childbirth Trust NCT newsletter. This was all supported by an active education programme for the local midwives undertaken by the study midwife (TK).

A central telephone number and email address were provided for midwives and potential participants to contact. Our study administrator (LG) or one of a number of part-time research assistants (JR, LB, EG, EO) would then phone potential participants, briefly describe the study and send the detailed study information sheet. They would then phone back a week later and if the potential participant agreed to take part in the study, would book an appointment for them to see one of the study research fellows (KG or EO). Usually this was a home visit but sometimes it would be a visit arranged to take place at either Winchester or Andover hospitals. At this visit, informed written consent was obtained (see Appendix A). A baseline questionnaire giving information on socio-economic, environmental and family allergy history was collected (see appendix B)

The recruiting period for this study was from September 2005 through to September 2007.

At delivery, midwives collected a 20 ml sample of cord blood (divided into a plain and an EDTA tube) and a 10 ml sample of maternal serum. These samples were transported by the NHS intra-hospital transport system to the Pathology Department at Southampton General Hospital. They were then delivered to the Wellcome Trust Clinical Research Facility (WTCRF) where the laboratory technician processed the specimens and froze the serum at -80°C. Batches of samples were then shipped to Charite, Berlin for storage. The cord and maternal samples of any child who attended the WTCRF (either for a symptomatic or control appointment) were assayed for Specific IgE to cows' milk, egg, peanut, soy, wheat, cod.

Parents were contacted after the birth to complete the post-natal information required for the baseline questionnaire. From this time and throughout the first year diaries were sent out bimonthly and freepost envelopes were provided for their return to the study office. This mailing also contained a symptom sheet that was to be sent back with the food diaries. This enabled parents/carers to inform the study team prospectively of any symptoms their infant was suffering from that may have been food allergy related. Parents were contacted by a member of the study team if symptoms persisted for two or more months.

When each infant reached the age of 12 and then 24 months they were contacted by a member of the study team to arrange an appointment to administer the telephone questionnaire. The questionnaire was developed from the INFABIO study (an EU Framework 5 funded project), and the International study of asthma and allergy in childhood (ISAAC) questionnaire (appendices D and E). The questionnaire covered nutrition including breast feeding and the introduction of solids, symptoms suggestive of atopic diseases and their treatment, detail of any allergic reactions to food, the use of antibiotics by the child, their family's health, environmental exposures such as exhaled cigarette smoke, and childcare. For the non-English speaking birth cohort centres, the questionnaire was translated into each of their national languages and then back

translated by a second person to ensure that it had face validity. The questionnaire took between 30 to 60 minutes to complete and those members of the study team who administered the questionnaire had been trained to do so. The questionnaires were hosted on the EuroPrevall website that was developed by Baigent, UK. The questionnaire was designed such that data could be entered while the participant's parents were interviewed with data storage on a remote backed up server. A paper questionnaire of the results was printed out to be included in the participant's study records.

Infants were not seen for a clinical assessment unless there was a possibility that they had had an adverse reaction to food. Parents of participants in the birth cohort were asked to contact the study team if their child developed signs of atopic diseases. Examples of such symptoms were atopic dermatitis, recurrent wheeze, recurrent vomiting or diarrhoea and adverse reactions to a food. They were reminded of this when they received their food diary at 2 monthly intervals.

Additionally, any possible symptomatic children whose parents had not contacted the study team could be identified by their answers to the 12 and 24 month questionnaire (e.g. if they thought their child had had a reaction to a food)

Possible cases were assessed via telephone (KG, GR) and those fulfilling the criteria for assessment were invited to the Wellcome Trust Clinical Research Facility for a clinical assessment. Criteria for invitation for assessment included hypersensitivity symptoms with food and eczema that did not respond to topical emollients (see appendix G) The symptomatic visit consisted of skin prick testing, blood sample, SCORAD for eczema, and auscultation (assessment for respiratory symptoms) The symptomatic questionnaire was completed (appendix H), and a physical examination undertaken by the attending paediatrician (appendix I).

Skin prick testing was undertaken with extracts to the standard panel of allergenic foods consisting of cows' milk, egg, peanut, soy, wheat, cod and a positive (histamine) and a negative control (saline). Additionally, the infant was skin prick tested with any other potential food allergen that had been identified by clinical history. A single headed lancet (ALK, Denmark) was used with wheals being read after 15 minutes. The average of the widest diameter and the diameter perpendicular to this was taken. The test was postponed if the participant had taken any antihistamine the week prior to the assessment. Additionally, a blood sample was taken. This was spun and a serum stored at -80C. The specimens were shipped to Charite Hospital, Berlin where specific IgE levels were assayed to cows' milk, egg, peanut, soy, wheat, cod and any other potential food allergen that had been identified by clinical history (Pharmacia CAP system, Phadia, Sweden).

For every participant with a potential food allergy, two randomly selected age-matched control children from the birth cohort were invited to attend. Two controls were selected to increase the statistical power and allow for drop out of controls during the follow up annual reviews. These were selected by approaching parents of infants with birthdays just before or after the index participant until two controls were found. Control participants were assessed with the same symptomatic questionnaire and physical examination. Additionally, they had a blood sample taken for measurement of serum specific IgE as per the symptomatic participants. They were not skin prick tested nor did they undergo a food challenge.

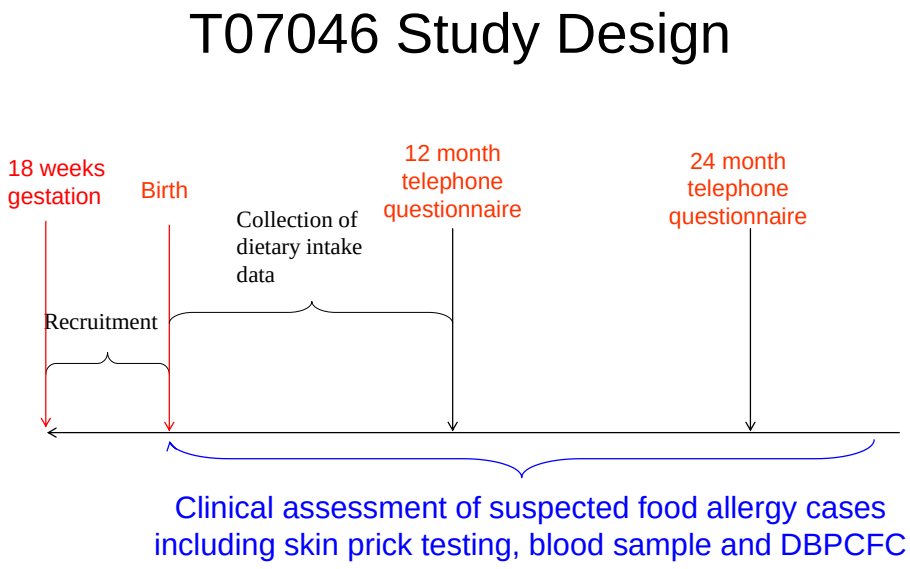
Any infant with SpIgE to food ≥0.35kU$_A$/l, and/or a positive skin prick test (wheal diameter ≥3 mm) and/or a convincing clinical history of food allergy was placed on an exclusion diet for the suspected food. If symptoms improved then the child attended the WTCRF for

a double blind placebo controlled food challenge (DBPCFC). The final outcome measure for this study was food allergy diagnosed by DBPCFC.

Children under 6 months of age were not challenged to eggs, and children under 12 months of age were not challenged to seeds, tree nuts, peanuts, fish or shellfish due to the EuroPrevall study protocol. For atopic dermatitis, challenges were undertaken if a 14 day elimination diet improved the eczema. In children who were fully breastfed, food challenges were postponed until the child was taking adequate amounts of infant formula or other food that could be used as a vehicle for the food challenge. The suspected allergen was excluded from the child's diet for a minimum of a week prior to challenge. Active and placebo challenges were carried out on separate days in a random order with at least 48 hours between challenges. Where a child's eczema worsened after the first part of the food challenge, the second part was postponed until it had returned to its pre-challenge state. Doses of increasing quantities of allergen were given at least 20 minutes apart. The doses were 3µg, 30µg, 300µg, 3mg, 30mg, 90mg, 300mg, 900mg and 3 g of allergenic protein. If there were subjective symptoms, the next dose was not given until 40 minutes had passed. Children remained under supervision for a minimum of 2 hours after the last dose and were only discharged if they were medically stable. A follow-up phone call was made to the family the next day. Full details of the challenge protocol are given in appendix J. All challenges were supervised by an experienced paediatric research nurse with training in paediatric food challenges. Additionally, they were supervised by a paediatrician who was immediately available for any severe reactions. A EuroPrevall expert committee was established to support centres with difficult clinical cases.

Symptomatic participants and controls were reviewed annually. At each review, the symptomatic questionnaire was again completed, the child examined and a further sample of blood was taken for measurement of serum specific IgE. Additionally, the symptomatic children had repeat skin prick testing to the food allergens and a repeat challenge if they were not tolerating the suspect food.

Figure 4.1 Diagrammatic representation of study design of T07046



Pregnant women were recruited at mid-trimester and their new born child was followed until 2 years of age. Routine questionnaire assessments were undertaken at 12 and 24 months. If a participant became symptomatic with possible food allergy, they, and two age matched controls, were assessed.

4.1.1 Definition of food allergy

Different studies have used different diagnostic criteria for food allergy depending on their design. Four definitions of food allergy were used in this study and across the EuroPrevall centres although the primary outcome measure was DBPCFC diagnosed food allergy (definition iv).

i. Parent perceived food allergy. This was defined as a parent notifying the research team that they suspected their child had a problem with a food allergy, or their report of symptoms suggestive of food allergy at the 12 or 24 month questionnaire assessment.
ii. Physician perceived food allergy. This was defined with meeting the criteria on the triage form for an invitation for a symptomatic evaluation (appendix G).
iii. Provisionally diagnosed suspected food allergy. This was defined as meeting the criteria for a double blind placebo control food challenge (i.e. any infant with SpIgE to food ≥0.35kU$_A$/l, and/or a positive skin prick test (wheal diameter ≥ 3mm) and/or a convincing clinical history of food allergy).
iv. Challenge diagnosed food allergy. This was defined as a positive double blind placebo control food challenge with objective signs of an allergic reaction to a food.

4.1.2 Inclusion/Exclusion Criteria

The inclusion criteria were:

- Written informed consent from the mother.
- Gestational age of 34 weeks or above.
- Apgar[i] score of 7 or greater at 5 minutes.

The study exclusion criteria were:

- Decision by attending obstetrician and/or paediatrician that they are unsuitable for the study.
- Participation of the infant or infant/mother pair in any other research study

4.1.3 Data processing and analysis

Data from all questionnaires and symptomatic visits were entered in the EuroPrevall database managed by Baigent UK. The data was reviewed by the data management team at Charite in Berlin and implausibility queries were run looking for data queries that were then resolved by the birth cohort centres by returning to source data. The data was exported into SPSS version 17 or STATA version 9 for analysis. The rate of key outcome

[i] Apgar is an assessment scale to document the health of a new born where 10 represents perfect health in terms of colour, heart rate, respiratory effort, tone and response to stimulus.

measures such as atopic disease and exposures such as breast feeding will be documented with frequency (%), mean (standard deviation) or median (inter-quartile range) as appropriate.

4.2 Collection of dietary intake information

At recruitment onto the birth cohort study, all parents were invited to complete diaries about their children's dietary intake (both milk and solids) from birth until their child's first birthday. Since the primary purpose of T07046 was a food allergy prevalence study, if parents did not wish to complete the food diaries but still wanted to take part in the study that was allowable as we did not wish the food diary completion to adversely affect recruitment onto the study. The food diaries consisted of a front sheet detailing how to complete the diary and 4 A4 sheets which had a table on which to record the child's intake over one week (see appendix F). Parents/carers were asked to record anything their child ate or drank. They were asked to note the name and manufacturer of any commercially prepared food consumed by their child. This included details of any infant formula given. If homemade food was given parents/carers were asked to give details of the recipes used. They were given these instructions at recruitment along with the first diary set so they could start recording their infant's intake immediately after birth. Further diary sets were sent out every two months with parents being asked to return each diary to the study office once it was completed. Freepost envelopes were provided for this purpose. It is recognised that food diary completion is a difficult task, so to reduce the work involved in completing the food diary records it was decided that quantitative data would only be recorded once in a four week period, for the other weeks parents/carers were requested just to record what the child consumed by the child (they did not need to record details of amounts of food taken). Once the diaries were received into the study office they were studied to ensure they were fit for purpose. If they lacked adequate detail (e.g. type of infant formula given) the parents were contacted by phone so this data could be recorded.

The food diaries were analysed using two different methodologies. The first was a nested within a cohort, case control study, the second was where the feeding patterns for all children who had food diaries returned were recorded and further analysed using principal component analysis.

4.2.1 Nested case control study

The quantitative food diaries which were completed the fourth week of every four week food diary were analysed for every child diagnosed with food allergy and their two age-matched controls. Analysis used the dietary analysis package 'CompEatPro' [Nutrition Systems] which had been modified to include nutritional data for all formula milks and baby food products recorded in the food diaries. This information was obtained from the relevant food companies and was current for the time the food diaries were completed. Portion sizes were established by weighing the household measures recorded by mothers. Homemade mixed purees were assumed to be in equal proportions of the ingredients recorded and whilst this may not have been 100% accurate in all cases, it ensured continuity of entry for all diaries.

Many infants received breast milk and 'CompEatPro had nutritional values for breast milk within its database but since many mothers did not record the duration and frequency of breast feeds we were unable to use an algorithm derived from published intake data to estimate breast milk intake (Marriott et al. 2008;Paul et al. 1988). However, a guide to

average breast milk intake by age (Scipien et al. 1975) allowed an estimated value for breast milk intake to be entered into the database. They quoted average intake by age to be as follows:

0-2 months- 2-5oz per feeding- 26oz per day (737g)
2-4 months- 4-6oz per feeding- 30oz per day (850g)
4-6 months- 5-7 oz per feeding- 31 oz per day (878g)
(1 oz = 28.35g)

These values were obtained from data from a number of research studies and they also agree with values obtained from other literature (Haisma et al. 2003;Kent et al. 2006;Waterlow and Thomson 1979). Although these values are estimates and cannot take into account the differences there are between each mother's milk, using them in all cases does ensure each infants analysis has been completed in the same manner.

'CompEatPro' was used to analyse the food diary records that had been entered for all nutrients and mean values for nutrients over 7 days were produced. These values were then transferred to the Statistical Package SPSS for further analysis. All macro- and micro-nutrients were compared between the two groups using a General Linear Model Repeated Measures analysis of variance (RM-ANOVA). A one-way analysis of variance (ANOVA) was used to establish the mean values with their 95% Confidence Intervals for Energy, Protein, Fat, Carbohydrate, Calcium, Iron, Zinc, Selenium, Vit A, Vit C and Vit E.

An analysis of the quantitative diet diaries from infants diagnosed as having a milk allergy and two-aged matched controls was also carried out. The same methodology was used as is described previously in this section to investigate whether there were any obvious nutritional differences in major macro and micro nutrient intakes between infants fed on a milk exclusion diet (because of cows' milk allergy symptoms) and infants fed on a 'normal' diet including cows' milk. The diet diaries of 13 infants who followed a milk exclusion diet after developing the symptoms of cows' milk allergy were be examined, along with 26 control infants who followed a 'normal' diet for the same number of diaries (2 control children for each symptomatic child). Case and control infants were age matched and the level of breast feeding amongst the two groups was also matched (so as to reduce the confounding effect of breast milk). For further detail of this work see addendum.

4.2.2 Principal Component Analysis

4.2.2.1 Background

Whole diet analysis is of particular interest as it is becoming apparent that it is often dietary patterns that effect health outcomes as opposed to distinct dietary components or nutrients (Hu 2002). This type of analysis can identify aspects of the infant diet that are related to health outcome (Gale et al. 2009). Such an approach was adopted by Zutavern (2004) in her work looking at solid food introduction and the development of asthma and eczema.

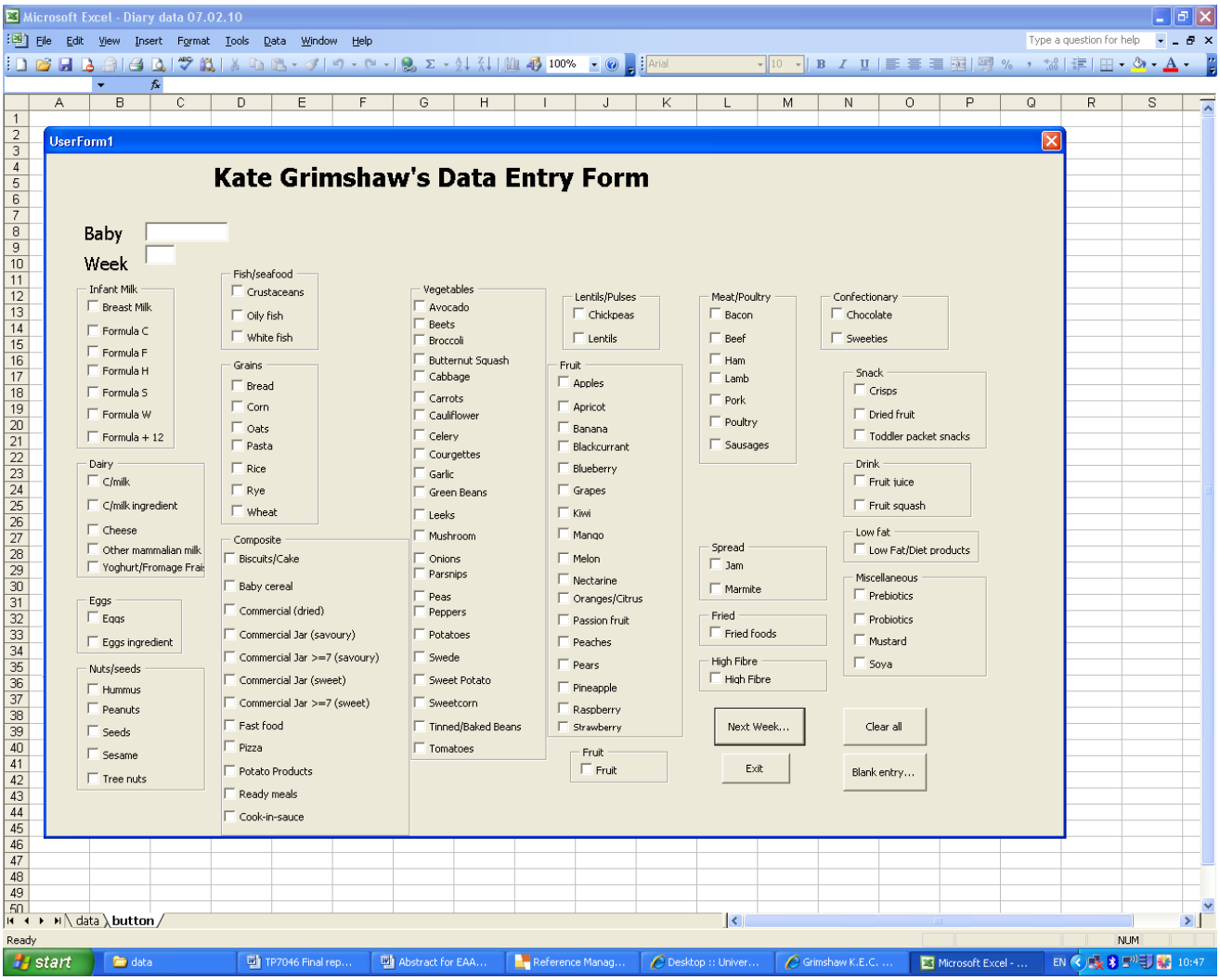
Principal components analysis is a type of whole diet analysis that enables dietary patterns to be described at a population level (Joliffe and Morgan 1992). It is a method that reduces an original set of variables (such as type of foods) into a smaller set of uncorrelated components that represent most of the information found in the original variables. The first principal component accounts for the maximal amount of variation, the second component accounts for the maximal amount of the variation that remains after

the first component, and so on until all the variation is accounted for. Within each component the contribution that each of the original variables makes to the variation can be expressed to get a sense of which of these variables are explaining most of the variation within the study population. Each derived principal component can be treated as a new independent variable, with each subject in the study having a score for that component which can then be used in further statistical tests to see if the dietary patterns they describe are associated with clinical outcome (which in this case is the development of food allergy).

4.2.2.2 Methodology

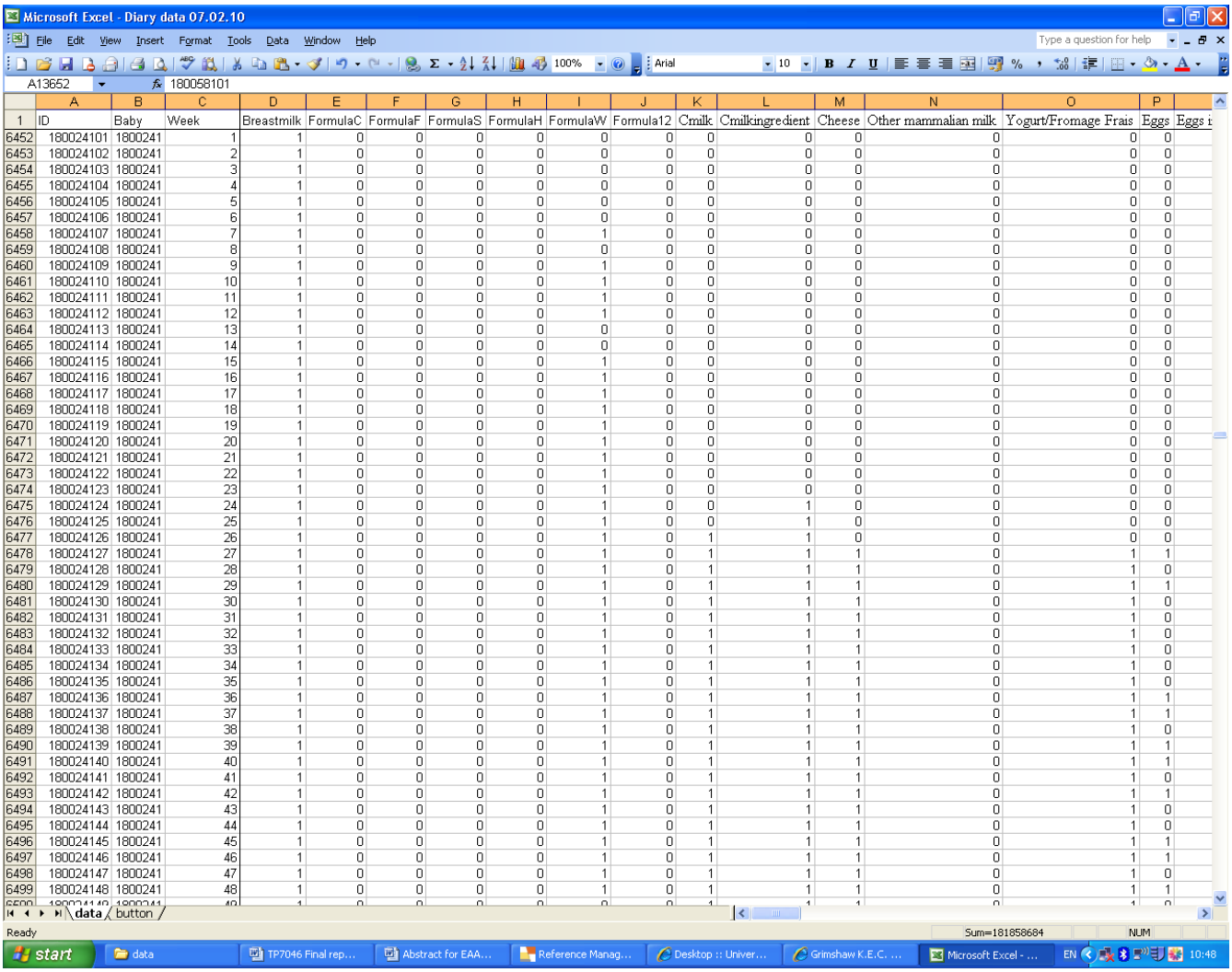
The food diaries for infants diagnosed with a food allergy (by double blind placebo controlled food challenge) and 2 age-matched controls were analysed. For each weeks diary what foods the child had eaten in each week were recorded by using an excel data entry front page (see figures 4.2). This then recorded into the excel sheet whether an infant had a food in a certain week. If the food was present the relevant cell was populated with a 1 if the food was not present then the cell was populated with a 0 (figure 4.3). The resultant data in the excel file (figure 4.3) was run through an SAS data manipulation programme written for the purpose which converted the weekly data into new variables such as the number of weeks an infant was breastfed, when an infant first had a particular food ingredient, how many weeks in total did they have that ingredient, and how many consecutive weeks did they have the ingredient (Figure 4.4). These new SAS variables were then imported into SPSS where further analyses including principal component analysis where carried out. In addition, the analysis was 'directed' to look at particular patterns including length of time of breastfeeding/complementary feeding overlap, timing of weaning, order of allergen introduction, allergen frequency and dose, diversity of diet (including predominance of fruit and vegetables), formula type used, and commercial versus homemade meals. These variables were selected as they represent theories that have been developed regarding allergy prevention strategies e.g., delaying the introduction of allergenic foods, having an LCPUFA rich diet, having a fruit and vegetable rich diet, and composition of infant formula.

Figure 4.2 Screenshot of Excel data entry front sheet used to record what foods were eaten by the infant that week



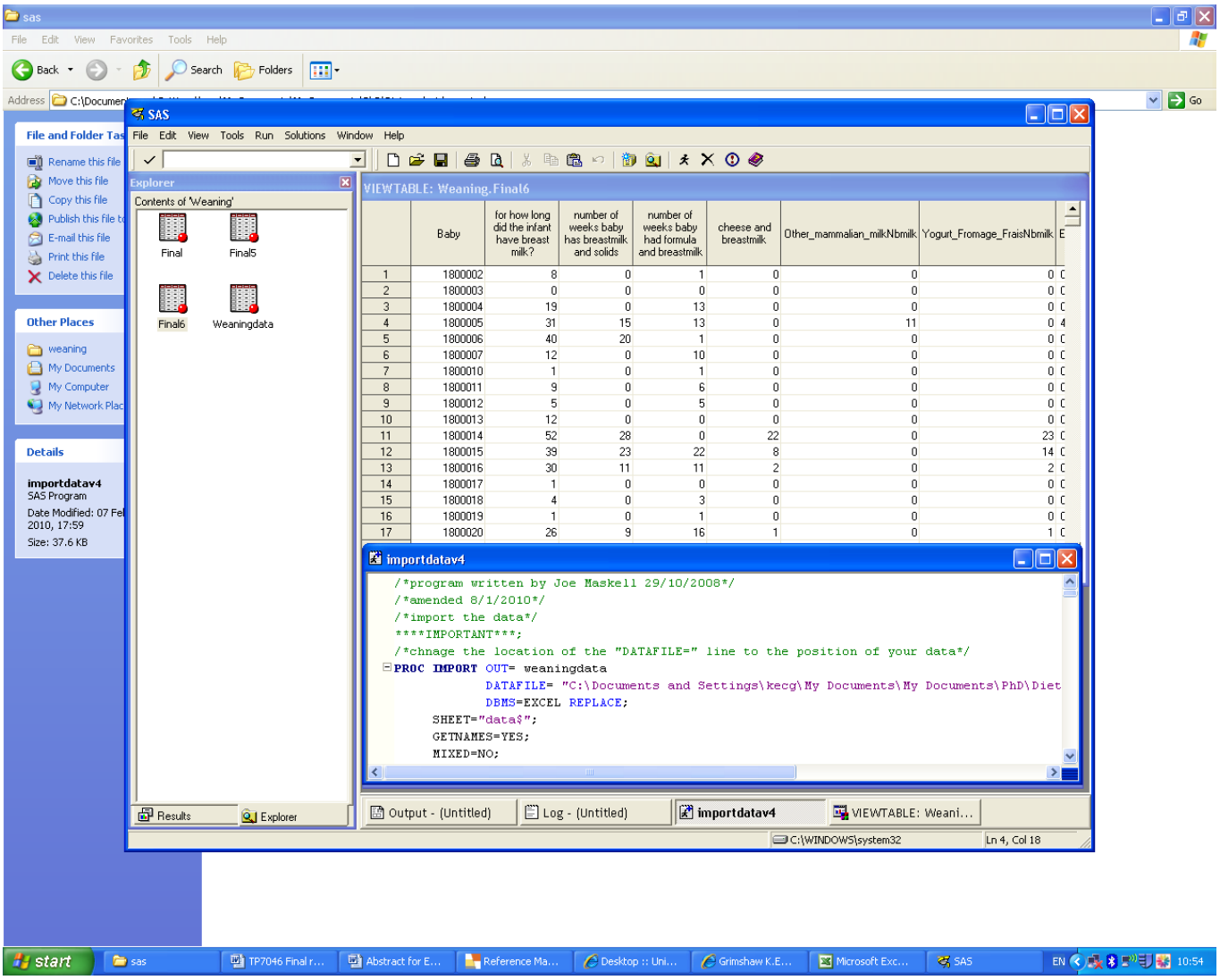
This figure shows the excel data entry screen. The tick box was selected if the infant had eaten the food that week. This then populated the excel data sheet with either a 1 if the food had been eaten that week or a 0 if it had not eaten that food

Figure 4.3 Screenshot of diet data entered showing if the food was present for each infant for each diary week completed (1= food was present, 0= food was not present)



This figure shows the data entry sheet after foods have been entered for each individual baby's weekly diary. 1= food was eaten that week 0= food was not eaten that week

Figure 4.4 Screenshot showing new SAS output variables after conversion of data from excel database



This figure shows the SAS output, log, data and import data screens. A SAS programme was written to convert the weekly 'yes/no' data into new variables e.g. how long the baby received breast milk, duration of breast feeding. The 'importdatav4' screen seen in the screenshot has the programme syntax for conversion of the '0's and '1's from the excel spread sheet to variables such as 'how long did the infant have breast milk'. Some of these variables can be seen in the 'VIEWTABLE: Weaning Final6' table also visible in the screen shot.

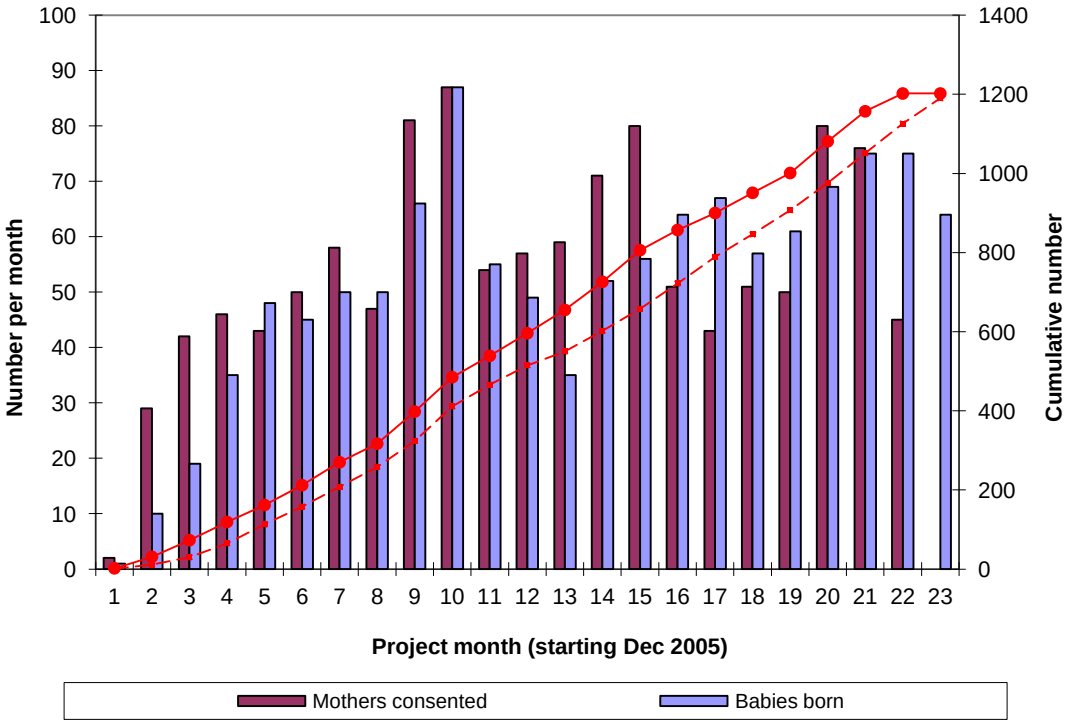
5. Results

5.1. Recruitment

5.1.1. Recruitment strategies

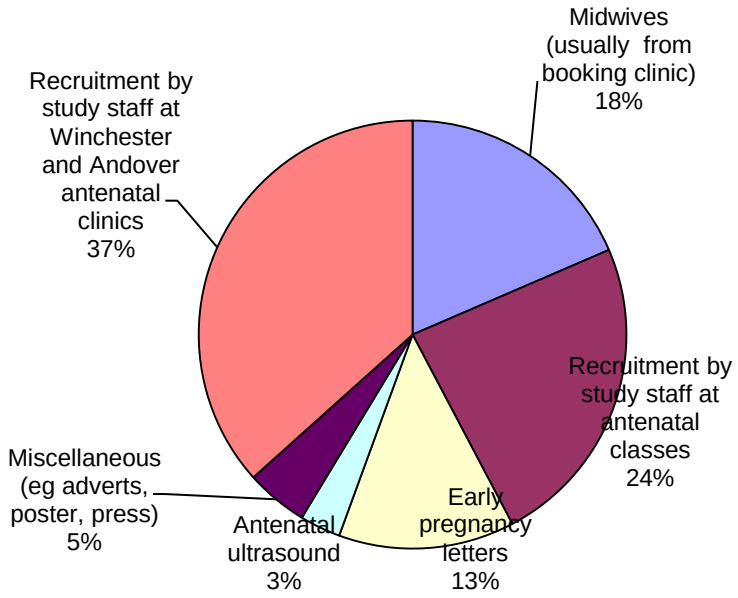
The initial recruitment strategy was for the midwives to approach pregnant women over 18 weeks gestational age and pass the names of interested women to the study team. This was supported by advertisements around the hospital, in the booking paperwork to general practitioners and patient support groups such as the National Childbirth Trust. Our monthly recruitment monitoring rapidly highlighted that this was not going to be a successful strategy. The strategy was, therefore, changed with the employment of a second research fellow who focussed on recruitment in antenatal ultrasound and the antenatal clinics. Additionally, to facilitate recruitment, both the study research fellows saw most pregnant women at home as this was more convenient to the mothers.

Figure 5.1 Monthly cumulative recruitment into the UK birth cohort



Bars demonstrate the number of pregnant women enrolling into the study (purple) and number of babies born (blue) on a monthly basis during recruitment. The lines show the cumulative totals of enrolled mothers (line) and babies delivered (dotted line).

Figure 5.2 Recruitment of mothers into the UK Birth Cohort



Percentage of mothers recruited into the study by each method.

The initial target was to recruit 1500 mothers. This was reduced to 1200 because the additional sites were recruited to the EuroPrevall multi-centre study and therefore less infants were needed from each site for the EuroPrevall project in order to be able to generate robust estimates of food allergy prevalence from the study as a whole. This did not impede delivery of the T07046 objectives. Recruitment of 1192 pregnant women (delivering 1203 infants as 11 women had twins) was achieved by October 2007 (Figure 5.1). Of the 1605 women who initially expressed an interest in taking part, 402 mothers refused to participate mainly due to time commitments or unwillingness for their child to have blood tests. We were not able to record any data about their characteristics. Of the 1203 infants, 6 were excluded as they did not satisfy the inclusion criteria (low apgar, premature delivery or delivery outside the recruitment period). No further data, including birth data, was available from 27 families meaning that the number of infants in the baseline dataset for the cohort was 1170.

Most of the recruits came from the antenatal clinics in Winchester and Andover; these mothers were approached by the study staff (37%). The next largest group were recruited by the study staff at antenatal classes (24%). Our intended strategy of utilising the midwives to recruit brought in only a relatively small number of women (18%). Other women were recruited as a result of sending letters out in the first trimester to pregnant women, as a result of local advertising in press or by poster or from the antenatal ultrasound suite as shown in Figure 5.2

5.1.2 Details of recruited participants (UK cohort)

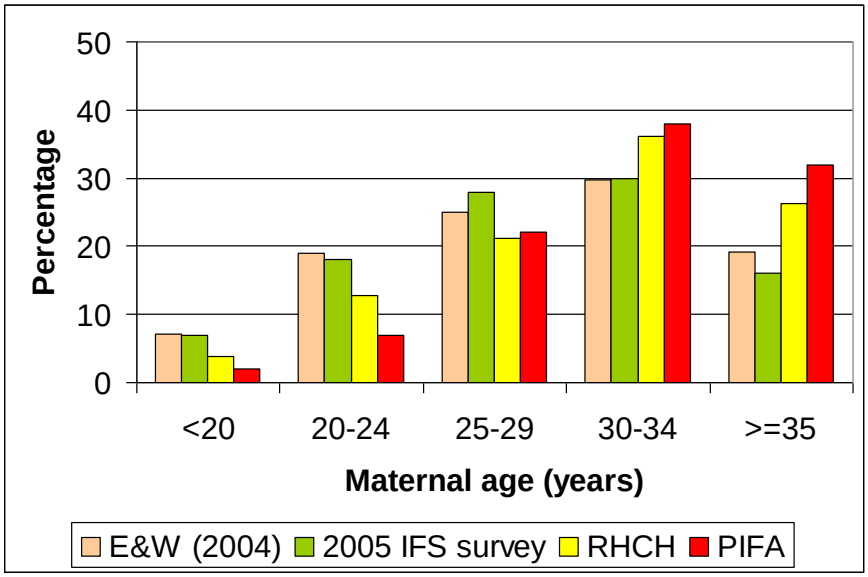
Pregnant women recruited to the study tended to be older and better educated than the average for the UK population because they were more representative of women booking under the Eastleigh and Winchester midwives (Figure 5.3.) as this is a

relatively affluent area compared with the general UK population. The area covered by the Eastleigh and Winchester midwives can be seen in figure 5.4. Additionally, they were recruited from across the entire recruitment area (Table 5.1, Figure 5.4). Women were recruited from across the entire area (Table 5.1) with most women coming from Eastleigh/Chandlers Ford (32%) then Winchester (24%) and then Andover (15%). The remainder were from the smaller towns and villages such as Colden Common (9%), Bishops Waltham (6%), Alresford/Alton (4%) and Botley/Hedge End (4%). As such, this represents a good spread of both urban and rural communities (Table 5.5). As expected in Hampshire, most mothers and fathers were Caucasian (greater than 95%) (Table 5.2).

The rate of allergic disease in the pregnant mothers and their partners was similar to values expected for a UK population (Tables 5.3 and 5.4). Maternal nutrition during pregnancy was recorded (Table 5.8) as consumption of different food groups and whether there had been any change during pregnancy (reasons for any change were not recorded in the questionnaire). Additionally, maternal consumption of supplements was recorded (Table 5.7). Most, but not all, had taken folic acid supplements with smaller numbers taking multi vitamins. Few (less than 5%) took fish oil capsules or vitamin D supplements.

Of the 1203 infants delivered to mothers enrolled in the study, a total of 1172 infants were entered into the cohort (six were excluded as they failed to satisfy the inclusion/exclusion criteria with another 25 who were lost follow-up in the neonatal period). Of the 1172, 51% were male, 2.5% were twins and 48.7% had an older sibling (Table 5.10). A total of 36% were given something other than breast milk in the first week of life, normally this was a cows' milk formula (Table 5.10).

Figure 5.3 Comparison between maternal age in UK birth cohort and similar populations



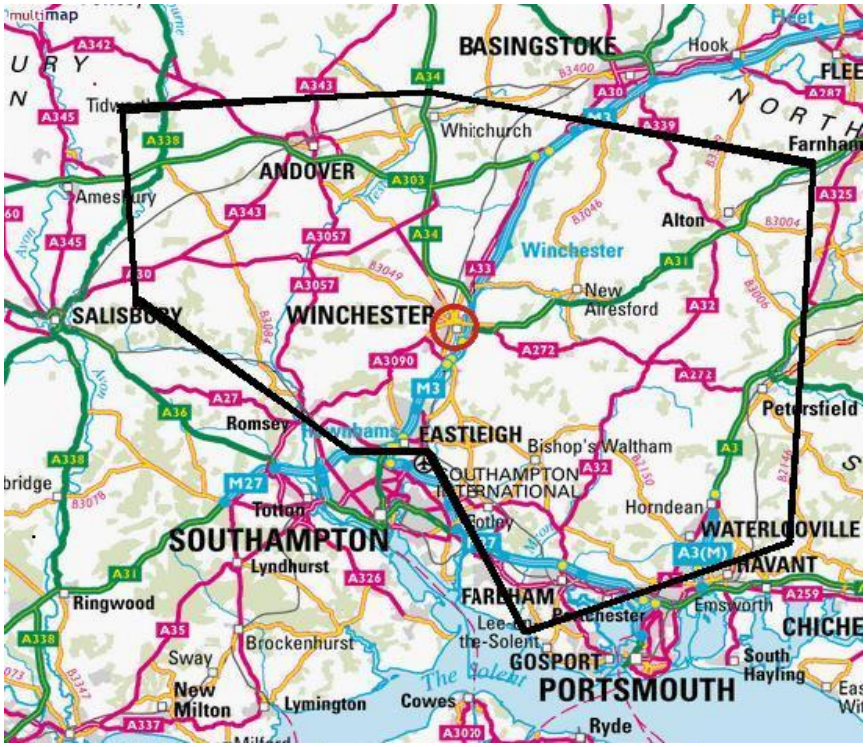
Percentage of mothers in each age range at enrolment into the UK birth cohort (PIFA) in comparison with England and Wales population; 2004 (E&W), 2005 infant feeding survey (IFS) (Bolling *et al*, 2007) and women delivering at Royal Hampshire Country Hospital, Winchester (data from routine hospital data, 2007) (RHCH).

Table 5.1 Locality of participants

Town / Village	Percentage of participants
Winchester	24%
Eastleigh / Chandlers Ford	32%
Andover	16%
Colder Common	9%
Bishop's Waltham	6%
Alresford / Alton / Petersfield	4%
Botley / Hedge End	4%
Fareham	3%
Basingstoke	1%

Percentage of mothers recruited into the UK birth cohort from each part of the recruitment area.

Figure 5.4 Map of the recruitment area



The recruitment area is bounded within the black line.

Table 5.2 Parental socioeconomic factors

	Frequency/total responses (%)
Maternal smoking	
Yes	71/1170 (6.1)
No, ex-smoker	429/1170 (36.2)
No never smoked	683/1170 (57.7)
Stopped or reduced when found out that they were pregnant	
Yes, stopped completely	110/474 (23.4)
Yes reduced	68/474 (14.1)
No, continued	10/474 (2.1)
Stopped before became pregnant	290/474 (59.9)
Other smokers in the house	195/1170 (16.7)
Regularly exposed to passive cigarette smoke while pregnant	94/1170 (8.0)
Maternal age (years)	31.9 (5.2)
Paternal age (years)	34.1 (5.6)
Maternal highest educational level	
Did not complete basic education (<10-12 years) ie left school before 16 years of age	10/1165 (0.9)
Completed basic education (10-12 years) ie left school after O-levels/GCSE's	123/1165 (10.6)
Sixth form/ vocational training	351/1165 (30.1)
University or Further/Higher education college	681/1165 (58.5)
Paternal highest educational level	
Did not complete basic education (<10-12 years)	12/1146 (1.0)
Completed basic education (10-12 years)	213/1146 (18.6)
Junior college / vocational training	340/1146 (29.7)
University or college	581/1146 (50.7)
Maternal ethnic group	
Caucasian	1117/1163 (96.0)
Asian	22/1163 (1.9)
African	3/1163 (0.3)
Other	21/1163 (1.8)
Paternal ethnic group	
Caucasian	1124/1157 (97.1)
Asian	16/1157 (1.4)
African	5/1157 (0.4)
Other	12/1157 (1.0)

Data presented as frequencies (percentages) except for ages (means (SD). Not all participants provided an answer to each question and so the total number of mothers or fathers is not consistent between questions. Data was available on maternal and paternal age for 1166 and 1154 respectively. Basic education in the UK represents education to GCSE level.

Table 5.3 Details of mothers' medical histories

	Frequency /total responses	(%)	Medically diagnosed? (%)		Still present? (%)	
Pollen-related rhinitis ('hay fever')?						
No	700/1169	(59.8)				
Yes	477/1169	(40.1)	309/472	(65.5)	390/466	(83.7)
An allergic reaction to house dust?						
No	991/1168	(84.7)				
Yes	177/1168	(15.1)	100/175	(57.1)	153/173	(88.4)
An allergic reaction to animals?						
No	938/1168	(80.3)				
Yes	230/1168	(19.7)				
React to dogs?	104/1168	(8.9)	57/104	(54.8)	96/104	(92.3)
React to cats?	201/1168	(17.2)	81/197	(41.1)	185/197	(93.9)
React to birds?	27/1168	(2.3)	16/28	(57.1)	24/26	(92.3)
React to rodents?	47/1168	(4.0)	22/46	(47.8)	45/46	(97.8)
React to horses?	80/1168	(6.8)	35/77	(46.7)	73/77	(94.8)
Eczema / Atopic Dermatitis?						
No	793/1169	(67.8)				
Yes	376/1169	(32.2)	331/376	(88.0)	208/374	(55.6)
Does or did the baby's mother ever suffer from asthma?						
No	897/1169	(76.7)				
Yes	272/1169	(23.3)	265/268	(98.9)	157/267	(58.8)*
Does or did the baby's mother ever have an adverse reaction to any foods?						
No	890/1150	(77.4)				
Yes	260/1150	(22.6)	-		190/230	(82.6)**
Body size						
Height (cm)	165.2	(6.9)				
Pre-pregnancy weight (kg))	65.5	(13.6)				

*152/245 (62.0%) take asthma mediation regularly or as required.
**Foods included (in order of frequency) milk, fruit, cereal, crustaceans, peanuts, vegetables, fish, tree nuts, eggs, cereals, meat, poultry, chocolate and soya.
Figures are frequencies/totals (percentages) or means (standard deviations). Not all participants provided an answer to each question. Gap in table is where data not collected.
Height and weight data were available for 1015 and 1011 mothers respectively.

Table 5.4 Details of fathers' medical histories

	Frequency /total responses	(%)	Medically diagnosed? (%)	Still present? (%)
Pollen-related rhinitis ('hay fever')?				
No	749/1150	(65.1)		
Yes	401/1150	(34.9)	253/367 (69.8)	358/378 (94.7)
An allergic reaction to house dust?				
No	1030/1148	(89.7)		
Yes	118/1148	(10.3)	55/105 (52.4)	198/104 (94.2)
An allergic reaction to animals?				
No	947/1144	(82.8)		
Yes	197/1144	(17.2)		
React to dogs?	72/1144	(6.3)	39/65 (60.0)	60/70 (85.7)
React to cats?	173/1144	(15.1)	64/162 (39.5)	149/164 (90.9)
React to birds?	8/1144	(0.6)	2/11 (18.2)	7/8 (87.5)
React to rodents?	16/1144	(1.4)	7/16 (43.8)	16/16 (100.0)
React to horses?	31/1144	(2.7)	12/29 (41.4)	27/29 (93.1)
Eczema / Atopic Dermatitis?				
No	947/1150	(82.3)		
Yes	203/1150	(17.7)	179/196 (90.4)	137/197 (68.8)
Does or did the baby's father ever suffer from asthma?				
No	917/1150	(79.7)		
Yes	233*	(20.3)	221/228 (96.9)	165/230 (71.7)*
Does or did the baby's father ever have an adverse reaction to any foods?				
No	997/1134	(87.9)		
Yes	137/1134**	(12.1)	-	101/121 (83.5)**

Data presented as frequencies/total responses (percentages). Not all participants provided an answer to each question.
*149 (70.6%) take asthma mediation regularly or as required.
**Foods included (in order of frequency) milk, fruit, peanuts, crustaceans, vegetables, fish, tree nuts, eggs, cereals, chocolate, meat, poultry and soya.
Gap in table is where data were not collected.

Table 5.5 Housing, cleaning and bedding characteristics

	Frequency/total responses (%)
Environment of home	
Urban	279/1170 (23.8)
Suburban/Rural*	891/1170 (76.2)
Live on a main road where heavy vehicles pass by	139/1155 (11.9)
Number of adults in house	2 (2 - 2)
Number of children living in house (including new baby)	1 (1 - 2)
Number of bedrooms in house	3 (3 – 4)
Mould in the house	123/1155 (10.6)
For cleaning kitchen work surfaces	
Non-bactericidal cleaning product	366/1154 (31.7)
Bactericidal cleaning product	679/1154 (58.8)
Neither of these	109/1154 (9.4)
For cleaning table where family eat	
Spray cleaner	613/1163 (52.7)
Soap and water	289/1163 (24.8)
Just water	78/1163 (6.7)
None of these	183/1163 (15.7)
Floor in baby's bedroom	
Carpet	994/1148 (86.6)
Wooden, laminate, parquet	143/1148 (12.5)
Linoleum or vinyl tiles	7/1148 (0.6)
Sea-grass or coir-type matting	3/1148 (0.3)
Rug	1/1148 (0.1)
Mattress that baby sleeps on	
Raw hair	1/1026 (0.1)
Foam	784/1026 (76.4)
Synthetic (other than foam)	154/1026 (15.0)
Other**	87/1026 (8.5)
Baby shares bed with parents	101/1098 (9.2)
Plastic surface or cover over baby's mattress	577/978 (49.3)
Baby lies on a sheepskin	161/1079 (14.9)

Data presented as frequencies /total responses (percentages) or median (interquartile range).
Not all participants provided an answer to each question. *18 live on a farm. **8 "anti-allergy"

Table 5.6 Details of animals

	Frequency / number responded (%)
Animals at home	568/1170 (49.5)
Median (IQR) number of animals*	2 (1,3)
Type of animal	
Cat	329/1170 (28.1)
Dog	210/1170 (17.9)
Rodent	84/1170 (7.2)
Fish	68/1170 (5.8)
Bird	19/1170 (1.6)
Reptile	15/1170 (1.3)
Chicken	14/1170 (1.2)
Horse	10/1170(0.9)
Cow	5/1170 (0.4)
Pig	1/1170 (0.1)

Data presented as frequencies / number responding (percentages). *Includes only families with animals.

Table 5.7 Maternal consumption of supplements during pregnancy

	Frequency			
When you were pregnant, did mother take	**No (%)**	**Yes regularly at least several times a week (%)**	**Yes for a specific period eg 1st trimester (%)**	**Yes occasionally (%)**
Multi-vitamin	410/914 (44.9)	356/914 (38.9)	96/914 (10.5)	52/914 (5.7)
Folic acid	109/917 (11.9)	270/917 (29.4)	529/917 (57.7)	9/917 (1.0)
Vitamin D	895/907 (98.7)	5/907 (0.6)	3/907 (0.3)	4/907 (0.4)
Fish oil capsules	802/906 (88.5)	75/907 (8.3)	16/907 (1.8)	13/907 (1.4)

Data presented as frequencies / total number responding (percentages). Not all participants provided an answer to each question. Details of dosage were not collected

Table 5.8 Maternal diet during pregnancy

	Frequency eating food /total responses	If eaten any change in amount consumed compared to amounts consumed before pregnancy			If not eaten, actively avoided?
		Same amount consumed	Increased intake	Decreased intake	
	(%)	(%)	(%)	(%)	(%)
Milk, dairy products	918/929 (98.8)	551/923 (59.7)	333/923 (36.1)	37/923 (4.0)	2/923 (0.2)
Soy products	209/929 (22.6)	871/922 (94.5)	12/922 (1.3)	11/922 (1.2)	28/922 (3.0)
Egg	863/931 (92.7)	679/924 (73.5)	41/924 (4.4)	172/923 (18.6)	32/923 (3.5)
Peanuts	487/925 (52.6)	310/922 (33.6)	16/922 (1.7)	188/922 (20.4)	408/922 (44.3)
Tree nuts	628/924 (68.0)	557/919 (60.6)	42/919 (4.6)	167/919 (18.2)	153/919 (16.6)
Seeds	620/928 (66.6)	809/924 (87.6)	43/924 (4.7)	41/924 (4.4)	31/924 (3.4)
Fish	827/929 (89.0)	687/926 (74.2)	143/926 (15.4)	81/926 (8.7)	15/926 (1.6)
Shell fish	328/928 (27.3)	387/923 (41.9)	10/923 (1.1)	141/923 (15.3)	385/923 (41.7)
Cereal, cereal products	920/926 (99.4)	753/922 (81.6)	157/922 (17.0)	10/922 (1.1)	2/922 (0.2)
Vegetables	925/931 (99.4)	649/925 (70.2)	254/925 (27.5)	22/925 (2.4)	0/925 (0.0)
Legumes	706/915 (77.2)	823/911 (90.3)	64/911 (7.0)	16/911 (1.8)	7/911 (0.9)
Fruit	914/924 (98.9)	531/918 (57.8)	366/918 (39.9)	20/918 (2.2)	1/918 (0.1)
Meat, meat products	845/926 (91.3)	802/921 (87.1)	64/921 (6.9)	46/921 (5.0)	8/921 (1.0)
Coffee and/or tea	672 (72.6)	362/912 (39.7)	18/912 (2.0)	393/912 (43.1	139/912 (15.2)
Alcohol	511/922 (55.4)	109/917 (11.9)	4/917 (0.4)	413/917 (45.0)	391/917 (42.6)
Sugar and sweets	898/926 (97.0)	446/923 (48.3)	357/923 (38.7)	111/923 (12.0)	9/923 (1.0)
Fish liver oil	92/928 (9.9)	827/913 (90.6)	25/913 (2.7)	13/913 (1.4)	48/913 (5.3)
Probiotics	276/921 (30.0)	800/909 (88.0)	32/909 (3.5)	18/909 (2.0)	59909 (6.5)

Figures represent numbers / total responding (%). Not all mothers answered every question so denominators are not consistent.

Table 5.9 Perinatal details

	Number	Range	Mean (SD) or Median (IQR)
Parity	1089	1 – 9	1 (1-2)
Gravida	1080	1 – 13	2 (1-2)
Duration of pregnancy: (completed weeks)	1142	34 – 43	39.4 (1.52)
Birth weight (grams)	1141	1745 -5060	3461 (524)
Length (cm)	1055	41 – 61	52.8 (3.1)
Head circumference (cm)	1065	25 -45	34.6 (1.6)
Apgar score at 5 min	1135	7– 10	10 (10-10)
Apgar score at 10 min	1102	8-10	10 (10-10)

	Frequency	(%)
Form of delivery		
Normal unassisted	583/1136	(51.3)
Forceps/vacuum assisted	106/1136	(9.3)
Vacuum extraction	98/1136	(8.6)
Caesarean section, planned	155/1136	(13.6)
Caesarean section, emergency	194/1136	(17.1)
Where was the baby born?		
Hospital	1116/1122	(99.5)
Home	6/1122	(0.5)

Data presented as mean and standard deviation (SD) or median and interquartile range (IQR) or frequency and percentage. Number of responses varies as data not available for all variables for all participants.

Table 5.10 Infants' demographics and early nutrition

	Frequency	(%)
Males	596/1168	(51.0)
Females	572/1168	(49.0)
Singleton	1137/1165	(97.6)
Twin	28/1165	(2.4)
Older sib	568/1164	(48.8)
Anything interfered with breastfeeding in hospital	112/911	(12.3)
Given something other than breast milk in first week of life; if yes, what:	370/1017	(36.4)
Sugar water	11/370	(3.0)*
Cows' milk formula	356/370	(96.2)*
Soy milk formula	2/370	(0.5)*
Hypoallergenic formula	1/370	(0.3)*

Data presented as frequencies (percentages). Number of responses varies as data not available for all variables for all participants. *represent percentage of infants given something other than breast milk in the first week of life.

5.1.3. Recruitment at other EuroPrevall sites

All the EuroPrevall sites recruited well. As of July 2009, a total of 12274 had been recruited into the study (Figure 5.5). The Netherlands and Italian sites are still recruiting.

Figure 5.5 Recruitment across all EuroPrevall Birth Cohort sites

	Germany	Poland	Greece	UK	Spain	Netherlands	Iceland	Lithuania	Italy	total
participants	**1537**	**1513**	**1132**	**1204**	**1540**	**951***	**1339**	**1558**	**1500**	**12274**
refused	1352	123	282	401	531	107	435	88	191	3510
total	2889	1636	1414	1605	2071	1058	1774	1646	1691	15784

*recruitment continues

Recruitment to July 2009 to entire EuroPrevall cohort. Differences in 'success rate' of recruitment due to slight differences in how recruitment took place. Differences mainly due to what was ethically permissible which was determined by national/regional committees and national differences in accessibility to healthcare.

5.2 Dietary intake data – food diary return

The number of mothers completing food intake diaries for their infants dropped off as the child grew older. Table 5.11 details the rate of food diary return.

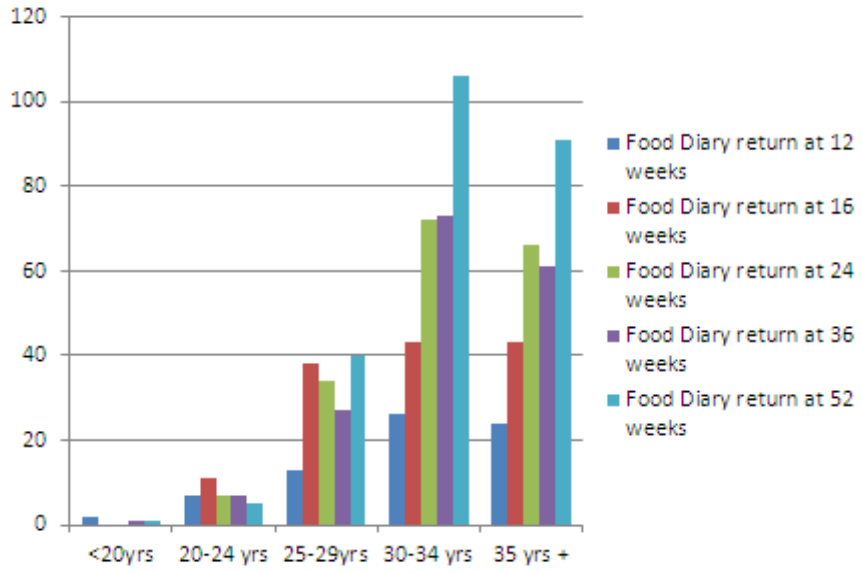
Table 5.11 Details of Food Diaries Returned

Number of Food Diaries Completed					
4 Weeks	12 Weeks	16 Weeks	24 Weeks	36 Weeks	52 Weeks
900	797	725	594	410	241

Numbers represent the number of food diaries returned at each time point (diaries were sent out on a bi-monthly basis, mothers completed them daily detailing infants consumption. The diaries were returned to the study office every 4 weeks).

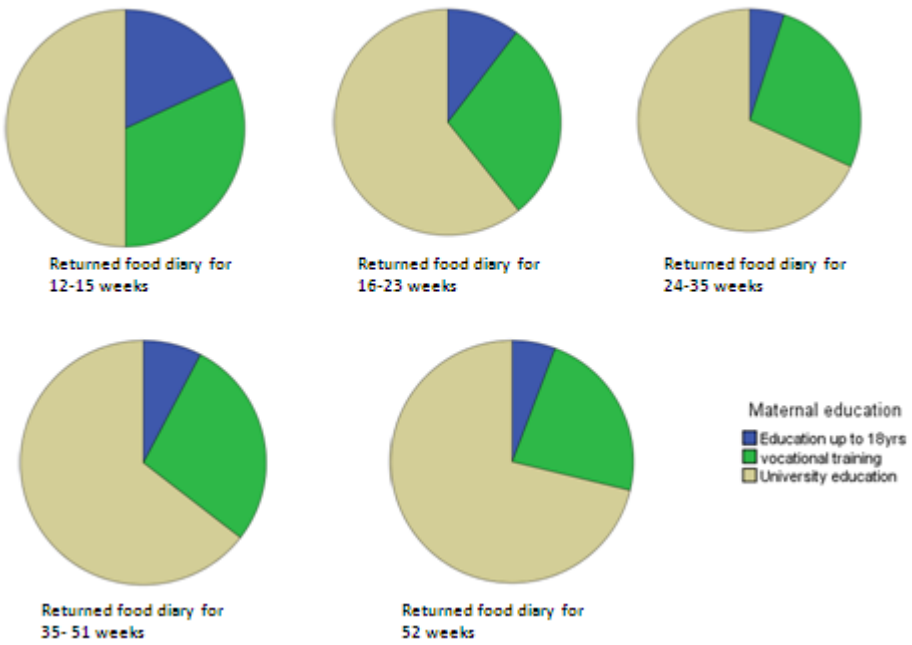
As has been mentioned earlier, the demographics of the UK study cohort are skewed towards higher education/age of the mothers. Looking at the education levels and age of the mothers who returned their food diaries at the different time points it becomes apparent that the older/more educated mothers kept the food diaries for their infant for longer than their younger/less educated counterparts. This has resulted in the younger/less well educated mothers being under-represented and the older/more educated mothers being over represented. This is demonstrated graphically in Figures 5.6, and 5.7.

Figure 5.6 Food Diary return and maternal age



Bars represent the percentage of families returning food diaries for different time periods by maternal age. Older mothers were more likely to complete the diaries for longer.

Figure 5.8 Food Diary return and maternal education



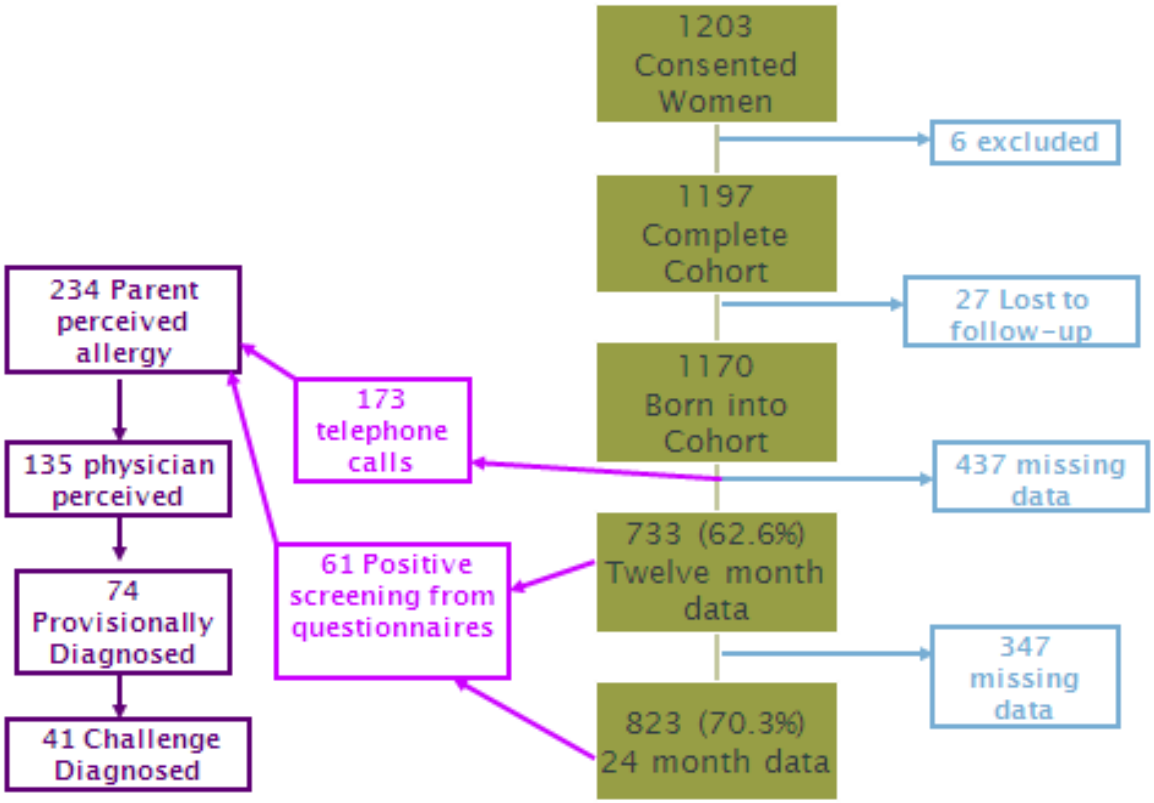
Pie charts represent the percentage of mothers completing food diaries for different lengths of time by their level of education. In general, the higher the level of maternal education, the longer the period during which the diaries were maintained.

5.3 Results of the clinical evaluation of allergic sensitisation and allergy to foods

5.3.1 Parent perceived food allergy (definition i)

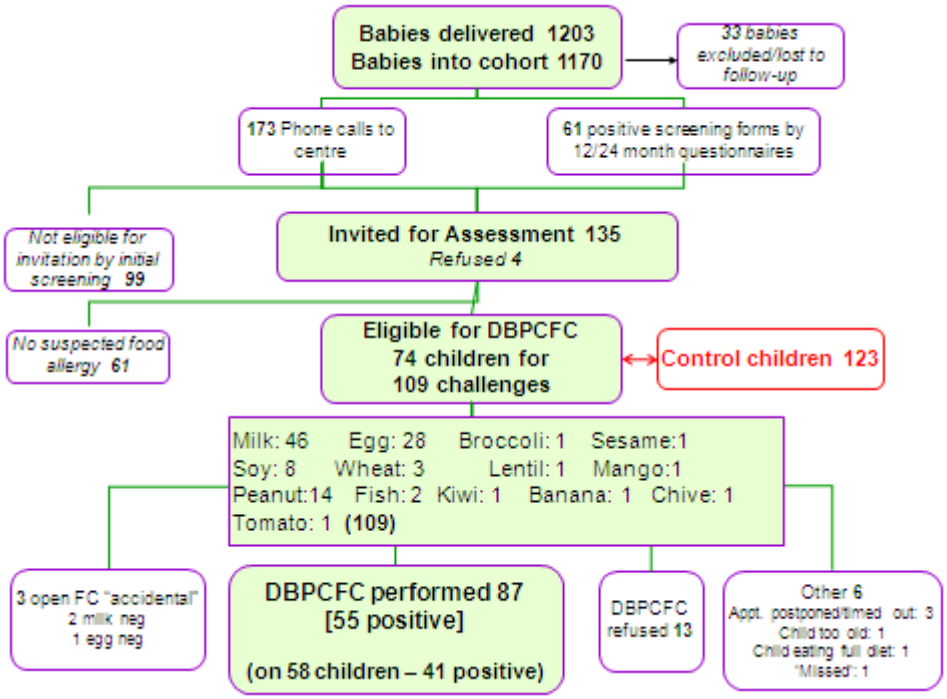
A total of 1197 eligible infants were born into the cohort but we were unable to contact 25 leaving a cohort of 1170 infants (Figure 5.9). A total of 733 were assessed at 12 months and 823 at 24 months. Given this follow up rate, 823 has been used as the denominator for the rest of the study findings. A total of 173 parents called the research team with concerns about a possible food allergy in their child. A further 61 infants were identified from their responses to questions in the 12 or 24 month questionnaires. This gave a total of 234 participants in whom there was parentally perceived food allergy. This equates to a rate of cumulative incidence of parental perceived food allergy of 28.4% (95% confidence interval 25.4 to 31.6) (Table 5.13).

Figure 5.9 Participants recruited into the UK EuroPrevall Birth Cohort



This figure details progression of numbers from recruitment to the 24 month questionnaire (green boxes), numbers of contacts regarding perceived reactions to food (pink-edged boxes) and progression of numbers from perceived allergy to dbpcfc diagnosed allergy (purple-edged boxes)

Figure 5.10 Participants with suspected and proven food allergy



Flow chart detailing progression of infants with parent perceived food allergy through diagnostic steps of study protocol.

5.3.2 Physician perceived food allergy (definition ii)

The presenting history of the 234 infants with parent perceived allergy was reviewed by the investigators (KG, GR) (Figure 5.10). Following the triage form (appendix G), 135 were perceived to possibly have food allergy. Of these, 131 consented to be assessed on the WTCRF. This equates to a physician perceived cumulative incidence of food allergy of 16.4% (13.9 – 19.1) (Table 5.13).

Table 5.12 Summary of characteristics of participants eligible for DBPCFC, part 1

	Cows' milk			Egg			Wheat		
	All (n=45)	**Positive DBPCFC (20/45)**	**Negative DBPCFC (15/45)**	**All (n=30)**	**Positive DBPCFC (22/30)**	**Negative DBPCFC (4/30)**	**All (n=3)**	**Positive DBPCFC (2/3)**	**Negative DBPCFC (1/3)**
Male gender	28/45 (62.2%)	11/20 (55.0%)	7/15 (46.7%)	19/30 (63.3%)	15/22 (68.2%)	2/4 (50.0%)	2/3 (66.7%)	1/2 (50.0%)	1/1 (100.0%)
Eczema	17/45 (37.8%)	6/20 (30.0%)	7/15 (46.7%)	11/30 (36.7%)	9/22 (40.9%)	1/4 (25.0%)	2/3 (66.7%)	1/2 (50.0%)	1/1 (100.0%)
Age baseline symptoms (months)	2.7 (1.4-5.2) [0.3-14.8]	1.6 (0.9-3.8) [0.3-13.0]	3.9 (2.2-6.6) [0.4-14.8]	6.7 (2.0-10.7) [0.8-20.1]	6.7 (2.2-7.9) [0.8-20.1]	10.8 (3.5-12.5) [3.5-12.5]	3.9 (2.2-7.1) [2.2-7.1]	4.6 (2.2-7.1) [2.2-7.1]	3.9
Presenting symptoms									
Immediate*	5/45 (11.1%)	3/20 (15.0%)	1/15 (6.7%)	20/30 (66.7%)	14/22 (63.6%)	3/4 (75.0%)	0/3 (0.0%)	0/2 (0.0%)	0/1 (0.0%)
Repetitive*	36/45 (80.0%)	14/20 (70.0%)	13/15 (86.7%)	4/30 (13.3%)	4/22 (18.2%)	0/4 (0.0%)	2/3 (66.7%)	1/2 (50.0%)	1/1 (100.0%)
Both	4/45 (8.9%)	3/20 (15.0%)	1/15 (6.7%)	3/30 (10.0%)	2/22 (9.1%)	0/4 (0.0%)	1/3 (33.3%)	1/2 (50.0%)	0/1 (0.0%)
None	0 (0.0%)	0/20 (0.0%)	0/15 (0.0%)	3/30 (10.0%)	2/22 (9.1%)	1/4 (25.0%)	0/3 (0.0%)	0/2 (0.0%)	0/1 (0.0%)
Baseline serum specific IgE									
<0.35	35/39 (89.7%)	15/18 (83.3%)	12/12 (100.0%)	6/26 (23.1%)	2/19 (10.5%)	2/3 (66.7%)	1/2 (50.0%)	1/2 (50.0%)	0/0 (0.0%)
0.35 to 0.7	1/39 (2.6%)	0/18 (0.0%)	0/12 (0.0%)	4/26 (25.4%)	3/19 (15.8%)	0/3 (0.0%)	0/2 (0.0%)	0/2 (0.0%)	0/0 (0.0%)
>0.7 to 3.5	2/39 (5.1%)	2/18 (11.1%)	0/12 (0.0%)	10/26 (38.5%)	9/19 (47.4%)	1/3 (33.3%)	1/2 (50.0%)	1/2 (50.0%)	0/0 (0.0%)
>3.5 to 17.5	1/39 (2.6%)	1/18 (5.6%)	0/12 (0.0%)	4/26 (15.4%)	3/19 (15.8%)	0/3 (0.0%)	0/2 (0.0%)	0/2 (0.0%)	0/0 (0.0%)
>17.5- 50	0/39 (0.0%)	0/18 (0.0%)	0/12 (0.0%)	2/26 (7.7%)	2/19 (10.5%)	0/3 (0.0%)	0/2 (0.0%)	0/2 (0.0%)	0/0 (0.0%)
Baseline SPT (mm)									
<2	38/44 (88.4%)	16/20 (80.0%)	14/15 (93.3%)	6/28 (21.4%)	2/21 (9.5%)	2/4 (50.0%)			
2	1/44 (2.2%)	1/20 (5.0%)	0/15 (0.0%)	0/28 (0.0%)	0/21 (0.0%)	0/4 (0.0%)			
3	1/44 (2.2%)	1/20 (5.0%)	0/15 (0.0%)	5/28 (17.9%)	5/21 (23.8%)	0/4 (0.0%)			
4	3/44 (6.6%)	2/20 (10.0%)	0/15 (0.0%)	3528 (17.9%)	4/21 (19.1%)	1/4 (25.0%)	SPT to wheat not carried out due to poor positive predictive value of results		
5	1/44 (2.2%)	0/20 (0.0%)	1/15 (6.7%)	6/28 (21.4%)	4/21 (19.1%)	1/4 (25.0%)			
6	0/44 (0.0%)	0/20 (0.0%)	0/15 (0.0%)	1/28 (3.6%)	1/21 (4.8%)	0/4 (0.0%)			
7	0/44 (0.0%)	0/20 (0.0%)	0/15 (0.0%)	2/28 (7.1%)	2/21 (9.5%)	0/4 (0.0%)			
≥8	0/44 (0.0%)	0/20 (0.0%)	0/15 (0.0%)	3/28 (10.7%)	3/21 (14.2%)	0/4 (0.0%)			

Table 5.12 Summary of characteristics of participants eligible for DBPCFC, part 1 continued

	Cows' milk			Egg			Wheat		
	All (n=45)	**Positive DBPCFC (20/45)**	**Negative DBPCFC (15/45)**	**All (n=30)**	**Positive DBPCFC (22/30)**	**Negative DBPCFC (4/30)**	**All (n=3)**	**Positive DBPCFC (2/3)**	**Negative DBPCFC (1/3)**
DBPCFC indicated									
Performed	36/45 (80.0%)	20/20 (100.0%)	12/15 (80.0%)	27/30 (90.0%)	22/22 (100.0%)	4/4 (100.0%)	3/3 (100.0%)	2/2 (100.0%)	1/1 (100.0%)
Accidently performed	3/45 (6.7%)	0/20 (0.0%)	3/15 (20.0%)	0/30 (0.0%)	0/22 (0.0%)	0/4 (100.0%)	0/3 (0.0%)	0/2 (0.0%)	0/1 (0.0%)
Postponed	0/45 (0.0%)	0/20 (0.0%)	0/15 (0.0%)	0/30 (0.0%)	0/22 (0.0%)	0/4 (100.0%)	0/3 (0.0%)	0/2 (0.0%)	0/1 (0.0%)
Not necessary	1/45 (2.2%)	0/20 (0.0%)	0/15 (0.0%)	0/30 (0.0%)	0/22 (0.0%)	0/4 (100.0%)	0/3 (0.0%)	0/2 (0.0%)	0/1 (0.0%)
Refused	5/45 (11.1%)	0/20 (0.0%)	0/15 (0.0%)	3/30 (10.0%)	0/22 (0.0%)	0/4 (100.0%)	0/3 (0.0%)	0/2 (0.0%)	0/1 (0.0%)
Age at DBPCFC (months)	9.8 (6.4 – 14.3) [3.5 – 26.1]	9.5 (6.0-12.0) [3.5-23.4]	11.8 (9.4-16.2) [5.3-26.1]	19.0 (12.5 – 21.2) [9.4-31.6]	19.0 (13.3-21.2) [9.5-31.6]	14.8 (11.0-20.9) [9.4-24.8]	14.3 (12.4– 15.4) [12.4 – 15.4]	14.9 (14.3-15.4) [14.3-15.4]	12.4
DBPCFC result									
Positive	20/39 (51.3%)	20/20 (100.0%)	0/15 (0.0%)	22/27 (81.5%)	22/22 (100.0%)	0/4 (0.0%)	2/3 (66.7%)	2/2 (100.0%)	0/1 (0.0%)
Negative	15/39 (38.5%)	0/20 (0.0%)	15/15 (100.0%)	4/27 (14.8%)	0/22 (0.0%)	4/4 (100.0%)	1/3 (33.3%)	0/2 (0.0%)	1/1 (100.0%)
Negative but symptoms on reintroduction	3/39 (7.7%)	0/20 (0.0%)	0/15 (0.0%)	0/27 (0.0%)	0/22 (0.0%)	0/4 (0.0%)	0/3 (0.0%)	0/2 (0.0%)	0/1 (0.0%)
Inconclusive	1/39 (2.6%)	0/20 (0.0%)	0/15 (0.0%)	1/27 (3.7%)	0/22 (0.0%)	0/4 (0.0%)	0/3 (0.0%)	0/2 (0.0%)	0/1 (0.0%)

Values are frequencies (percentages) or medians (IQR) [range] for each food. Data not available for all participants.
*Repetitive includes symptoms such as chronic eczema, colic and vomiting or possetting; immediate included rapid onset symptoms such as urticaria, immediate vomiting or diarrhoea.

Table 5.13 Summary of characteristics of participants eligible for DBPCFC, part 2

	Soy			Peanut			Cod		
	All (n=8)	**Positive DBPCFC (3/8)**	**Negative DBPCFC (5/8)**	**All (n=15)**	**Positive DBPCFC (6/15)**	**Negative DBPCFC (3/15)**	**All (n=2)**	**Positive DBPCFC (1/2)**	**Negative DBPCFC (0/2)**
Male gender	6/8 (75.0%)	2/3 (66.7%)	4/5 (80.0%)	11/15 (73.3%)	4/6 (66.7%)	2/6 (33.3%)	1 (50.0%)	1/1 (100.0%)	-
Eczema	3/8 (37.5%)	1/3 (33.3%)	2/5 (40.0%)	6/15 (40.0%)	2/6 (33.3%)	2/3 (66.7%)	1/2 (50.0%)	1/1 (100.0%)	-
Age baseline symptoms (months)	9.1 (7.5-13.2) [5.7-14.4]	11.5 (8.5-14.4) [8.5-14.4]	8.3 (5.7-11.2) [5.7-13.2]	4.7 (3.3-14.5) [3.3-14.5]	-	9.6 (4.7-14.4) [4.7-14.4]	8.3	8.3	-
Presenting symptoms									
Immediate	2/8 (25.0%)	1/3 (33.3%)	1/5 (20.0%)	2/15 (13.3%)	1/6 (16.7%)	0/3 (0.0%)	2/2 (100.0%)	1/1 (100.0%)	-
Repetitive	6/8 (75.0%)	2/3 (66.7%)	4/5 (80.0%)	1/15 (6.7%)	0/6 (0.0%)	1/3 (33.3%)	0/2 (0.0%)	0/1 (0.0%)	-
Both	0/8 (0.0%)	0/3 (0.0%)	0/5 (0.0%)	2/15 (13.3%)	0/6 (0.0%)	1/3 (33.3%)	0/2 (0.0%)	0/1 (0.0%)	-
None	0/8 (0.0%)	0/3 (0.0%)	0/5 (0.0%)	10/15 (60.0%	5/6 (83.3%)	1/3 (33.3%)	0/2 (0.0%)	0/1 (0.0%)	-
Baseline serum specific IgE									
<0.35	6/8 (75.0%)	2/3 (66.7%)	4/5 (80.0%)	5/14 (35.5%)	2/6 (33.3%)	1/3 (33.3%)	2/2 (100.0%)	1/1 (100.0%)	-
0.35 to 0.7	1/8 (12.5%)	1/3 (33.3%)	1/5 (20.0%)	1/14 (7.1%)	1/3 (16.7%)	2/3 (66.7%)	0/2 (0.0%)	0/1 (0.0%)	-
>0.7 to 3.5	1/8 (12.5%)	0/3 (33.3%)	0/5 (0.0%)	6/14 (42.6%)	2/6 (33.3%)	0/3 (0.0%)	0/2 (0.0%)	0/1 (0.0%)	-
>3.5 to 17.5	0/8 (0.0%)	0/3 (33.3%)	0/5 (0.0%)	2/14 (14.2%)	1/6 (16.7%)	0/3 (0.0%)	0/2 (0.0%)	0/1 (0.0%)	-
>17.5- 50	0/8 (0.0%)	0/3 (33.3%)	0/5 (0.0%)	0/14 (0.0%)	0/6 (0.0%)	0/3 (0.0%)	0/2 (0.0%)	0/1 (0.0%)	-
Baseline SPT (mm)									
<2	7/8 (87.5%)	2/3 (66.7%)	5/5 (100.0%)	2/13 (15.4%)	1/6 (16.7%)	0/3 (0.0%)	1/1 (100.0%)	1/1 (100.0%)	-
2	0/8 (0.0%)	0/3 (0.0%)	0/5 (0.0%)	0/13 (0.0%)	0/6 (0.0%)	0/3 (0.0%)	0/0 (0.0%)	0/0 (0.0%)	-
3	0/8 (0.0%)	0/3 (0.0%)	0/5 (0.0%)	1/13 (7.7%)	1/6 (16.7%)	0/3 (0.0%)	0/0 (0.0%)	0/0 (0.0%)	-
4	1/8 (12.5%)	1/3 (33.3%)	0/5 (0.0%)	4/13 (30.8%)	2/6 (33.3%)	1/3 (33.3%)	0/0 (0.0%)	0/0 (0.0%)	-
5	0/8 (0.0%)	0/3 (0.0%)	0/5 (0.0%)	2/13 (15.4%)	0/6 (0.0%)	1/3 (33.3%)	0/0 (0.0%)	0/0 (0.0%)	-
6	0/8 (0.0%)	0/3 (0.0%)	0/5 (0.0%)	2/13 (15.4%)	1/6 (16.7%)	0/3 (0.0%)	0/0 (0.0%)	0/0 (0.0%)	-
7	0/8 (0.0%)	0/3 (0.0%)	0/5 (0.0%)	0/13 (0.0%)	0/6 (0.0%)	0/3 (0.0%)	0/0 (0.0%)	0/0 (0.0%)	-
≥8	0/8 (0.0%)	0/3 (0.0%)	0/5 (0.0%)	2/13 (15.4%)	1/6 (16.7%)	1/3 (33.3%)	0/0 (0.0%)	0/0 (0.0%)	-

Table 5.13 Summary of characteristics of participants eligible for DBPCFC, part 2 continued

	Soy			Peanut			Cod		
	All (n=8)	**Positive DBPCFC (3/8)**	**Negative DBPCFC (5/8)**	**All (n=15)**	**Positive DBPCFC (6/15)**	**Negative DBPCFC (3/15)**	**All (n=2)**	**Positive DBPCFC (1/2)**	**Negative DBPCFC (0/2)**
DBPCFC indicated									
Performed	8/8 (100.0%)	3/3 (100.0%)	5/5 (100.0%)	10 (66.7%)	6/6 (100.0%)	3/3 (100.0%)	1/2 (50.0%)	1/1 (100.0%)	-
Accidently performed	0/8 (0.0%)	0/3 (0.0%)	0/5 (100.0%)	1 (6.7%)	0/6 (0.0%)	0/3 (0.0%)	0/2 (0.0%)	0/1 (0.0%)	-
Postponed	0/8 (0.0%)	0/3 (0.0%)	0/5 (100.0%)	0 (0.0%)	0/6 (0.0%)	0/3 (0.0%)	0/2 (0.0%)	0/1 (0.0%)	-
Not necessary	0/8 (0.0%)	0/3 (0.0%)	0/5 (100.0%)	0 (0.0%)	0/6 (0.0%)	0/3 (0.0%)	0/2 (0.0%)	0/1 (0.0%)	-
Refused	0/8 (0.0%)	0/3 (0.0%)	0/5 (100.0%)	4 (26.7%)	0/6 (0.0%)	0/3 (0.0%)	1/2 (50.0%)	0/1 (0.0%)	-
Age at DBPCFC (months)	21.1 (17.6– 24.0) [13.4 – 26.5)	24.4 (18.6-26.5) [18.6-26.5]	19.4 (16.6-23.1) [13.4-23.4]	23.6 (19.7–28.3) [17.2 – 33.2]	21.5 (19.9-24.8) [19.8-28.3]	26.6 (17.2-33.3) [17.2-33.3]	19.1	19.1	-
DBPCFC result									
Positive	3/8 (37.5%)	3/3 (100.0%)	5/5 (100.0%)	6 (60.0%)	6/6 (100.0%)	0/3 (0.0%)	1/1 (100.0%)	1/1 (100.0%)	-
Negative	5/8 (62.5%)	0/3 (0.0%)	0/5 (0.0%)	3 (30.0%)	0/6 (0.0%)	3/3 (100.0%)	0/1 (0.0%)	0/1 (0.0%)	-
Negative but symptoms on reintroduction	0/8 (0.0%)	0/3 (0.0%)	0/5 (0.0%)	0 (0.0%)	0/6 (0.0%)	0/3 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	-
Inconclusive	0/8 (0.0%)	0/3 (0.0%)	0/5 (0.0%)	1 (10.0%)	0/6 (0.0%)	0/3 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	-

Values are frequencies (percentages) or medians (IQR) [range] for each food. Data not available for all participants.
*Repetitive includes symptoms such as chronic eczema, colic and vomiting or possetting; immediate included rapid onset symptoms such as urticaria, immediate vomiting or diarrhoea.

Table 5.13 Cumulative incidence of food allergy

Food allergy definition	Number	Cumulative incidence (95% CI)	Source data
Parent perceived	234	28.4% (25.4 – 31.6)	Parent phone call to office or 12/24 month questionnaire
Physician perceived	135	16.4% (13.9 – 19.1)	Eligible for symptomatic assessment (from triage form)
Provisionally diagnosed	74	9.0% (7.1 – 11.2)	Eligible for DBPCFC
DBPCFC diagnosed	41	5.0% (3.6 – 6.7)	Positive DBPCFC

Cases of food allergy acquired as participants developed symptoms and parents contacted the research team. Figures therefore represent the cumulative incidence (95% confidence interval)

Table 5.14 Cumulative incidence of DBPCFC diagnosed allergy to individual foods

	Eligible for DBPCFC	Positive DBPCFC	Cumulative incidence (95% CI) n=891
Cows' milk	35	25	3.0% (2.0-4.5)
Egg	25	21	2.6% (1.6-3.9)
Peanut	10	6	0.7% (0.3-1.6)
Soy	8	3	0.4% (0.0-1.1)
Wheat	3	2	0.2% (0.0-0.9)
Fish	1	1	0.1% (0.0-0.7)

Data represent numbers of subjects eligible for a DBPCFC and with a positive DBPCFC by food plus the cumulative incidence (95% confidence interval) for each food. Denominator is the 823 infants followed up to 24 months.

5.3.3 Provisional diagnosed suspected food allergy (definition iii)

Of the 131 participants assessed at the WTCRF, food allergy could be ruled out in 61 instances. There remained 74 children who fulfilled the criteria for a DBPCFC. Their characteristics are described in Table 5.12. The majority were, as expected, male and had a high prevalence of eczema. The age of presentation varied by food group with cows' milk being the earliest to present and peanut being the last. The cumulative incidence of food allergy using this third provisionally diagnosed definition was 9.0% (7.1 to 11.2%) (Table 5.13).

5.3.4 Challenge diagnosed food allergy (definition iv)

The gold standard definition was a positive DBPCFC. This meant that the infant had objective signs of a hypersensitivity reaction to the active day without any symptoms on the placebo day. A total of 41 participants had a positive challenge giving a cumulative incidence of 5.0% (3.6 to 6.7) (Table 5.13). The most frequent food allergen was milk (prevalence 3.0%, 2.0-4.5), the next egg (2.6%, 1.6-3.9), then peanut (0.7%, 0.3-1.6), soy (0.4%, 0.0-1.1), wheat (0.2%, 0.0-0.9) and finally fish (0.1%, 0.0-0.7) (table 5.14).

A total of 11 participants had positive food challenges to more than one food. Eight reacted to 2 foods, two to 3 and one to 4 foods. The most frequent combination was cows' milk and egg (6 participants, one of whom was additionally allergic to soy and fish). The other combination was egg and peanut (3 participants, one additionally allergic to wheat).

5.3.5 Safety of study participants undergoing food challenges

The majority of reactions at food challenge involved urticaria or angioedema. One infant experienced anaphylaxis with an egg challenge. She was well on the day of her admission. The challenge proceeded without incident until dose 5 when she had a small, non-raised red mark on her top lip. This rapidly disappeared so dose 6 was given, after dose 6 she again had small non-raised red areas above and below her lips which then disappeared. She was given dose 7 40 minutes later without any further symptoms developing. After dose 8 she developed 3 clear areas of urticaria on her face and therefore the challenge was stopped. The urticaria spread 30 minutes later, and an hour later she became wheezy. A dose of intra-muscular adrenaline was given and she also received nebulised salbutamol. She rapidly improved. As per our hospital protocol for anaphylaxis, she was observed as an inpatient overnight. This was her first known dietary exposure to egg.

5.4. Analysis of dietary intake information results

5.4.1. Dietary intake data from the whole birth cohort

Diaries from 905 infants were analysed to provide general data about the whole cohort (Table 5.15)

As mentioned previously, these results cannot be compared with population data as the demographics are skewed towards older mother. However the data can be adjusted to enable a comparison to be made with those previously published. Table 5.16 shows the values adjusted using the demographic profile of the 2005 Department of Health infant feeding study (Bolling et al. 2007) and the values from that survey.

The dietary intake data can also show what percentage of infants have had allergenic foods introduced into their diet at different time points. Since the number of food diaries returned at each time point reduces throughout the year, a Kaplan Meier survival analysis was carried out in order to take account of this. A survival analysis was carried out for each food type investigated and the results of these analyses are shown in table 5.17.

The analysis showed that over two-thirds of infants had cows' milk protein introduced into their diet by 13 weeks of age and that this is in the form of infant formula. Cows' milk in the diet as an ingredient is generally introduced from 4 months of age with more than half the infants having had cows' milk as an ingredient in their diet by 26 weeks of age. Conversely, cows' milk (as a drink or on breakfast cereal) is not routinely introduced into the diet until the second half of the first year of life. Hen's egg is introduced into the diet from 6 months of age, with more infants having it in their diet as an ingredient rather than as egg *per se*. Despite there being a general recommendation not to introduce wheat into an infant's diet until they are 6 months of age (Department of Health 2009) 42% of infants had wheat in their diet in one form or another by this time, with nearly all infants (98.5%) having wheat in their diet by 1 year of age. Fish is introduced into the infant's diet in the second half of the year with white fish being introduced first and oily first introduced in the final quarter of the year. Peanuts, tree nuts, sesame and kiwi fruit are also introduced into the infant's diets in the second half of the year but at much lower frequencies.

Table 5.15 Summary of feeding characteristics

	All analysed	Maternal age (years) <20	20-24	25-29	30-34	35+
Mean breastfeeding initiation rate (n=905)	91%	86%	70%	89%	94%	93%
Mean breastfeeding duration in weeks(range) (n=905)	16.5 (0-52)	49.7 (0-50)	8.29 (0-52)	13.9 (0-52)	17.2(0-52)	18.6 (0-52)
Mean length of exclusive breastfeeding in weeks (range) (n=839)	5.7 (0-26)	1.8 (0-11)	1.8 (0-23)	4.7 (0-25)	6.3 (0-27)	6.3 (0-26)
Percentage infants receiving breast milk at 4 months (17 weeks) (n=905)	44.9%	14.3%	21.3%	35.3%	48%	50.6%
Percentage infants receiving breast milk at 6 months (26 weeks) (n=905)	28.1%	14.30%	12.8%	20.9%	29%	34.%
Mean age of solid introduction in weeks (range) (n=647)	19.0 (6-29)	12 (12-12)	15.9 (11-25)	17.8 (6-26)	19.3 (11-28)	19.5 (0-29)
Percentage infants receiving solids by 4 months (17 weeks) (n=647)	36.6%	100%	78.6%	57.7%	31.4%	29.4%
Percentage infants receiving solids at 6 months (26 weeks) (n=647)	98.3%	100%	100%	100%	98.5%	97.0%

Table 5.16 Actual and adjusted feeding characteristics and IFS data

	All analysed	Adjusted values	2005 IFS values
Mean breastfeeding initiation rate (n=905)	91%	88%	77%
Mean breastfeeding duration in weeks (range) (n=905)	16.5 (0-52)	14.3	-
Mean length of exclusive breastfeeding in weeks (range) (n=839)	5.7 (0-26)	4.7	-
Percentage infants receiving breast milk at 4 months (17 weeks) (n=905)	44.9%	37.6%	35%
Percentage infants receiving breast milk at 6 months (26 weeks) (n=905)	28.1%	23.5%	26%
Mean age of solid introduction in weeks (range) (n=647)	19 (6-29)	17.9	-
Percentage infants receiving solids by 4 months (17 weeks) (n=647)	36.6%	51.3%	50%
Percentage infants receiving solids at 6 months (26 weeks) (n=647)	98.3%	100%	98%

Data was adjusted by using the values for each of the age ranges (table 5.15) for the measure of interest and changing the proportion it contributed to the value of the whole cohort to the proportion of that age range within the IFS cohort.

Table 5.17 Timing of introduction of allergenic foods into infant's diet. Data obtained using Kaplan Meier survival analysis.

Percentage of infants consuming each food at time point	3 months (13 weeks)	4 months (17 weeks)	6 months (21 weeks)	6 months (26 weeks)	6 months (30 weeks)	6 months (34 weeks)	9 months (39 weeks)	12 months (52 weeks)
Cows' milk (all forms) n=817	73	79	86	93	98	99.5	99.5	99.75
Cows' milk (formula) n=785	76	81	88	92	94	95	96	96.5
Cows' milk n=337	0	0	0.5	7	25	41	51	66
Cows' milk (ingredient) n=510	1	7	22	54	84	94	97	98.5
Hens' egg (all forms) n=400	0.5	1	2	10	32	54	74	91
Hens' egg n=355	0	0	0	2.5	20	34	53	76
Hens' egg (ingredient) n=330	0.5	1	2	9	23	45	65	86
Wheat n=509	1	5	15	42	82	92	97	98.5
Fish (all types) n=428	0	0.5	2	19	59	80	90	93
Oily fish n=366	0	0.5	1	6	31	50	69	80.5
White fish n=45	0	0	1.5	6	53	73	84	89

Peanuts n=245	0	0	0	0.5	1	1	3.5	9
Tree nuts n=241	0	0	0	0	1	1	2	3
Sesame n=256	0	0	1	1	2	7	13	21
Kiwi n=288	0	0	1	6	16	22	31	41

Table shows percentages of infants receiving different foods at time points with the first year of life. Data obtained by Kaplan Meier time course analysis

5.4.2. Analysis of diet data from those infants diagnosed with food allergy and their controls

A total of 39 of the 41 food allergic infants had food diaries for at least 13 weeks which could be analysed and each of their two controls had food diaries for at least the same number of weeks. There was no significant difference between the groups for any baseline characteristics including maternal education, maternal age, ethnicity, birth order, pet ownership, allergic status of the mother, gender of infant, and smoking status of mother (See table 5.18).

Using the Mann-Whitney U test for independent samples, there was no difference between symptomatic or control infants for breastfeeding initiation or duration rates and length of exclusive breastfeeding. There was a significant difference between the groups for mean age at solid introduction (p=0.049) and cows' milk as an ingredient (p=0.025) but not for any other individual food (see table 5.19).

Table 5.18 Baseline characteristics of symptomatic and control children

	Symptomatic (n=41)	Control (n=82)	P value†
Male sex (%)	24 (58)	43 (53)	0.568
Birth weight (g) mean ±SD	3419.9 ± 481.8	3478.0 ± 524.4	0.572§
Length (cm) ±SD	52.5 ± 2.69	52.7 ± 2.98	0.099§
Maternal age (yr) mean ±SD	32 ± 5.4	33 ± 4.4	0.940§
Paternal age(yr) mean ±SD	33 ± 4.6	35 ± 5.5	1.930§
Maternal education			0.471
Completed basic education	4	6	
Junior college/vocational training	11	15	
University/college	26	60	
Maternal Asthma	11	11	0.072
Maternal Allergy	22	32	0.118
Maternal smoker	1	3	0.711
Siblings	17	33	0.585
Urban dwelling	8	10	0.292
Animal ownership	26	40	0.161

Data are expressed as number (percentage) unless indicated
† Chi-square test of homogeneity unless indicated
§ ANOVA F test

Table 5.19 Infant feeding characteristics for symptomatic and control infants

	Symptomatic	Control	p value
Breast feeding initiation (%)	89.7	96.3	0.154
Mean breast feeding duration (weeks) n=120	19.69	20.6	0.496
Mean exclusive breast feeding duration (weeks) n=119	5.7	6.5	0.374
Mean age at introduction of food (weeks)			
-solids n=112	18.7	20.0	0.049
- Infant formula n=116	7.5	8.3	0.371
- Cows' milk (ingredient) n=91	23.1	25.5	0.025
- Cows' milk n=39	43.7	37.3	0.215
- Cows' milk (all forms) n=116	7.2	8.3	0.235
- Hen's egg n=58	36.1	36.6	0.863
- Hen's egg (ingredient) n=65	33.8	35.7`	0.348
- Hen's egg (all forms) n=78	33.5	33.6	0.838
- Wheat n=95	26.7	26.7	0.980
- Soya n=24	28.8	31.3	0.949
- White fish n=80	28.4	30.8	0.232
- Oily fish n=74	33.6	34.3	0.787
- Fish (all types) n=84	28.0	30.2	0.261
- Peanut n=7	37.7	43.5	0.480
-Tree nuts n=3	30.0	44.0	0.221
- Sesame n=13	36.8	38.1	0.884
-Kiwi fruit n=27	33.1	36.4	0.438

Summary of the descriptive statistics for the analysis of age at solid introduction are given in table 5.20 and the distribution of solid introduction between the two groups is shown graphically in figure 5.11. These show that although some control infants (that is those infants with no food allergy) were introduced to solids earlier than any symptomatic infants, the mean, median and mode value for solid introduction is higher for control infants compared with the symptomatic infants. The kurtosis and skewness values indicate that the distribution is bunched and to the right of the normal distribution (norm) for controls but neither are statistically significantly different from the norm. For the symptomatic infants the converse is true with the distribution being flatter and to the left of the norm but again this is not statistically significant.

A Kaplan Meier survival analysis showed the pattern of solid introduction to be broadly the same with the shape of the curve being similar for both symptomatic and controls infants apart from at the very beginning of the plot where some control children were introduced to solids earlier than the symptomatic children. After this point the symptomatic infants 'overtake' the control infants and their survival curve remains to the left of the control curve (Figure 5.12)

Table 5.20 Descriptive Statistics for timing of solid introduction for symptomatic and control infant groups

	Symptomatic n=39	Control n=78
Mean age at solid introduction	18. 7	20
Median age at solid introduction	18	20
Mode age of solid introduction	16	21
Range	15	21
Minimum age at solid introduction	12	7
Maximum age at solid introduction	27	28
Standard deviation of timing of solid introduction	3.98	4.0
Kurtosis	-0.7	0.7
Standard error of kurtosis	0.79	0.54
Skewness	0.40	-0.49
Standard error of skewness	0.40	0.27

Figure 5.11 Distribution for timing of solid introduction for symptomatic and control infants

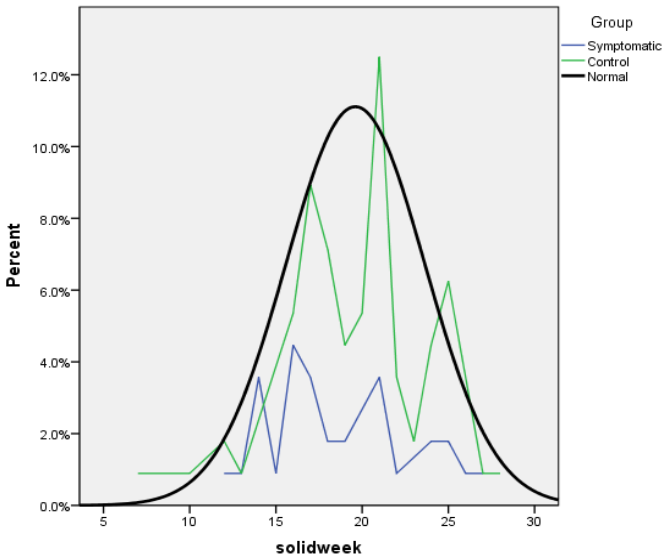


Figure showing percentage of infants receiving solids at different time points. The curves have points demonstrating that infants received solids at defined time points such as 3, 4, 5 and 6 months (13, 17, 21 and 26 weeks respectively)

Figure 5.12 Kaplan Meier survival analysis plot showing timing of solid introduction for symptomatic and control infants

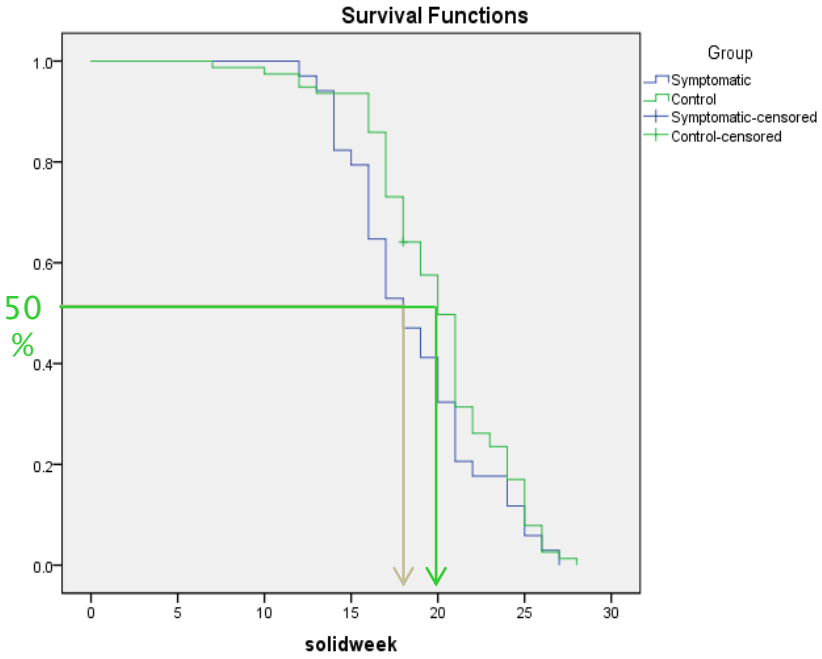


Figure graphically shows when infants had solid food introduced into their diet. At 0 weeks no infants had solids introduced, represented by a survival of 1.0. All infants had received solids by 28 weeks represented by a survival of 0.0.

There was no significant difference in the timing of introduction of any allergenic food itself apart from for cows' milk ingredient with the mean timing for symptomatic infants being 23.1 weeks compared to 25.5 weeks for control infants (p=0.021). Summary of the descriptive statistics for the introduction of Cows' milk as an ingredient are given in table 5.21 and the distribution of solid introduction between the two groups is shown graphically in figure 5.13. These show that symptomatic infants had cows' milk introduced into the diet as an ingredient sooner than the control infants. The kurtosis and skewness values indicate that the distribution is significantly skewed to the left and is significantly bunched ("pointy") for the symptomatic infants. This is not the case for the larger number of control infants whose skewness or kurtosis is not statistically different from the norm.

A Kaplan Meier survival analysis showed the pattern of introduction of cows' milk as an ingredient to be broadly the same with the shape of the curve being similar for both symptomatic and controls. The symptomatic curve is to the left of the control curve throughout the graph until the last 10% where introduction of cows' milk as an ingredient effectively stops and this will be representative of the cows' milk allergic infants who will not be having cows' milk in their diet. (Figure 5.14)

Table 5.21 Descriptive Statistics for timing of cows' milk ingredient for symptomatic and control infant groups

	Symptomatic n=20	Control n=71
Mean age at introduction of cows' milk ingredient	23.1	25.5
Median age at introduction of cows' milk ingredient	21.5	26
Mode age at introduction of cows' milk ingredient	17	21
Range	36	36
Minimum age at introduction of cows' milk ingredient	13	15
Maximum age at introduction of cows' milk ingredient	49	52
Standard deviation of timing of cows' milk introduction	7.96	5.44
Kurtosis	5.3	6.7
Standard error of kurtosis	0.99	0.56
Skewness	1.89	1.46
Standard error of skewness	0.51	0.29

Figure 5.13 Distribution for timing of cows' milk ingredient introduction for symptomatic and control infants

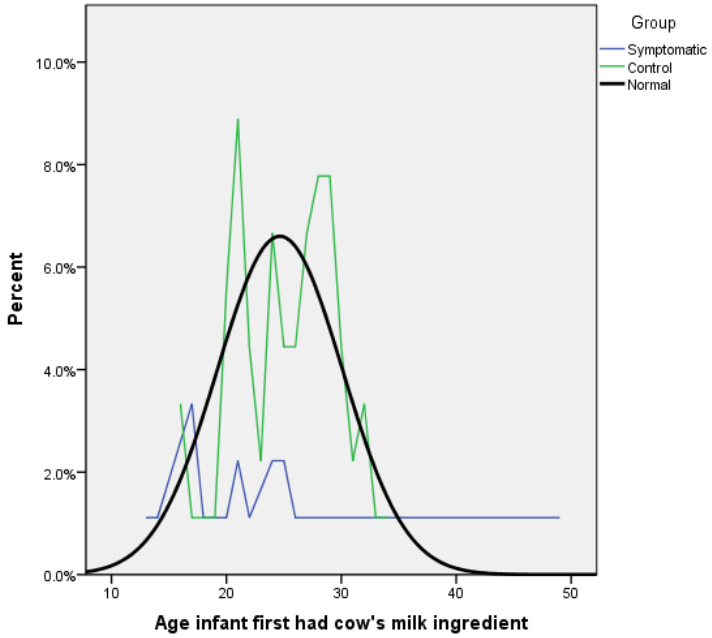


Figure showing percentage of infants receiving cows' milk as an ingredient at different time points. The curves have points demonstrating that infants received solids at defined time points such as 4, 5 and 6 months (17, 21 and 26 weeks respectively)

Figure 5.14 Kaplan Meier survival analysis plot showing timing cows' milk ingredient introduction for symptomatic and control infants

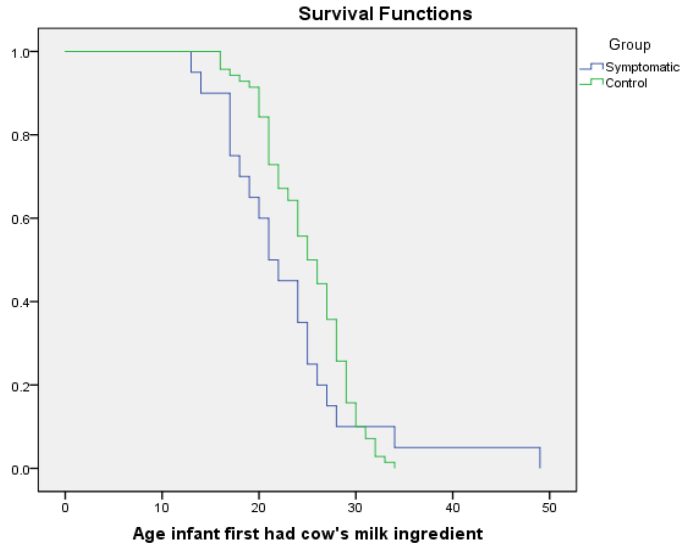


Figure graphically shows when infants had cows' milk as an ingredient introduced into their diet. At 0 weeks no infants had cows' milk as an ingredient introduced, represented by a survival of 1.0. All control infants had received cows' milk as an ingredient by 34 weeks represented by a survival of 0.0. Not all symptomatic infants had received cows' milk as an ingredient by 50 weeks as some were requiring a milk free diet.

A total of 31 of the food allergic infants had complete food diaries containing adequate quantitative data until symptoms developed and these were analysed along with diaries from 62 age-matched controls.

The RM-ANOVA found no significant difference between the dietary intake of the food allergic infants and their controls for any of the pre-specified nutrients. The one-way analysis of variance (ANOVA) found a significant difference between the two groups for protein intake at month 10 ($p=0.05$) and month 11 ($p=0.03$), calcium at month 11 ($p=0.02$) and vitamin E at month 9 ($p=0.04$). However since there was no difference found in the RM-ANOVA analysis and the study numbers are small at these time points these results are unlikely to be due to any causative mechanisms. For full details of the mean values with their Confidence Intervals for Energy, Protein, Fat, Carbohydrate, Calcium, Iron, Zinc, Selenium, Vitamin A, Vitamin C and Vitamin E see tables 5.22, 5.23 and 5.24. Since there were no significant differences in dietary intake found between the groups and the background demographics of the two groups were similar between the two groups analyses taking into account the effect of potential confounding factors were not carried out.

Even though no significant differences were found between the dietary intakes of the two groups it is interesting to note that all the nutrient values increase each month for both groups. It's expected that infants consume more as they get older and these results do reflect this however this has not previously been demonstrated in the literature using prospective food diaries kept for the first year of life.

5.4.3 Additional analysis of infant dietary data to investigate the nutritional adequacy of a milk exclusion diet

Results of this work can be found in the addendum to this report.

Table 5.22 Mean macronutrient intake per day for dietary intake prior to diagnosis for cases and their controls

	Macronutrients											
	Mean Energy (Kcal)			Mean Protein (g)			Mean Total Fat (g)			Mean CHO (g)		
Month (n)	Symptomatic (CI)	Control (CI)	P value	Symptomatic (CI)	Control (CI)	P value	Symptomatic (CI)	Control (CI)	P value	Symptomatic (CI)	Control (CI)	P value
Month 1 (symptomatic :31) (control:62)	518.4 (497.3-539.4)	512.6 (501.4-523.9)	0.60	10.1 (9.5-10.7)	9.9 (9.7-10.2)	0.55	29.9 (28.9-30.9)	29.7 (28.9-30.4)	0.74	55.0 (52.3-57.8)	54.1 (52.8-55.3)	0.46
Month 2 (symptomatic:18) (control:36)	573.5 (547.0-600.1)	587.5 (572.2-602.7)	0.32	11.0 (10.5-11.5)	11.6 (11.1-12.1)	0.12	33.6 (31.9-35.2)	33.7 (32.5-34.8)	0.90	60.4 (57.5-63.2)	62.6 (60.7-64.4)	0.17
Month 3 (symptomatic:18) (control:36)	587.6 (550.1-625.1)	608.5 (592.2-624.9)	0.22	11.3 (10.6-12.0)	12.1 (11.5-12.7)	0.12	34.0 (31.7-36.4)	34.6 (33.7-35.6)	0.54	62.2 (58.2-66.2)	65.0 (62.8-67.3)	0.18
Month 4 (symptomatic:14) (control:28)	643.1 (608.9-677.3)	675.9 (609.1-742.6)	0.50	12.9 (11.9-14.0)	13.8 (12.0-15.6)	0.51	36.4 (34.5-38.3)	37.9 (34.2-41.6)	0.57	69.4 (64.5-74.3)	72.8 (65.5-80.1)	0.53
Month 5 (symptomatic:14) (control:28)	688.6 (600.0-777.2)	646.2 (622.5-670.0)	0.21	14.9 (11.8-18.1)	13.2 (12.3-14.0)	0.15	36.8 (33.3-40.2)	35.2 (33.9-36.6)	0.30	78.4 (65.4-91.4)	71.5 (67.8-75.2)	0.17
Month 6 (symptomatic:12) (control:23)	707.4 (630.4-784.4)	708.2 (659.4-757.0)	0.98	14.5 (12.6-16.3)	15.1 (13.5-16.6)	0.63	35.5 (32.4-38.7)	35.6 (33.2-37.9)	0.98	86.0 (71.4-100.6)	84.4 (76.6-92.2)	0.82
Month 7 (symptomatic:8) (control:16)	812.1 (716.2-908.0)	739.6 (686.2-793.0)	0.13	19.6 (13.7-25.5)	19.8 (16.5-23.1)	0.93	36.7 (32.1-41.4)	31.6 (26.0-37.1)	0.21	102.8 (86.3-119.4)	91.8 (85.7-98.0)	0.10
Month 8 (symptomatic:4) (control:8)	774.9 (658.4-891.4)	788.0 (699.9-876.0)	0.83	24.9 (17.9-31.9)	20.5 (14.6-26.4)	0.29	30.8 (19.2-42.5)	34.1 (30.4-37.8)	0.36	102.3 (81.2-123.4)	103.2 (84.4-122.9)	0.95
Month 9 (symptomatic:3) (control:6)	862.6 (610.6-1114.6)	838.3 (721.2-955.5)	0.76	26.9 (20.5-33.2)	23.8 (17.7-29.9)	0.43	33.9 (2.0-65.7)	36.1 (30.2-42.0)	0.72	116.2 (97.4-135.0)	108.2 (83.8-132.6)	0.59
Month 10	1047.1	881.0	0.18	34.1	25.3	0.05	46.2	35.2	0.14	129.0	118.9	0.44

(symptomatic:2) (control:6)	(180.3-1913.8)	(734.1-1027.9)		(15.7-83.8)	(21.1-29.5)		(-52.2-144.7)	(27.7-42.8)		(86.9-171.1)	(101.8-136.1)	
Month 11 (symptomatic:2) (control:4)	1045.3 (93.8-2184.4)	880.8 (645.0-1116.6)	0.26	35.3 (21.0-49.6)	27.3 (22.9-32.2)	0.03	40.6 (37.9-119.1)	36.4 (22.4-50.3)	0.61	137.1 (23.4-250.9)	115.6 (86.6-144.6)	0.22
Month 12 (symptomatic:2) (control:4)	1041.8 (495.1-1588.5)	1154.5 (741.0-1568.0)	0.60	33.2 (9.3-57.2)	34.2 (25.8-42.6)	0.82	38.5 (34.8-42.3)	48.5 (30.1-67.0)	0.31	143.9 (22.5-310.3)	151.3 (92.1-210.5)	0.81
Month 13 (symptomatic:2) (control:4)	1083.9 (242.7-1925.1)	1085.0 (684.4-1485.6)	0.99	37.6 (13.1-62.0)	36.7 (30.0-43.5)	0.82	42.3 (18.9-103.4)	45.6 (22.3-68.9)	0.78	142.3 (226.8-511.4)	137.5 (90.1-185.0)	0.88

Values are mean monthly intakes and 95% confidence intervals for energy, protein, carbohydrate, and fat for symptomatic and control infants.

Table 5.23 Mean mineral intake per day for dietary intake prior to diagnosis for cases and their controls

	Minerals											
	Mean Calcium (mg)			Mean Iron (mg)			Mean Zinc (mg)			Mean Selenium (ug)		
Month (n)	Symptomatic (CI)	Control (CI)	P value	Symptomatic (CI)	Control (CI)	P value	Symptomatic (CI)	Control (CI)	P value	Symptomatic (CI)	Control (CI)	P value
Month 1 (symptomatic:31)) (control:62)	282.1 (256.8-307.3)	270.9 (257.4-284.5)	0.39	1.4 (0.8-2.1)	1.4 (1.0-1.8)	0.91	2.3 (1.9-2.7)	2.3 (2.1-2.6)	0.94	8.3 (7.6-9.1)	8.5 (8.0-9.1)	0.70
Month 2 (symptomatic:18) (control:36)	303.2 (278.6-327.9)	341.0 (301.5-380.5)	0.20	1.2 (0.6-1.8)	2.0 (1.3-2.7)	0.15	2.4 (2.1-2.8)	2.9 (2.5-3.3)	0.09	8.9 (8.2-9.7)	9.7 (9.1-10.3)	0.14
Month 3 (symptomatic:18) (control:36)	324.7 (295.3-354.1)	364.9 (317.6-412.1)	0.25	1.7 (0.9-2.4)	2.4 (1.5-3.2)	0.28	2.6 (2.1-3.0)	3.3 (2.8-3.7)	0.06	9.5 (8.6-10.5)	10.2 (9.4-11.0)	0.29
Month 4 (symptomatic:14) (control:28)	381.8 (325.9-437.6)	425.0 (349.3-500.6)	0.44	2.4 (0.8-4.0)	3.5 (2.2-4.8)	0.32	2.6 (1.9-3.3)	3.7 (2.9-4.5)	0.06	10.3 (9.0-11.6)	11.1 (9.7-12.6)	0.44
Month 5 (symptomatic:14) (control:28)	399.3 (328.8-469.8)	410.5 (362.4-458.5)	0.78	3.3 (1.3-5.2)	3.7 (2.7-4.8)	0.63	3.2 (2.4-4.0)	3.6 (2.9-4.2)	0.51	11.4 (9.0-13.8)	11.6 (10.7-12.6)	0.83
Month 6 (symptomatic:12) (control:23)	418.0 (335.2-500.9)	445.7 (378.6-512.9)	0.60	3.5 (1.5-5.5)	4.7 (3.6-5.8)	0.22	3.2 (2.3-4.2)	4.0 (3.4-4.7)	0.14	11.2 (9.3-13.1)	11.9 (10.8-13.0)	0.44
Month 7 (symptomatic:8) (control:16)	552.4 (400.4-704.5)	574.9 (485.0-664.8)	0.77	6.5 (3.5-9.5)	6.9 (5.1-8.8)	0.78	4.8 (3.7-5.9)	4.7 (3.9-5.6)	0.88	15.6 (11.1-20.0)	12.7 (10.0-15.4)	0.22
Month 8 (symptomatic:4) (control:8)	661.1 (417.2-905.0)	561.9 (410.3-713.4)	0.37	6.7 (1.4-12.0)	6.9 (3.7-10.2)	0.91	4.5 (3.6-5.4)	4.6 (3.6-5.7)	0.86	13.8 (6.7-20.9)	13.9 (11.6-16.2)	0.97
Month 9 (symptomatic:3) (control:6)	631.6 (325.0-938.2)	630.8 (420.2-841.5)	0.99	8.0 (1.1-17.1)	8.7 (5.8-11.7)	0.75	4.6 (3.7-5.5)	5.4 (3.9-7.0)	0.38	12.6 (3.4-21.9)	15.6 (10.7-20.4)	0.37

Month 10 (symptomatic:2) (control:6)	678.5 (-932.4-2289.4)	675.8 (416.3-935.3)	0.99	6.6 (-8.0-21.3)	9.4 (5.8-13.1)	0.34	5.1 (4.4-5.7)	5.8 (3.6-8.0)	0.67	14.6 (-6.0-35.1)	15.4 (11.0-19.7)	0.81
Month 11 (symptomatic:2) (control:4)	822.4 (-101.9-1746.7)	574.3 (479.6-669.0)	0.02	10.2 (5.3-15.1)	7.0 (3.9-10.1)	0.10	6.2 (4.5-7.8)	4.9 (2.4-7.4)	0.33	17.6 (2.5-32.7)	13.7 (8.9-18.4)	0.17
Month 12 (symptomatic:2) (control:4)	728.5 (470.8-986.1)	688.7 (588.3-789.1)	0.46	9.5 (-11.5-30.4)	8.2 (6.1-10.3)	0.46	5.5 (2.0-9.0)	5.7 (3.5-8.0)	0.85	18.7 (-41.9-79.2)	15.0 (10.0-20.0)	0.39
Month 13 (s:2) (c:4)	713.9 (295.8-1132.0)	675.8 (453.9-897.6)	0.74	8.6 (-18.9-36.1)	6.8 (5.7-7.9)	0.27	5.9 (-1.2-12.9)	5.1 (3.9-6.3)	0.31	19.6 (12.9-26.3)	19.7 (16.3-23.0)	0.97

Values are mean monthly mineral intakes and 95% confidence intervals for symptomatic and control infants.

Table 5.24 Mean vitamin intake per day for dietary intake prior to diagnosis for cases and their controls

	Vitamins								
	Mean Vitamin A (ug)			Vitamin C			Mean Vitamin E (mg)		
Month (n)	Symptomatic (CI)	Control (CI)	P value	Symptomatic (CI)	Control (CI)	P value	Symptomatic (CI)	Control (CI)	P value
Month 1 (symptomatic:31) (control:62)	476.4 (453.8-499.0)	483.8 (466.4-501.3)	0.61	38.3 (32.3-44.3)	37.8 (34.1-41.5)	0.88	3.7 (2.8-4.6)	3.6 (3.1-4.2)	0.85
Month 2 (symptomatic:18) (control:36)	521.7 (496.2-547.2)	544.3 (532.6-600.0)	0.06	38.9 (32.9-44.9)	45.4 (39.7-51.0)	0.15	3.8 (2.7-4.9)	4.5 (3.6-5.4)	0.34
Month 3 (symptomatic:18) (control:36)	536.7 (503.1-570.3)	568.1 (546.1-590.2)	0.11	43.7 (36.4-51.0)	48.9 (42.3-55.5)	0.33	4.4 (3.1-5.8)	4.8 (3.9-5.8)	0.63
Month 4 (symptomatic:14) (control:28)	554.9 (452.4-657.4)	654.0 (547.7-760.3)	0.23	49.2 (38.3-60.0)	61.5 (47.4-75.6)	0.24	5.1 (3.1-7.2)	5.9 (4.6-7.3)	0.49
Month 5 (symptomatic:14) (control:28)	666.4 (514.5-818.3)	662.4 (616.0-708.8)	0.95	54.0 (41.7-66.3)	61.8 (53.4-70.3)	0.28	5.2 (3.5-7.0)	6.3 (5.1-7.6)	0.31
Month 6 (symptomatic:12) (control:23)	807.4 (436.8-1178.0)	797.4 (696.0-898.8)	0.94	63.2 (49.0-77.5)	73.2 (62.3-84.0)	0.26	6.5 (4.2-8.7)	6.9 (5.6-8.2)	0.70
Month 7 (symptomatic:8) (control:16)	1210.8 (313.7-2107.8)	929.6 (751.6-1107.6)	0.34	71.5 (54.7-88.2)	85.5 (72.1-99.0)	0.18	11.6 (0.6-22.5)	6.9 (5.5-8.3)	0.18
Month 8 (symptomatic:4) (control:8)	723.5 (521.4-925.6)	1032.4 (594.9-1469.8)	0.28	68.3 (51.6-85.1)	71.5 (53.9-89.1)	0.79	5.9 (2.1-9.8)	5.5 (4.5-6.5)	0.68
Month 9 (symptomatic:3) (control:6)	790.2 (120.4-1700.7)	881.3 (602.7-1159.9)	0.68	70.5 (2.9-138.1)	73.3 (48.2-98.4)	0.88	13.6 (6.7-33.8)	5.5 (4.2-6.8)	0.04

Month 10 (symptomatic:2) (control:6)	731.0 (124.0-1338.1)	818.3 (570.5-1066.1)	0.69	81.8 (13.9-149.7)	77.1 (41.2-112.9)	0.88	16.2 (1.3-31.1)	5.9 (4.0-7.8)	0.12
Month 11 (symptomatic:2) (control:4)	717.9 (119.7-1316.1.5)	729.6 (446.5-1012.7)	0.94	84.0 (18.2-149.9.)	56.5 (28.6-84.3)	0.21	14.6 (1.8-27.4)	4.9 (1.9-7.9)	0.19
Month 12 (symptomatic:2) (control:4)	568.1 (56.8-1080.2)	747.3 (622.1-872.4)	0.09	108.9 (32.9-184.9)	61.1 (51.2-71.0)	0.09	28.2 (2.7-51.7)	5.5 (3.1-7.8)	0.20
Month 13 (symptomatic:2) (control:4)	642.8 (71.6-1214.0)	638.4 (350.7-926.0)	0.98	100.2 (27.6-172.8)	52.3 (34.5-70.1)	0.01	32.6 (3.3-61.9)	4.4 (2.4-6.3)	0.19

Values are mean monthly vitamin intakes and 95% confidence intervals for symptomatic and control infants.

5.5 Results of telephone questionnaires follow up at 1 and 2 years of age

5.5.1 Follow up at 12 and 24 months

All participants were contacted for the 12 month assessment. A total of 733 (63%) participants could be assessed using a telephone questionnaire during the during the age range 8 to 18 months. The median age for completion of the 12 month questionnaire was 15.9 months (inter-quartile range 14.2 to 17.1). There was no difference in the age of follow up for food allergic and control infants (Table 5.33).

All participants were contacted for the 24 month assessment. A total of 823 (77%) participants could be assessed using a telephone questionnaire during the during the age range 18 to 32 months. The median age for completion of the 24 month questionnaire was 27.6 months (inter-quartile range 26.1 to 28.8). There was no difference in the age of follow up for food allergic and control infants (Table 5.33).

5.5.2 Breast feeding, formula feeding and the introduction of solids

The 12 month questionnaire data indicates that 90.0% of children in the study were breast fed at least for some time. The median duration of breast feeding was 5.0 months (inter-quartile range 2.1 to 8.0) (Table 5.25).

When the data were reviewed by food allergy status, a relationship was seen with the duration of breast feeding but not with whether or not the infant was breast fed (Table 5.30). Infants with food allergy were breast fed for a median of 3.8 months (IQR 1.1-6.0) compared to 5.0 (2.8-8.0) for controls (p=0.023). The results were similar when the food allergic infants were compared to all other ones.

Data from the 12 month questionnaire suggests that by a year of age, most children were either solely on solids (50.3%,) or were receiving solids plus botle fed infant cows' milk based formula (38.1%) (Table 5.25). Most food groups were introduced in the first year of life. By 12 months, most (>80%) infants had started to consume cows' milk (median onset 6 months, IQR 5-7), wheat (6, 6-7), white fish (8, 6-9), oily fish (8, 7-10) and egg (9, 7-10) (Table 5.26). Few had consumed soy (18.0%) or peanuts (18.0%).

The timing of introduction of each major food group was assessed by food allergy status. This analysis is complicated by the assessment being made at 12 months of age, a long time after many of the infants with food allergy had presented with symptoms. Therefore, any association seen may be due to reverse causality (where the association seen is due to the presence of symptoms, not the cause of those symptoms) highlighting the value of collecting prospective daily food diary data as this records actual intake with the possibility of future symptoms accuracy of recall.

In comparison with all others, significantly less infants with food allergy had tried cows' milk by 12 months (86.1 verses 98.4%, 0<0.001) (Table 5.35). However, there was no difference in the comparison with the controls nor in the age cows' milk was introduced. Again since these data are collected sometime after the events they are likely to be poorer quality than that of the prospective diary data.

Significantly more food allergic infants had tried soy by 12 months (47.2 verses 24.6% for controls, p=0.022) (Table 5.35). There was no difference in the age of

introduction. This is likely to be an example of reverse causality as mother of cows' milk allergic infants would be more likely to introduce soy.

Significantly less of the food allergic infants had introduced egg by 12 months of life compared to all the others (72.2 verses 90.0%, p=0.001) but there was no difference in the age of introduction (Table 5.35). Again this is likely to be due to reverse causality with mothers delaying the introduction of egg into the diet of infants with other food allergies. A similar pattern is also seen for wheat (Table 5.35).

Additional analysis has not been undertaken at the level of food allergy to individual allergens do the small number of each. This analysis will be undertaken within the whole Europrevall cohort where there are sufficient numbers to assess risk factors for food allergy to individual allergens.

Few infants were given supplementary minerals or vitamins in their first year of life (Table 5.27).

5.5.3 Cutaneous problems

More than a third of participants had a chronic rash in the first year of life, and a quarter in the second year (Table 5.28). In about half of these, the rash was itchy suggesting a period prevalence of eczema in this population of 12.2% in the first and 13.8% in the second years of life. In support of this, most of these rashes had a classical eczema distribution.

There was a highly significant association between eczema and food allergy (Table 5.36). Considering an itchy chronic rash, this was seen in half the cases of food allergy compared to only 13% of the control infants ($p<0.001$) or 10% of all the other infants ($p<0.001$). Furthermore, infants with food allergy had an earlier onset of their eczema (2.5 versus 5 months, $p<0.001$). A similar pattern was seen in the second year of life. This very early age of onset and the highly significant associations with food allergy implicates eczema as a potential causal factor in the aetiology of food allergy although eczema could also be symptoms of food allergy.

5.5.4 Gastrointestinal (GI) conditions

Possetting and repeated vomiting when otherwise well was relatively common in the whole cohort affecting about a fifth in the first year of life, less in the second year (Table 5.29). A quarter to a third reported to have colic, diarrhoea or constipation during the first year of life.

A significant association was seen between possetting and food allergy in a comparison between food allergic infants and all others (25.0 verses 11.0%, $p<0.001$) but not with the control infants (Table 5.37). However, significant association was seen for both repeated vomiting, colic and diarrhoea between food allergic infants and controls and all other infants ($p<0.01$) (Table 5.37). It is unclear from these retrospective data whether these could be causal factors or are symptoms of food allergy particularly as most persist into the second year of life.

5.5.5 Respiratory problems

Symptoms suggestive of a non-infectious rhinitis were relatively common, being reported by 16% in the first and second years of life (Table 5.30). A third reported wheeze in the first year of life with this figure halving in the second year of life. Since

very few were diagnosed with asthma, most of the episodes of wheeze are likely to have been associated with viral respiratory tract infections.

There were no associations between food allergy and either non-infectious rhinitis nor wheeze in the first year of life (Table 5.38). However, in the second year of life, there was a significant association between both non-infectious rhinitis and wheeze and food allergy in comparison with all others infants ($p<0.01$). There was also a significant association between wheeze and food allergy for the comparison with the control infants ($p<0.043$). This suggests that the development of wheeze is an association with food allergy and not on the causal pathway.

5.5.6 Infections and use of antibiotics

Unsurprisingly upper respiratory tract infections, bronchiolitis, middle ear and GI infections were common in the first two years of life (Table 5.31)..Half of the infants received antibiotics in their first year of life.

The number of episodes of bronchiolitis and GI infections and the age that antibiotics were first prescribed were significantly related with food allergy when compared with all other infants ($p<0.001$), but not for controls (Table 5.39).

5.5.7 Maternal employment and day care

Almost two-thirds of mothers had returned to work by the end of the first year of life with the median age of return of work of 8 months (IQR 6-10). Half the infants had attended day care or nursery in their first year of life going up to nearly two-thirds in their second year of life. The median age for starting day care was 9 months (IQR 6-12).

The mother of infants with food allergy were more likely than the controls and all others to be in paid employment at 12 months ($p=0.047$ and $p=0.02$ respectively). Mothers of the food allergic infants went back to work sooner than all others (6 verses 8 months, $p<0.001$) but not when compared with the controls. This correlates with an earlier age of attendance at day care (7 verses 8 months, $p=0.03$) for the food allergic infants.

Table 5.25 Breast and formula feeding from questionnaire data

Do you or did you ever breastfeed your child?	
No	72/719 (10.0%)
Yes, but not breastfeeding anymore	567/719 (78.9%)
Yes, still breastfeeding	80/719 (11.1%)
Duration of breast feeding (if started to breast feed)	5.0 (2.1 – 8) (n=572)
When breastfeeding, have you used, or do you use, any creams or oils on your breasts or nipples*	384/639 (60.1%)
When breast feeding, did you take	
Folic acid	72/617 (11.7%)
Multivitamins	222/628 (35.3%)
Vitamin D	4/613 (0.6%)
Fish oil capsule	44/604 (7.3%)
Influences on choice of formula	
Family history of allergies	24/609 (3.9%)
Child prefers the taste of the formula	49/608 (8.1%)
Prescribed or recommended by doctor or other health professional	130/611 (21.3%)
Price of formula	30/606 (5.0%)
Brand used in hospital	76/605 (12.6%)
How do you feed your child at present?	
Breast fed only	0/724 (0.0%)
Both breast and formula fed	1/724 (0.1%)
Breast fed plus solid food	61/724 (8.4%)
Both breast and formula plus solid food	18/724 (2.5%)
Bottle fed infant formula only	4/724 (0.6%)
Bottle fed infant formula plus solid foods	276/724 (38.1%)
Not breast or formula fed anymore	364/724 (50.3%)

Values are frequencies / total responses (%) or medians (IQR) (number of responses) with data collected at the 12 month assessment. Data were not available for all participants for each question. Most formula feed was cows' milk based.

Table 5.26 Introduction of food groups in the first year of life from questionnaire data

	Tried	Age when first tried (months)
Cows' milk[1]	717/733 (97.8%)	6 (5-7) (n=709)
Soy[2]	132/733 (18.0%)	9 (7-12) (n=77)
Egg[3]	653/733 (89.1%)	9 (7-10) (n=631)
Peanuts[4]	132/733 (18.0%)	12 (10-12) (n=124)
White fish[5]	676/733 (92.2%)	8 (6-9) (n=660)
Oily fish[6]	613/733 (83.6%)	8 (7-10) (n=595)
Wheat[7]	725/733 (98.9%)	6 (6-7) (n=711)

Values are frequencies / total number of responses (%) or medians (IQR) (number of responses) with data collected at the 12 or 24 month assessments. Data were not available for all participants for each question. Notes: 1. Pasteurised, non-pasteurised or UHT milk, or cheese or yoghurt. 2. Soy, soy milk, tofu or sprout. 3. Egg, boiled egg, scrambled egg or egg in baked products. 4. Peanuts, roasted peanuts, peanut butter, peanuts in shells or as an ingredient. 5. Cod or other white fish. 6. Any oily fish. 7. Wheat or bread.

Table 5.27 Use of vitamins and minerals in the first year of life from questionnaire data

	Responses	Age when first tried (months)
Multivitamins	53/722 (7.3%)	10 (6-12) (n=53)
Vitamin D	3/722 (0.4%)	8 (6-10) (n=3)
Fluoride	2/722 (0.2%)	6 (5-7) (n=2)
Fish oil	4/722 (0.6%)	13 (9-14) (n=4)
Fish oil capsules	5/722 (0.5%)	9 (8-12) (n=5)

Values are frequencies / total number of responses (%) or medians (IQR) (number of responses) with data collected at the 12 or 24 month assessments. Data were not available for all participants for each question.

Table 5.28 Details of cutaneous problems from 12 and 24 month questionnaire data

	12 month	24 month
Rash which was coming and going for at least 6 months in previous 12 months?*	105/723 (14.5%)	134/816 (16.4%)
A rash or eczema that has lasted at least 7 days in the previous 12 months?*	250/713 (35.1%)	194/763 (25.4%)
Have any of these rashes at any time affect the fold of the elbows, behind the knees, in front of the ankles, on the cheeks or around the neck, ears or eyes?*	193/339 (56.9%)	178/301 (59.1%)
Was the rash itchy?	89/250 (35.0%)	134/262 (51.2%)
Age of onset of rash (months)?	4 (2–7) (n=235)	12 (4-18) (n=243)
An rash that lasted at least 7 days or was coming and going for at least 6 months in the previous 12 months?	267/729 (36.6%)	194/763 (25.4%)
An itchy rash that lasted at least 7 days or was coming and going for at least 6 months in the previous 12 months?	89/729 (12.2%)	105/760 (13.8%)
An itchy rash that lasted at least 7 days or was coming and going for at least 6 months affecting affect the fold of the elbows, behind the knees, in front of the ankles, on the cheeks or around the neck, ears or eyes in the previous 12 months?	80/729 (10.1%)	85/760 (11.2%)
An itchy rash that lasted at least 7 days or was coming and going for at least 6 months affecting affect the fold of the elbows, behind the knees, in front of the ankles, on the cheeks or around the neck, ears or eyes that stared by 4 months of age in the previous 12 months?	42/729 (5.8%)	36/763 (4.7%)
Has your child had swollen lips in the previous 12 months?	12/720 (1.7%)	15/818 (1.8%)
Has your child had urticaria or hives in the previous 12 months?	31/724 (4.3%)	53/817 (6.5%)

Data collected at the 12 or 24 month assessments. Data were not available for all participants for each question. Numbers are frequencies / total number of responses (percentages) or medians (IQR) (number of responses).
*Asked to discount regular nappy rash.

Table 5.29 Details of gastrointestinal (GI) problems from 12 and 24 month questionnaire data

		12 month	24 month
Spitting up (possetting) without fever in the previous 12 months?	- occasionally	82/702 (11.7%)	40/800 (5.0%)
	- often	59/702 (8.4%)	10/800 (1.3%)
Repeated vomiting without any fever in the previous 12 months?	- occasionally	109/713 (15.3%)	92/806 (11.4%)
	- often	50/713 (7.0%)	16/806 (2.0%)
Colic in previous 12 months?	- occasionally	125/725 (17.2%)	71/814 (8.7%)
	- often	144/725 (19.9%)	56/814 (6.9%)
At what age did these GI symptoms begin (months)?		1 (0-2) (n=270)	1 (1-2) (n=120)
Diarrhoea (≥3 per day) without any fever in previous 12 months?	- once only	86/727 (11.8%)	95/816 (11.6%)
	- occasionally	194/727 (26.7%)	131/816 (16.1%)
	- often	22/727 (3.0%)	28/816 (3.4%)
Constipated in previous 12 months	- once only	98/725 (13.5%)	74/816 (9.1%)
	- occasionally	136/725 (18.8%)	99/816 (12.1%)
	- often	39/725 (5.4%)	17/816 (2.1%)

Data collected at the 12 or 24 month assessments. Data were not available for all participants for each question. Numbers are frequencies / total number of responses (percentages) or medians (IQR) (number of responses).

Table 5.30 Details of respiratory problems from 12 and 24 month questionnaire data

	12 month	24 month
In the last 12 months, has your child had a problem with sneezing or a runny or blocked nose when he/she did not have a cold or flu?	120/722 (16.6%)	134/815 (16.4%)
Has this nose problem been accompanied by itchy-watery eyes?*	43/145 (29.7%)	50/137 (36.5%)
In the last 12 months, has a doctor ever diagnosed your child as having hayfever?	3/725 (0.4%)	12/817 (1.5%)
In the last 12 months, has your child had wheezing or whistling in their chest?	234/728 (32.1%)	107/818 (13.1%)
In the last 12 months, has your child sounded wheezy during or after exercise?	25/725 (3.5%)	25/819 (3.1%)
In the last 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection?	95/726 (13.1%)	85/814 (10.4%)
In the last 12 months, did a doctor ever diagnose asthma in your child?	9/726 (1.2%)	18/813 (2.2%)
In the last 12 months, have bronchodilators been used?	63/715 (8.8%)	79/728 (10.9%)
In the last 12 months, have antihistamines been used?	75/717 (10.5%)	165/728 (22.7%)
In the last 12 months, have oral corticosteroids been used?	21/711 (3.0%)	22/722 (3.1%)
In the last 12 months, have inhaled corticosteroids been used?	24/690 (3.5%)	38/719 (5.3%)
Allergic reactions		
In the last 12 months, has your child had an allergic reaction when in contact with animals?**	12/727 (1.6%)	20/818 (2.4%)

Data collected at the 12 and 24 month assessments. Data were not available for all participants for each question. Numbers are frequencies / total number of responses (percentages) or medians (IQR) (number of responses).
*There was no seasonal variability in nasal problems without a cold or flu.
**Animals included were dogs and cats.

Table 5.31 Details of infections or antibiotics from 12 and 24 month questionnaire data

	12 month	24 month
Number of upper respiratory tract infections in the last 12 months	2 (2-3) (n=727)	2 (1-2) (n=819)
Number of episodes of bronchiolitis in the last 12 months	1 (1-1) (n=723)	1 (1-2) (n=818)
Number of episodes of middle ear infections in the last 12 months	1 (1-1) (n=727)	1 (1-1) (n=818)
Number of episodes of GI infections in the last 12 months	1 (1-1) (n=723)	1 (1-1) (n=817)
Antibiotics in the first year of life	357/720 (49.6%)	-
Number of times that have received antibiotics in the last 12 months	0 (0-1) (n=720)	0 (0-1) (n=817)
Age when first received antibiotics (months)	6 (3-10) (n=350)	-

Data collected at the 12 and 24 month assessments. Data were not available for all participants for each question. Numbers are medians (IQR) (number of responses).

Table 5.32 Details of maternal employment and day care from the 12 and 24 month questionnaire data

	12 month	24 month
Mother in paid employment - yes	454/726 (62.5%)	483/817 (59.1%)
- yes but on maternity leave	11/726 (1.5%)	100/817 (12.2%)
Age when mother went back to work (months)	8 (6-10) (n=451)	8 (6-11) (n=575)
Attendance at day care or nursery	347/713 (48.7%)	479/813 (58.9%)
Age when first attended day care (months)	8 (6-10) (n=346)	9 (6-12) (n=483)

Data collected at the 12 month assessment. Data were not available for all participants for each question. Numbers are frequencies / total number of responses (percentages) or medians (IQR) (total number of responses).

Table 5.33 Association between demographics and food allergy status in the first and second years of life from questionnaire data

a. First year of life

	Food allergy	All others	p-value (vs all others)	Controls	p-value (vs controls)
Age at 12 month follow up (months)	15.8 (14.2-16.5) (n=34)	15.9 (14.2-17.2) (n=695)	0.249	15.0 (13.1-16.6) (n=60)	0.359
Male sex	21/36 (58.3%)	362/697 (51.9%)	0.454	33/61 (54.1)	0.685

a. Second year of life

	Food allergy	All others	p-value (vs all others)	Controls	p-value (vs controls)
Age at 24 month follow up (months)	27.6 (26.3-28.3) (n=36)	27.6 (26.0-28.8) (n=786)	0.836	27.5 (25.8-28.3) (n=65)	0.658
Male sex	19 /36 (52.8%)	409/787 (52.0%)	0.924	38/65 (58.5)	0.581

Values are frequencies / total number of responses (%) or medians (IQR) (total number of responses) with data collected at the 12 or 24 month assessments. Food allergy is defined as any challenge proven food allergy during the first 24 months of life. Data was not available for all participants for each question. P-values represent comparison between the group of participants with food allergy with firstly all other participants and secondly the control group (2 other participants matched by age to food allergic one). Comparison uses chi squared test for frequencies or two sample Wilcoxon sum rank tests for medians.

Table 5.34 Association between breast and formula feeding and food allergy in the first year of life from questionnaire data

	Food allergy	All others	p-value (vs all others)	Controls	p-value (vs controls)
Do you or did you ever breastfeed your child?					
No	1/36 (2.8%)	71/683 (10.4%)	0.255	7/60 (11.7%)	0.309
Yes, but not breastfeeding anymore	32/36 (88.9%)	535/683 (78.3%)		48/60 (80.0%)	
Yes, still breastfeeding	3/36 (8.3%)	77/683 (11.3%)		5/60 (8.3%)	
Duration of breast feeding (months)	3.8 (1.1-6.0) (n=32)	5.0 (2.5-8.0) (n=540)	<0.001	5.0 (2.8 – 8.0) (n=48)	0.023
When breastfeeding, have you used, or do you use, any creams or oils on your breast or nipples	16/34 (47.1%)	369/606 (60.9%)	0.109	34/51 (66.7%)	0.072

Values are frequencies / total number of responses (%) or medians (IQR) (total number of responses) with data collected at the 12 month assessment. Food allergy is defined as any challenge proven food allergy during the first 24 months of life. Data was not available for all participants for each question. Most formula feed was cows' milk based. P-values represent comparison between the group of participants with food allergy with firstly all other participants and secondly the control group (2 other participants matched by age to food allergic one). Comparison uses chi squared test for frequencies or two sample Wilcoxon sum rank tests for medians.

Table 5.35 Association between introduction of food groups and food allergy status in the first year of life from 12 month questionnaire data

	Food allergy	Others	p-value (vs all others)	Control	p-value (vs controls)
Tried cows' milk	31/36 (86.1%)	686/697 (98.4%)	<0.001	58/61 (95.1%)	0.121
Age when first tried (months)	6 (5-7) (n=31)	6 (5-7) (n=678)	0.857	6 (5-7) (n=57)	0.601
Tried soy	17/36 (47.2%)	115/697 (16.5%)	<0.001	15/61 (24.6%)	0.022
Age when first tried (months)	7 (6-10) (n=13)	9 (7-12) (n=64)	0.136	7 (6-12) (n=6)	0.742
Tried egg	26/36 (72.2%)	627/697 (90.0%)	0.001	51/61 (83.6%)	0.181
Age when first tried (months)	8 (7-10) (n=25)	9 (7-10) (n=606)	0.735	9 (7-10) (n=49)	0.821
Tried peanuts	5/36 (13.9%)	127/697 (18.2%)	0.510	7/61 (11.5%)	0.727
Age when first tried (months)	9 (6-10) (n=5)	12 (10-12) (n=119)	0.174	12 (10-13) (n=7)	0.278
Tried white fish	30/36 (83.3)	646/697 (92.7%)	0.041	52/61 (85.3%)	0.801
Age when first tried (months)	7.5 (6-9) (n=30)	0.928 (6-9) (n=630)	0.310	8 (6-9) (n=48)	0.927
Tried oily fish	23/36 (63.9%)	590/697 (84.7%)	0.001	46/61 (75.4%)	0.226
Age when first tried (months)	7 (6-9) (n=23)	8 (7-10) (n=572)	0.0323	8.5 (7-10.5) (n=44)	0.047
Tried wheat	34/36 (94.4%)	691/697 (99.1%)	0.008	58/61 (95.1%)	0.891
Age when first tried (months)	6 (6-7) (n=34)	6 (6-7) (n=677)	0.071	6 (6-8) (n=55)	0.169

Values are frequencies / total responses (%) or medians (IQR) (total number of responses) with data collected at the 12 month assessment. Food allergy is defined as any challenge proven food allergy during the first 24 months of life. Data was not available for all participants for each question. P-values represent comparison between the group of participants with food allergy presenting during the first 24 months of life with firstly all other participants and secondly the control group (2 other participants matched by age to food allergic one).

Comparison uses chi squared test for frequencies or two sample Wilcoxon sum rank tests for medians. Notes: 1. Pasteurised, non-pasteurised or UNT milk, or cheese or yoghurt. 2. Soy, soy milk, tofu or sprout. 3. Egg, boiled egg, scrambled egg or egg in baked products. 4. Peanuts, roasted peanuts, peanut butter, peanuts in shells or as an ingredient. 5. Cod or other white fish. 6. Any oily fish. 7. Wheat or bread.

Table 5.36 Association between skin problems and food allergy status in the first and second years of life from questionnaire data

a. First year of life

Clinical problem	Food allergy	Other	p-value (vs all others)	Control	p-value (vs controls)
Rash which was coming and going for at least 6 months?*	20/35 (57.1%)	85/688 (12.4%)	<0.001	9/59 (15.3%)	<0.001
A rash or eczema that has lasted at least 7 days?*	24/31 (77.4%)	226/682 (33.1%)	<0.001	24/56 (42.9%)	0.002
Have any of these rashes at any time affect the fold of the elbows, behind the knees, in front of the ankles, on the cheeks or around the neck, ears or eyes?*	25/29 (86.2%)	168/310 (54.2%)	0.001	19/39 (48.7%)	0.001
Was the rash itchy?	19/28 (67.9%)	70/222 (31.5%)	<0.001	8/27 (29.6%)	0.005
Age of onset of rash (months)	2.5 (1-5) (n=28)	5 (2-7) (n=207)	<0.001	5 (2-9) (n=22	0.01
An rash that lasted at least 7 days or was coming and going for at least 6 months	28/35 (80.0%)	239/694 (34.4%)	<0.001	25/60 (41.7%)	<0.001
An itchy rash that lasted at least 7 days or was coming and going for at least 6 months	19/35 (54.3%)	70/694 (10.1%)	<0.001	8/60 (13.3)	<0.001
An itchy rash that lasted at least 7 days or was coming and going for at least 6 months affecting affect the fold of the elbows, behind the knees, in front of the ankles, on the cheeks or around the neck, ears or eyes?	18/25 (51.4%)	62/694 (8.9%)	<0.001	6/60 (10.0%)	<0.001
An itchy rash that lasted at least 7 days or was coming and going for at least 6 months affecting affect the fold of the elbows, behind the knees, in front of the ankles, on the cheeks or around the neck, ears or eyes that stared by 4 months of age?	14/35 (40.0%)	28/694 (4.0%)	<0.001	2/60 (3.3%)	<0.001

b. Second year of life

Clinical problem	Food allergy	Other	p-value (vs all others)	Control	p-value (vs controls)
Rash which was coming and going for at least 6 months in the last 12 months?*	15/36 (41.7%)	119/780 (15.3%)	<0.001	14/64 (21.9%)	0.04
A rash or eczema that has lasted at least 7 days in the last 12 months?*	17/28 (60.7%)	177/735 (24.1%)	<0.001	14/57 (24.6%)	0.001
Have any of these rashes at any time affect the fold of the elbows, behind the knees, in front of the ankles, on the cheeks or around the neck, ears or eyes?*	22/25 (88.0%)	156/276 (56.5%)	0.002	14/26 (53.9%)	0.007
Was the rash itchy?	18/24 (75.0%)	116/238 (48.7%)	0.014	12/20 (60.0%)	0.287
Age of onset of rash (months)?	2.5 (1-6) (n=22)	12 (6-18) (n=221)	<0.001	8.5 (4-12) (n=18)	0.006
An rash that lasted at least 7 days or was coming and going for at least 6 months in the last 12 months?					
An itchy rash that lasted at least 7 days or was coming and going for at least 6 months in the last 12 months?	14/28 (50.0%)	91/732 (12.4%)	<0.001	7/56 (12.5%)	<0.001
An itchy rash that lasted at least 7 days or was coming and going for at least 6 months affecting affect the fold of the elbows, behind the knees, in front of the ankles, on the cheeks or around the neck, ears or eyes in the last 12 months?	14/28 (50.0%)	71/732 (9.7%)	<0.001	6/56 (10.7%)	<0.001
An itchy rash that lasted at least 7 days or was coming and going for at least 6 months affecting affect the fold of the elbows, behind the knees, in front of the ankles, on the cheeks or around the neck, ears or eyes that stared by 4 months of age in the last 12 months?	10/28 (35.7%)	26/735 (3.5%)	<0.001	2/57 (3.5%)	<0.001

Values are frequencies (%) or medians (IQR) (number of observations) with data collected at the 12 and 24 month assessments. Food allergy is defined as any challenge proven food allergy during the first 24 months of life. Data was not available for all participants for each question. P-values represent comparison between the group of participants with food allergy with firstly all other participants and secondly the control group (2 other participants matched by age to food allergic one). Comparison uses chi squared test for frequencies or two sample Wilcoxon sum rank tests for medians.

Table 5.37 Association between gastrointestinal problems and food allergy status in the first and second years of life from questionnaire data

a. First year of life

Clinical problem		Food allergy	Other	p-value (vs all others)	Control	p-value (vs controls)
Spitting up without fever (posseting)	- occasionally	8/32 (25.0%)	74/670 11.0%)	<0.001	8/54 (14.8%)	0.094
	- often	9/32 (28.1%)	50/670 (7.5%)		8/54 (14.8%)	
Repeated vomiting without any fever	- occasionally	15/34 (44.1%)	94/679 (13.8%)	<0.001	12/58 (20.7%)	<0.001
	- often	7/34 (20.6%)	43/679 (6.3%)		2/58 (3.5%)	
Colic - occasionally		9/34 (26.5%)	116/691 (16.8%)	<0.001	12/59 (20.3%)	0.01
- often		14/34 (41.2%)	130/691 (18.8%)		10/59 (17.0%)	
At what age did these begin (months)?		1 (0-1) (n=23)	1 (0-2) (n=247)	0.047	1 (0-2) (n=23)	0.150
Diarrhoea (≥3 per day) without any fever	- once only	4/34 (11.8%)	82/693 (11.8%)	<0.001	6/59 (10.2%)	0.015
	- occasionally	6/34 (17.7%)	188/693 (27.1%)		17/59 (28.8%)	
	- often	7/34 (20.6%)	15/693 (2.2%)		1/59 (1.7%)	
Constipated - once only		3/33 (9.1%)	95/692 (13.7%)	0.328	13/60 (21.7%)	0.12
- occasionally		6/33 (18.2%)	130/692 18.8%)		18/60 (30.0%)	
- often		4/33 (12.1%)	35/692 (5.1%)		3/60 (5.0%)	

b. Second year of life

Clinical problem	Food allergy	Other	p-value (vs all others)	Control	p-value (vs controls)
Spitting up without fever (possetting) in the last 12 months? - occasionally	6/36 (16.7%)	34/764 (4.5%)	0.004	2/65 (3.1%)	0.042
- often	0/36 (0.0%)	10/764 (1.3%)		1/65 (1.5%)	
Repeated vomiting without any fever (posseting) in the last 12 months?					
- occasionally	13/35 (37.1%)	79/771 (10.3%)	<0.001	4/65 (6.2%)	<0.001
- often	0/35 (0.0%)	16/771 (2.1%)		0/65 (0.0%)	
Colic in the last 12 months? - occasionally	5/35 (14.3%)	66/779 (8.5%)	0.242	3/65 (4.6%)	0.132
- often	4/35 (11.4%)	52/779 (6.7%)		4/65 (6.2%)	
At what age did these begin (months)?	1 (0-1) (n=9)	1 (1-2) (n=111)	0.195	1 (1-1) (n=6)	0.946
Diarrhoea (≥3 per day) without any fever in the last 12 months? - once only	3/35 (8.6%)	92/781 (11.8%)	0.016	8/64 (12.5%)	0.184
- occasionally	9/35 (25.7%)	122/781 (15.6%)		10/64 (15.6%)	
- often	4/35 (11.4%)	24/781 (3.1%)		2/64 (3.1%)	
Constipated in the last 12 months?					
- once only	2/35 (5.7%)	72/781 (9.2%)	0.069	5/64 (7.8%)	0.206
- occasionally	9/35 (25.7%)	90/781 (11.5%)		7/64 (10.9%)	
- often	0/35 (0.0%)	17/781 (2.2%)		2/64 (3.1%)	

Values are frequencies (%) or medians (IQR) with data collected at the 12 and 24 month assessments. Food allergy is defined as any challenge proven food allergy during the first 24 months of life. Data were not available for all participants for each question. P-values represent comparison between the group of participants with food allergy with firstly all other participants and secondly the control group (2 other participants matched by age to food allergic one). Comparison uses chi squared test for frequencies or two sample Wilcoxon sum rank tests for medians.

Table 5.38 Association between respiratory problems and food allergy status in the first and second years of life from questionnaire data

a. First year of life

Clinical problem	Food allergy	Other	p-value (vs all others)	Control	p-value (vs controls)
In the last 12 months, has your child had a problem with sneezing or a runny or blocked nose when he/she did not have a cold or flu?	9/33 (27.3%)	111/689 (16.1%)	0.092	14/59 (23.7%)	0.707
In the last 12 months, has your child had wheezing or whistling in their chest?	15/34 (44.1)	219/694 (31.6%)	0.126	25/60 (41.7%)	0.817

b. Second year of life

Clinical problem	Food allergy	Other	p-value (vs all others)	Control	p-value (vs controls)
In the last 12 months, has your child had a problem with sneezing or a runny or blocked nose when he/she did not have a cold or flu?	12/35 (34.3%)	122/780 (15.6%)	0.004	13/65 (20.0%)	0.116
In the last 12 months, has your child had wheezing or whistling in their chest?	10/35 (28.6%)	97/783 (12.4%)	0.005	8/65 (12.3%)	0.043

Values are frequencies (%)with data collected at the 24 month assessment. Food allergy is defined as any challenge proven food allergy during the first 24 months of life. Data were not available for all participants for each question. P-values represent comparison between the group of participants with food allergy with firstly all other participants and secondly the control group (2 other participants matched by age to food allergic one). Comparison use chi squared test for frequencies.

Table 5.39 Association between infections and food allergy status in the first and second years of life from questionnaire data

a. First year of life

	Food allergy	Other	p-value (vs all others)	Control	p-value (vs controls)
Number of upper respiratory tract infections in the last 12 months	2 (2-3) (n=34)	2 (2-3) (n=693)	0.141	2 (2-3) (n=60)	0.518
Number of episodes of bronchiolitis in the last 12 months	1 (1-1) (n=34)	1 (1-1) (n=689)	<0.001	1 (1-1) (n=59)	0.068
Number of episodes of middle ear infections in the last 12 months	1 (1-1) (n=34)	1 (1-1) (n=693)	0.368	1 (1-1) (n=60)	0.345
Number of episodes of GI infections in the last 12 months	1 (1-1) (n=34)	1 (1-1) (n=689)	0.022	1 (1-1) (n=60)	0.103
Number of times that have received antibiotics	1 (0-2) (n=33)	0 (0-1) (n=687)	0.115	0 (0-2) (n=58)	0.070
Age when first received antibiotics (months)	3 (1-7) (n=21)	6 (4-10) (n=687)	<0.001	6 (2.5-9.5) (n=28)	0.170

b. Second year of life

	Food allergy	Other	p-value (vs all others)	Control	p-value (vs controls)
Number of upper respiratory tract infections in the last 12 months	2 (1-2) (n=35)	2 (1-2) (n=784)	0.709	2 (1-2) (n=65)	0.694
Number of episodes of bronchiolitis in the last 12 months	1 (1-1) (n=35)	1 (1-1) (n=783)	0.603	1 (1-1) (n=65)	1.00
Number of episodes of middle ear infections in the last 12 months	1 (1-1) (n=35)	1 (1-1) (n=783)	0.102	1 (1-1) (n=65)	0.190
Number of episodes of GI infections in the last 12 months	1 (1-1) (n=35)	1 (1-1) (n=782)	0.765	1 (1-1) (n=64)	0.828
Number of times that have received antibiotics in last 12 months	0 (0-2) (n=34)	0 (0-1) (n=783)	0.325	0 (0-2) (n=65)	0.735

Values are medians (IQR) (total number of responses) with data collected at the 12 and 24 month assessments. Food allergy is defined as any challenge proven food allergy during the first 24 months of life. Data were not available for all participants for each question. P-values represent comparison between the group of participants with food allergy with firstly all other participants and secondly the control group (2 other participants matched by age to food allergic one). Comparison by Wilcoxon sum rank test.

Table 5.40 Association between maternal employment and day care and food allergy status in the first and second years of life from questionnaire data

a. First year of life

Clinical problem		Food allergy	Other	p-value (vs all others)	Control	p-value (vs controls)
Mother in paid employment	- yes	28/34 (82.4%)	426/692 (61.6%)	0.047	32/59 (54.2%)	0.02
	- yes but on maternity leave	0/34 (0.0%)	11/692 (1.6%)		2/59 (3.4%)	
Age when mother went back to work (months)		6 (5-8.5) (n=28)	8 (6-10) (n=423)	<0.001	8 (6-11) (n=29)	0.13
Attendance at day care or nursery		18/34 (52.9%)	329/679 (48.5%)	0.61	25/59 (42.4%)	0.33
Age when first attended day care (months)		7 (6-8) (n=18)	8 (6-10) (n=328)	0.03	8 (7-12) n=25)	0.10

b. Second year of life

Clinical problem		Food allergy	Other	p-value (vs all others)	Control	p-value (vs controls)
Mother in paid employment	- yes	25/35 (71.4%)	458/782 (58.6%)	0.318	35/65 (53.9%)	0.215
	- yes but on maternity leave	3/35 (8.6%)	97/782 (12.4%)		7/665 (10.8%)	
Age when mother went back to work (months)		7 (5-9) (n=27)	8 (6-11) (n=548)	0.039	7.5 (6-11.5) (n=40)	0.165
Attendance at day care or nursery		21/35 (60.0%)	458/778 (58.9%)	0.894	33/65 (50.8%)	0.377
Age when first attended day care (months)		8 (7-10) (n=22)	9 (6-12 (n=461)	0.506	11 (7-14) (n=35)	0.442

Values are frequencies / total responses (%) or medians (IQR) (number of responses) with data collected at the 12 and 24 month assessments. Food allergy is defined as any challenge proven food allergy during the first 24 months of life. Data were not available for all participants for each question. P-values represent comparison between the group of participants with food allergy with firstly all other participants and secondly the control group (2 other participants matched by age to food allergic one). Comparisons use chi squared test for frequencies or two sample Wilcoxon sum rank tests for medians.

5.6. The identification of specific complementary feeding patterns associated with the development of food allergy by 1 and 2 years of age.

A total of 39 infants diagnosed with a food allergy had their dietary intake recorded and these were coded as previously described along with intake records of 78 age-matched controls. Descriptive analyses initially carried out on the dataset showed that there was no significant difference in baseline characteristics of the group (see table 5.18). There were no significant differences in breastfeeding initiation, duration or duration of exclusive breastfeeding. There was also no difference in, age at first infant formula, age at first cows' milk protein, age at first egg or age at first wheat introduction between the groups. There was however a significant difference in the age at which solids were first introduced (p=0.049) with the age at introduction being later for controls (20 weeks compared to 18.6 weeks). See section 5.4.2 for further details

Analysis of the diet data for patterns of feeding associated with the development of food allergy took place using two methodologies. The first looked at concurrent feeding of breast milk with solid introduction. The second methodology used Principal Component Analysis

5.6.1 Concurrent breastfeeding

Analysis of the data for concurrent breastfeeding practices showed that if egg or infant formula was introduced whilst the infant was still being breastfed, the infant was statistically less likely to develop a food allergy than if the egg or infant formula was introduced after breast feeding had stopped. (p=0.036 and p=0.049 respectively). The length of overlap (i.e. how long the infant received breast milk and egg or breast milk and infant formula) was also significantly different between the groups (p=0.043 for egg and breast milk overlap and p=0.044 for cows' milk ingredient and breast milk overlap. The mean length of overlap of breast milk and egg in the diet was 0.05 weeks for symptomatic infants compared to 0.69 weeks for control infants. The mean length of overlap of breast milk and infant formula was 6.9 weeks for symptomatic infants compared to 10.7 weeks for control infants. There was no protective effect seen for concurrent breast feeding and egg as an ingredient or concurrent breast feeding and cows' milk as an ingredient.

5.6.2 Principal Component Analysis

Principal Component Analysis was carried out to see if there were infant feeding patterns associated with the development of food allergy. There are two methodologies to determine such patterns. One is to identify feeding patterns for the cohort and assign the resultant scores for each pattern to each infant and then perform a Mann-Whitney U test to determine if there is a differences in pattern scores between the symptomatic infants and their controls. The alternative is to only run the pattern analysis on the symptomatic and control infants only. The former methodology was chosen for this work as it maximised the data included in the pattern analyses.

Both *a posteriori* and *a priori* pattern analyses were carried out on the infant feeding data. The *a posteriori* analyses put all feeding data into the analysis create a number of resultant feeding patterns. After that *a priori* analyses were carried out by selecting certain factors within the data on which to carry out the pattern analysis. Such factors were breastfeeding characteristics (including duration, exclusivity and overlap with

solid food introduction), solid introduction characteristics, diversity of the diet (number of solids food types in the diet), commercial vs home prepared infant foods, and 'healthy' versus 'unhealthy' weaning foods.

In the *a posteriori* analysis five principal components were identified (Table 5.41) which accounted for 50 % of the variance observed. The first component's main characteristic was diversity of the diet (indicated by the 'total' variables) whereas the main characteristic for the second component was anything related to breastfeeding. The third component's main characteristics were to do with solid introduction. The fourth component is characterised by sesame and the fifth by tree nuts, peanuts and crisps.

Further analysis of the data examined whether there was a significant difference in these patterns between the diets of symptomatic infants compared with their controls. Analysis of variance showed no difference between the groups for component 2 ('breastfeeding'), component 3 ('solid introduction'), component 4 ('sesame') or component 5 (peanuts, tree nuts and crisps). It did however find a significant difference for component 1 Details of this analysis are found in Table 5.42.

Table 5.41 Foods included in the *a posteriori* analysis and their contributions to differing components

Rotated Component Matrix[a]

	Component				
	1	2	3	4	5
Total no. of weeks infant had cows' milk	.589	.242	.014	.115	.180
Total no. of weeks infant had cows' milk ingredient	.864	.100	.027	-.124	-.151
Total no. of weeks infant had eggs	.695	.122	.001	.196	-.041
Total no. of weeks infant had eggs as an ingredient	.730	.114	-.125	.181	-.179
Total no of weeks infant had peanuts	.217	-.035	.024	.111	-.369
Total no. of weeks infant had sesame	.357	.032	.034	.661	.098
Total no. of weeks infant had oily fish	.783	.096	-.004	.065	-.035
Total no. of weeks infant had white fish	.801	.081	.054	-.093	-.016
Total no. of weeks infant had wheat	.891	.107	.046	-.058	-.135
Total no. of weeks infant had fruit	.639	.143	.108	.276	-.031
Total no. of weeks infant had toddler packet snacks	.758	.075	.211	-.063	.003
Total no. of weeks infant had crisps	.324	.002	-.169	-.194	-.509
Total no. of weeks infant had chocolate	.520	.100	-.256	-.189	-.226
No. of weeks infant received breast milk	.139	.800	.118	.026	-.024
No. of weeks infant received breast milk and solids	.386	.820	.007	.043	-.006
No. of weeks infant received infant formula and breast milk	.379	.239	.072	-.064	.025
No of weeks infant received eggs and breast milk	.419	.517	-.098	.292	.143

No of weeks infant received egg as an ingredient and breast milk	.422	.524	-.206	.301	.079
No of weeks infant received peanuts and peanuts and breast milk	.088	.093	-.009	.037	-.257
No. of weeks infant received sesame and breast milk	.225	.125	.014	.739	.118
No. of weeks infant received tree nuts and breast milk	.020	.030	-.009	.483	-.103
No of weeks infant received oily fish and breast milk	.433	.564	-.134	.163	.176
No of weeks infant received white fish and breast milk	.415	.646	-.110	.014	.084
No of weeks infant received wheat and breast milk	.443	.759	-.077	.099	.036
Age infant first received solids	-.059	.264	.561	.165	.038
No. of weeks infant was exclusively breast fed	-.021	.821	.175	.029	-.087
Age infant first had cows' milk	.195	-.145	.168	-.201	-.383
Age infant first had cows' milk ingredient	-.073	.211	.685	.173	.055
Age infant first had egg	.116	-.022	.482	-.238	-.051
Age infant first had egg ingredient	.065	-.077	.616	-.137	.049
Age infant first had any egg	.046	-.029	.702	-.196	-.014
Age infant first had peanut	.072	.087	.046	-.170	.670
Age infant first had tree nuts	.085	.072	.008	-.424	.503
Age infant first had oily fish	.034	-.090	.541	-.124	-.052
Age infant first had white fish	.011	-.009	.522	-.011	-.041
Age infant first had any fish	-.037	.018	.655	-.006	.005
Age infant first had sesame	.106	-.021	.110	-.503	.204
Age infant first had wheat	-.096	.159	.662	.057	.019
Age infant first had commercial savoury jar	.018	.188	.545	.193	.075
Age infant first had commercial sweet jar	-.042	.114	.533	.075	.064
Age infant first had 'fast food'	.100	.004	.357	-.131	.138
Age infant first had fruit	.105	-.200	.273	-.302	.012
Age infant first had chocolate	.072	-.090	.279	.045	.311
Age infant first had crisps	.078	-.059	.132	.029	.543
Age infant first had toddler packet snacks	-.018	-.053	.370	-.023	.078
Age infant first had formula	.049	.739	.169	-.044	-.105
Age infant first had any cows' milk protein	.005	.845	.201	.034	-.103

Principal Component Analysis with Varimax rotation method with Kaiser Normalization. The rotation (a) converged in 6 iterations. The variables important in each component are identified by those variables with the highest component numbers. For component 1 those variables which represent the total number of weeks that food was present in the infant diet. For component 2 the variables are those to do with breast milk and or infant formula. For component 3 the variables are to do with solid introduction. For component 4 the variables are those to do with sesame and for component 5 the variables are to do with age at introduction of peanuts and tree nuts.

Table 5.42 Details of Analysis of Variance of principal components from the *a posteriori* analysis

Descriptives

						95% Confidence Interval for Mean				
		N	Mean	Std. Deviation	Std. Error	Lower Bound	Upper Bound	Minimum	Maximum	Sig
Factor score for component 1	Symptomatic	41	.1294994	.93057478	.14533136	-.1642262	.4232250	-1.07942	2.59855	
	Control	81	.9433140	1.22256975	.13584108	.6729817	1.2136464	-.91619	4.12415	0.000
	Total	122	.6698190	1.19309806	.10801802	.4559688	.8836691	-1.07942	4.12415	
Factor score for component 2	Symptomatic	41	-.1746221	.91673484	.14316993	-.4639793	.1147351	-1.35615	1.97089	
	Control	81	-.1941896	1.14797389	.12755265	-.4480275	.0596483	-1.63801	3.31036	0.925
	Total	122	-.1876136	1.07201077	.09705529	-.3797602	.0045329	-1.63801	3.31036	
Factor score for component 3	Symptomatic	41	-.1090216	1.23865952	.19344612	-.4999908	.2819476	-3.78077	3.50021	
	Control	81	.2080050	1.37499272	.15277697	-.0960309	.5120409	-3.96042	4.56154	0.216
	Total	122	.1014633	1.33409020	.12078285	-.1376582	.3405848	-3.96042	4.56154	
Factor score for component 4	Symptomatic	41	.1236386	1.21322388	.18947374	-.2593022	.5065793	-1.68818	6.41257	
	Control	81	-.1314815	1.45719696	.16191077	-.4536942	.1907312	-3.72486	9.98131	0.337
	Total	122	-.0457444	1.38026845	.12496363	-.2931429	.2016541	-3.72486	9.98131	
Factor score for component 5	Symptomatic	41	-.2523142	1.89478871	.29591628	-.8503833	.3457549	-8.51605	3.40309	
	Control	81	-.0700553	1.14908067	.12767563	-.3241379	.1840273	-4.22099	2.88709	0.511
	Total	122	-.1313062	1.43781321	.13017349	-.3890190	.1264065	-8.51605	3.40309	

Mean, standard deviation, 95% confidence intervals and significance level of analysis of variance between mean component scores for symptomatic versus control infants for the 5 component scores identifies in the *a posteriori* analysis on infant feeding data.

Other patterns that were found to be significantly different between the two groups were: -

i) concurrent feeding of breast milk whilst solids were introduced (p=0.044), with breast milk appearing to be protective
ii) concurrent feeding of breast milk and formula (p=0.008), with breast milk appearing to be protective
iii) diversity of diet (p=0.02) with the control infants having a more diverse diet compared to the symptomatic infants
iv) 'infant feeding guidelines' where a diet following infant feeding guidelines appears to have a protective effect (0.027). The infant guidelines food pattern was characterised by high component scores for fresh fruit, dried fruit and fish and low scores for crisps, daily commercial baby foods and potato products.

The effect of maternal and environmental characteristics on dietary pattern scores was examined. A higher score for breastfeeding 'overlap' was associated with higher maternal age but not education or any other factors such as smoking habits, urban living environment. A high diversity score was associated with maternal allergy and higher maternal education and age. A higher 'healthy' score was associated with higher maternal age and education, maternal allergies and maternal non-smoking.

6. General Discussion

6.1 Recruitment of a birth cohort

Birth cohorts represent an ideal approach to assessing problems at a population to local level. As such, this approach is perfect for assessing infant nutrition and its role in the development of food allergy. Birth cohorts are a precious resource that need to be valued given the challenges associated with their successful recruitment.

In this study, a cohort of over 1200 pregnant women was recruited (Objective 1). This revised target is less than was originally envisaged due to the inclusion of additional sites in the EuroPrevall project. The recruitment strategy had to be fundamentally changed to prevent a local NHS staffing problem fatally impeding the study. As a result of the pressures on the midwifery staff, they did not have the time to engage as fully with the study as they and we had hoped that they would. The problem was highlighted by the monthly system of reporting employed by the study team. This also allowed us to optimise the recruitment strategy on a month by month basis. The study was undertaken at a time when NHS service support costs were not visible in Trust's budgets. Now that this has changed, it should be easier in future to engage local NHS staff and managers to facilitate this type of project.

The characteristics of the recruited birth cohort (Section 3) suggest that it is broadly representative of the local population in central Hampshire. As such it is predominately caucasian, with older and more educated mothers than the average UK region. Through our multiple recruitment initiatives, we were able to recruit across the entire geographical patch and obtain good representation from all parts of the population. This means that skewing of the data can be addressed, where necessary, by standardising analyses to a UK average population.

6.2 Collection and analysis of dietary intake information

Infant food diaries were returned by the majority of mothers (Objective 2). A total of 594 completed them until 24 weeks of age with 241 completing them for the whole first year. It is a common phenomenon that research studies/surveys tend to have a higher level of older/well educated mothers than those seen in the population from which the study participants were drawn (Bolling et al., 2007), so it is not a surprise that the demographics of this study population differ from the demographics of the community from which it was recruited. Additional skewing of the data occurred due to the fact that food diary return rate was higher in the older/well educated mothers. This means that the data cannot be extrapolated *per se* to the UK population and needs to be interpreted with care. However, as cohort data is often not fully representative of the larger population, statistical techniques can allow for observed differences, making conclusions more useful for population-wide conclusions.

Despite the skewed nature of the data, the infant feeding characteristics of the cohort provides some interesting and useful information as to how children were being fed in their first year between mid-2006 and late 2008. In 2003 the Department of Health changed their advice regarding infant feeding to be in line with the recommendations of the World Health Organisation. This new advice stated that infants should be breastfed exclusively for 26 weeks and then solid introduction should commence while the infant is still being breastfed. Other professional bodies provided

clarification of this advice by stating that solid introduction should commence when the infant is ready and that time may be before 26 weeks but that solids should never be introduced before 17 weeks of age. Prior to the revised advice from the Department of Health the recommendation was to introduce solids into the infant's diet between 4-6 months.

When the Department of Heath infant feeding study was published in 2007 (Bolling et al. 2007) (reporting on data collected in 2005) it was obvious that the majority of mothers where not meeting the new recommendation of 2003, although the number of mothers breastfeeding at both 17 and 26 weeks had increased from the levels seen in 2000 and the number of infants receiving solid foods by 17 weeks had reduced. The adjusted data from the T07046 cohort shows that although only the minority of mothers are meeting these new recommendations, the trend seen in the IFS is continuing towards later weaning and longer exclusive breastfeeding, demonstrating that the advice of 2003 is being taken up by a larger proportion of the UK population.

Additionally, the data collectively demonstrate that both maternal age and maternal education have an effect on how infants are fed, with older and better educated mothers being more likely to meet the Department of Health's Infant feeding guidelines. This has an implication as to which population groups should be targeted to increase compliance to infant feeding guidelines.

6.3 Determination of the frequency of food allergy

The study was successful in ascertaining cases of food allergy (Objective 3) with 173 parents contacting the study team directly and a further 61 being picked up from the 12 and 24 month questionnaires (Objective 5). With parents contacting us with the onset of symptoms, we were able to record a cumulative incidence rate. It is unlikely that many cases were missed as the two study paediatricians (GR, KF) run the local paediatric allergy clinics where they would have been referred. As expected, there was a very high rate of parent perceived food allergy (28.4%, 95% confidence interval 25.4 – 31.6%). On the basis of the triage documentation (Appendix G), only 74 / 823 (9.0%, 7.1 – 11.2%) were considered likely to have a food allergy. In almost half the cases, a double-blind, placebo-controlled food challenge ruled out allergy giving a rate of food allergy in the whole cohort of 5.0% (3.6 – 6.7%). This is comparable to the current literature as reviewed by the recent EuroPrevall meta-analysis (Rona et al. 2007) and the recently reported cumulative incidence to age 3 years in the Isle of Wight (Venter et al. 2008). It is also the cumulative incidence rate that we were expecting. The trigger foods were, in order of importance, milk, egg, peanut, soy, wheat and fish. These were as expected for this age group. Uptake of clinical visits and food challenges was high, possibly because of the education and advice that the multidisciplinary study team were able to provide families.

The relatively low rate of food allergy means that even with a cohort of 1200, the number of affected participants is low. Within the cohort we were able to provide prevalence figures for allergies to the individual foods (table 5.14) but with the number of UK participants, the 95% confidence interval for these are relatively large. With a pan-European cohort of over 15000 and at least 500 infants with food allergy, it will be possible to improve the precision of these prevalence figures. We also have a considerable amount of data on presenting symptoms, baseline serum specific IgE

and baseline skin prick testing as well as clinical thresholds for reactions. Again, the UK birth cohort is too small to be able to make sensible conclusions about these for individual foods. This though will be possible and is planned within the wider EuroPrevall dataset when this becomes available later in the year. Additionally, repeat challenges were undertaken on participants with challenge proven food allergy providing data on outgrowing of the allergy. Again, the UK dataset for these is small but will contribute to the pan European analysis.

The challenges associated with successfully assessing most of the symptomatic children in the cohort were considerable. Yet of the 135 who we wanted to assess further, only 4 (3%) refused. Of the 74 children that we wanted to undertake a challenge on, only 13 (18%) refused despite the need for two separate day admissions for the active and placebo parts of the challenge (Rance et al. 2009)]. This was achieved utilising a multidisciplinary team with support and information being provided by a paediatric allergist, paediatric dietician and paediatric nursing staff. Additionally, the team were able to support the child's and family's ongoing needs as they coped with a child with food allergy. The dangers associated with food challenge are often quoted as being good reasons for not undertaking them. We had one episode of anaphylaxis during the PIFA food challenges. This was the child's first known dietary exposure to egg and the family were grateful that this reaction occurred in hospital and not at home when they first fed their child a food containing egg. This rate of severe allergic reactions was as expected from our previous experience (Torr et al. 2002). It does, though, emphasise the need for trained staff that are prepared to manage emergencies which was in place for this study.

The other achievement for the study was the recruitment of appropriate controls for the food allergic patients. We were aiming for 2 controls for each participant eligible for a DBPCFC. A total of 123 controls were recruited giving a ratio of 1.7 to 1. Recruitment was challenging for staff as it required a high level of altruism from the families, particularly as we needed to obtain a sample of blood from the control children. The case and control participants will be used to explore the pathogenesis of food allergy and how our current serological diagnostic tests can be improved. This will be undertaken as part of the EuroPrevall analysis.

6.4 Infant nutrition and food allergy

Analysis of the infant feeding data and allergy outcome took two forms, one looked at the infant feeding patterns such as timing of solid introduction, breastfeeding duration etc. and the use of Principal Component Analysis to see if there were any statistical differences in how the symptomatic infants were fed compared to their controls. The second looked at the nutritional profiles of the diets to see if there were any differences in intake between the two outcome groups.

The findings of the nutritional analysis of the quantitative intake data kept by the parents of symptomatic and control children seems to suggest that the levels of specific macro- and micro-nutrients in an infant's diet do not impact on the later development of food allergy (Objective 4). However, breast milk samples were not collected so standard values for the nutrient content of breast milk were used. This means that should there have been differences in an infant's diet due to differences in maternal breast milk composition they would not have been detected in the analysis. Further work that incorporates the nutritional composition of breast milk

needs to be undertaken before it can be confidently stated that macro- and micronutrient intake in infancy does not affect allergy risk.

Breast milk does, however, appear to have a protective effect on the development of food allergy but this apparent protective effect is only seen when breastfeeding and solid food introduction happen concurrently. The finding regarding concurrent feeding ('overlap') showed that if egg or infant formula are first given whilst the infant was still being breast fed then the risk of food allergy is significantly reduced compared to if those foods are introduced into the diet after the infant has stopped receiving breast milk($p=0.036$ and $p=0.049$ respectively). Also, it is not just that the overlap occurs, the duration of overlap is also important ($p=0.043$ for egg and breast milk overlap and $p=0.044$ for cows' milk ingredient and breast milk overlap. The mean length of overlap of breast milk and egg in the diet was 0.05 weeks for symptomatic infants compared to 0.69 weeks for control infants. The mean length of overlap of breast milk and infant formula was 6.9 weeks for symptomatic infants compared to 10.7 weeks for control infants. This overlap is more likely to occur in older, better educated mothers, the mothers who are more likely to breast feed in the first place. In this work the protective effect of breast milk when being given concurrently to solid introduction has only been found for egg and infant formula. Such a protective effect concurrent feeding with breast milk has previously been shown for concurrent has breast feeding and the introduction of wheat into the diet (Poole, et al. 2006) and it can be reasoned that an association was not found in this work because there were only 2 confirmed wheat allergic children in this cohort.

The timing of solid introduction does seem to have an effect on food allergy since, from the infant food diaries, there was a significance difference between the groups ($p=0.010$) with the age at introduction being later for controls (20.0 weeks compared to 18.7 weeks). However to establish whether the effect is linear i.e. delaying the introduction of solids continues to have a protective effect, or "U" shaped (where there is an ideal 'window in time' for solids to be introduced and if they are introduced earlier or later than this window then the risk of allergy development is increased) the results were further analysed. These analyses show that although some infants in the control groups had solids introduced earlier than infants in the symptomatic group, the mean, median and mode for solid introduction in the control group were all higher than the values for the symptomatic infants. We do not know if the protective effect of delaying solid introduction continues indefinitely but since it is not recommended for the introduction of solids to be delayed beyond the age of 26 weeks, this is largely an academic question. Also, this association has been made for the introduction of any solid food, it has not looked at each food individually.

An association was also seen between the groups for the age at introduction of cows' milk as an ingredient, but not cows' milk in any other form, with food allergic infants having cows' milk containing foods introduced into their diet earlier than control infants. If the likely sources of milk as an ingredient in infants' diets are further examined, it is seen that the only common milk-containing food which was introduced significantly earlier into the symptomatic infants' diet compared with the control infants is baby cereal. This is often the first food introduced into an infant's diet so this association is likely to be a reflection of the fact that symptomatic infants had solids introduced into their diets earlier than was the case for control infants as opposed to their being something particular as to the form in which it was introduced.

Objective 6 split the PCA analysis of the symptomatic children into those children who developed a food allergy at 12 months of age and those who were food allergic at 24 months. Since there were only 41 infants diagnosed with a food allergy in total the PCA analysis was performed on all food allergic infants as sample size

recommendations for carrying out such an analysis states there should be 5-10 participants per variable (Field A, 2005), so maximising the number of participants in the analysis allowed more variables to be included in the pattern analyses.

The Principal Component Analysis carried out identified three major feeding patterns that were statistically more prevalent in control infants compared to symptomatic infants. One was concurrent breastfeeding and solid introduction, the second was diversity of the infant diet and the third was the 'healthiness' of the infant diet.

Concurrent breastfeeding has already been identified in this work as reducing the risk of the infant developing allergic disease from the non-parametric statistical tests carried out. The theory that breast milk may be protective if it is feed concurrently to the infant appears plausible since breast milk has a number of immunologically active components (such as immunoglobulins, oligosaccharides), nucleotides and long chain fatty acids (Das 2002) which may be more likely to exert their modifying effects in the presence of the potential allergen. This fact may also explain why the literature has papers both supporting and disputing the protective effect of breast milk in food allergy since none of these works looked at whether breast feeding and solid introduction were happening concurrently (Matheson et al. 2007) (Laubereau et al. 2004). The only work to date to look at this is that of Poole (2006) who found that concurrent breast feeding whilst wheat was first introduced into the diet appeared to reduce the risk of the infant developing a food allergy.

The 'diversity' dietary pattern is more likely to be a result of the fact that infants following an exclusion diet of any type are likely to be receiving fewer food products in their diet compared with infants able to follow a full diet than an actual causative mechanism being involved. Consequently, this association needs to be investigated further by looking at dietary patterns only before diagnosis and comparing these between the symptomatic and control groups before any firm conclusions are formed regarding the part diversity of the infant diet may or may not have in the development of food allergy. This work is outside the scope of this study.

The 'healthiness' of the diet is a pattern that could play a part in the development of food allergy as previous work has recognised an association between fruit and vegetable intake and allergic disease (Heinrich et al. 2001). The foods that scored highly positively in this analysis were eggs, fish, hummus, fruit as fruit (as opposed to as a puree or in a yoghurt), marmite, and dried fruit. The foods that had low scores in this pattern were sausages, crisps, potato products, and chocolate. The lower scores were also associated with high use of commercial baby foods and ready meals.

The influence of maternal and environmental factors on the dietary patterns identified higher maternal age as being associated with higher scores (which were protective in all three patterns). Maternal allergy affected feeding patterns with mothers with an allergic history being more likely to concurrently breast feed and feed the 'healthy' dietary pattern. Maternal education also affected feeding patterns with the higher educated mothers being more likely to concurrently breast feed, and deliver the 'diverse' and 'healthy dietary patterns.

The infant food diaries represent a unique dataset that can be a resource to answer other research questions. For example, for the first time they provide data on how an infant's nutrient intake increases over the first year. As such they will represent a novel contribution to the literature. The dataset also provides a current perspective on how infants are fed today. For example, when considering the guidelines to exclusively breast feed for the first 6 months of life, we found that feeding was heavily associated with maternal age and education suggesting that these factors should be

considered when targeting education to improve adherence to the infant feeding recommendations.

6.5 12 and 24 month questionnaires

The rate of follow-up for the 12 and 24 month questionnaires was lower than anticipated. A total of 733 (63%) 12 month questionnaires were undertaken and 823 (70%) 24 month questionnaires were undertaken. The 12 month questionnaire was not available in time due to issues with its development and placing it into the web based database. This meant that a significant number of infants were too old for it to be completed. We found it impossible to complete more than a few questionnaires during the daytime working hours. This necessitated taking on additional administrative staff to call mothers in the evenings. In spite of this, we found that many parents were un-contactable, not available at the times that had been arranged for the telephone interview, or simply did not want to complete the questionnaire. The length of the questionnaire may have influenced this follow-up rate.

As expected, the majority of mothers started to breast feed their new infant but the questionnaire data suggest that the median duration of breast feeding was only 3.5 months (inter-quartile range 0.2 to 7.0). By the time of the 12 month questionnaire, most infants were taking solids with a minority also in an infant (usually cows' milk) formula in addition.

The rates of allergic type symptoms in this cohort are similar to other populations. The answers to the ISAAC questions suggest that about a fifth have eczema. Allergic rhinitis is less usual at this age and it is likely that many of the parents who felt their child had a problem with sneezing, runny or blocked nose when they did not have a cold, were actually describing infective rhinitis. Wheeze or whistling is very common in the first year of life and is usually due to a bronchiolitis illness or viral associated wheeze rather than asthma. These are often treated with bronchodilators explaining the difference between the rates of these and the low rate of doctor diagnosed asthma. The 12 and 24 month questionnaires were very useful in picking up potential cases of food allergy that had not been reported to the study team. This has been described in section 3.

7. Dissemination activities and publications

A number of publications have already emerged from this project:

1. Grimshaw KEC, Allen K, Edwards CA, Beyer K, Boulay A, Van der Aa LB, Sprikkelmann A, Belohlavkova S, Clausen M, Dubakiene R, Duggan E, Frutos MR, Marino L, Norhede P, Ogorodova L, Schoemaker A, Stanczyk-Przyluska A, Szepfalusi Z, Vassilopoulou E, Veehof S, Vlieg-Boerstra B, Wjst M, Dubois AEJ.
   Infant feeding and allergy prevention: review of current knowledge and recommendations.
   Allergy 2009;64:1407-1416

2. Keil T, McBride D, Grimshaw K, Niggemann B, Xepapadaki P, Zannikos K, Sigurdardottir ST, Clausen M, Reche M, Pascual C, Przyluska Stanczyk A, Kowalski ML, Dubakiene R, Drasutiene G, Roberts G, Schoemaker A-FA, Sprikkelman AB, Fiocchi A, Martelli A, Dufour S, Hourihane J, Kulig M, Wjst M, Yazdanbakhsh M, Szépfalusi Z, van Ree R, Willich SN, Wahn U, Mills ENC, Beyer K.
   The multinational birth cohort of EuroPrevall: background, aims and methods.
   Allergy 2010;65;482-490

3. Grimshaw K, Maskell J, King R, Oliver E, Gudgeon L, Roberts G, Margetts B
   Dietary Patterns in the first year of life and food allergy risk.
   Oral abstract presentation EAACI London 2010 meeting.

4. Oliver E, Grimshaw K, K Scally, Garland J, Gudgeon L, Roberts G
   Nutritional intake and allergy outcome.
   Poster abstract presentation EAACI London 2010 meeting.

Lastly it is expected that the EuroPrevall data will contribute to position papers focusing on food allergy and be extensively referenced at international meetings and in peer reviewed publications as a unique pan-European study of food allergy.

8. Conclusions, implications and need for further work

8.1 Conclusions

8.1.1 Recruitment

- T07046 study has successfully recruited a large birth cohort in the Winchester area using the EuroPrevall study methodology with 1172 infants being enrolled into the cohort.
- The UK birth cohort contributes to a pan-European birth cohort of 12274 infants born up to July 2009.

8.1.2 Food Intake data

- The collection of infant food diaries in the first year of life was unique to the UK birth cohort of EuroPrevall
- A total of 594 diaries were completed prospectively 24 weeks of age with 241 being completed for the whole first year.
- Analysis of food diaries for symptomatic and control infants for macro and micronutrient content showed no, significant differences in any pre- specified nutrients
- Analysis of the food intake pattern from the diaries of infants diagnosed with a food allergy and their age-matched controls demonstrated allergic infants were introduced to solids significantly earlier (18.7 verses 20.0 weeks, p=0.049).
- Concurrent breast feeding during the introduction of solids appears to give a have a significantly protective effect for food allergy development (p=0.036 and 0.049 for egg and cows milk formula respectively).

8.1.3 Prevalence of Food Allergy T07046 birth cohort

- 28.4% (95% confidence interval (CI) 25.4 – 31.6%) of all participants in the cohort had parent perceived food allergy over the first two years of life.
- After triage by the study team, only 16.4% (CI 13.9 – 19.1%) of all the participants in the cohort were thought to possibly have food allergy over the first two years of life.
- An assessment with a history and allergy testing concluded that 9.0% (CI 7.1 – 11.2%) of all participants in the cohort had a food allergy over the first two years of life but only 5.0% (CI 3.6 – 6.7%) of all participants had food allergy on the basis of a DBPCFC.
- The trigger foods were cows' milk (3.0%, CI 2.0 – 4.5%), egg (2.6%, CI 1.6 – 3.9%), peanut (0.7%, CI 0.3 – 1.6%), soy (0.4%, CI 0.0 – 1.1%), wheat (0.2%, CI 0.0 – 0.9%) and fish (0.1 CI 0.0 – 0.7%).

8.2 Implications from the results from the UK EuroPrevall Birth Cohort

Data from the UK Europrevall birth cohort demonstrates that over a quarter of parents are concern that their young child has a food allergy. A large number of families are therefore concerned about food allergy, generating a need for **consumer advice about food allergy in infants** on government websites (eg Food Standard Agency) and also third sector ones (eg Anaphylaxis Campaign). After a clinic assessment (equivalent to the usual routine diagnostic standard in the UK), only approximately 1 in 10 children in the first two years of life were felt to be food allergic. On the basis of a randomised, double-blind, placebo-controlled food challenge, the rate of diagnosed food allergy dropped by 50% to 1 in 20. This explains why challenges are still the gold standard diagnostic test although they are not available in many hospitals due to the patchy nature of the allergy services in the UK. Infants with food allergy in all areas of the UK need to be able to **access to a paediatric allergy service**. The **trigger foods were as expected** (cows' milk, egg, peanut, soy, wheat and fish). All are included in the current EU food labelling directive.

The findings that food allergic infants were introduced to solids significantly earlier than their controls (p=0.049) and that **concurrent breast feeding during the introduction of solids appears to give a protective effect** against the development of food allergy are important. To date the evidence for the optimal infant diet are limited and conflicting. The use of food diaries to collect concurrent data and a multifactorial PCA analysis has provided a new view of this area. If these results can be replicated in further studies, it has important implications for the advice given to mothers.

The study data demonstrate that although 90% of mothers commence breast feeding, the median duration of breast feeding was only 5 months. If concurrent breast feeding during the introduction of solids prevents the development of food allergy, then this further underlines the importance of breastfeeding and of concurrent breastfeeding and solid introduction.

The relationship between infant nutrition and food allergy was only apparent in the infant food dairy data in this study, not in the questionnaires data. Food diaries are rarely used in this context. The reliance of questionnaire data in other studies may explain why the literature in this area is not clear. Future studies need to strongly **consider using food diaries** for at least a proportion of their participants to ensure valid data is collected that is not subject to recall or other biases.

8.3 Further work within the EuroPrevall Birth Cohort Project

By employing the same protocol and questionnaires in centres across Europe, each country's experience of food allergy can be compared and contrasted. Preliminary results already suggest that the burden of food allergy varies widely between different countries. Given the huge nutritional, cultural and climatic differences across the continent, there is a potential to highlight important influences on the

pathogenesis of food allergy. This is only possible with the critical mass of participants that the EuroPrevall birth cohort has successfully recruited and followed.

The critical mass of infants with food allergy in the EuroPrevall Birth Cohort will also allow us to optimise our diagnostic tests for food allergy by the use of sera from food allergic participants, symptomatic ones who do not react at challenge and control individuals. Additionally, the collection of DNA from cases and controls will allow us to explore whether or not there is a genetic basis for the development of food allergy.

As already mentioned, birth cohorts are challenging and expensive to recruit. It is therefore important to have a plan to continue to follow them. An application has been made under the EU F7 scheme to assess the EuroPrevall Birth Cohort in a project named Allerbiome. This aimed to address the relationship between food allergy and later allergic diseases such asthma and rhinitis. Unfortunately, while the application was scored very highly by reviewers, other projects received higher scores. Further applications for funds to reassess the EuroPrevall Birth Cohort are in preparation.

Lastly, the infant food diary data has the potential to be exploited to answer additional research questions. An obvious one is whether or not retrospective food frequency diaries are valid. There is also a potential to see whether patterns of weaning influence the development of other childhood medical problems such as wheeze. Lastly we can look at whether or not those diagnosed with food allergy had previous dietary exposure to the food, knowingly or unknowingly.

8.4 Further work outside the EuroPrevall Birth Cohort.

The analysis of the infant food diaries has highlighted a few intriguing relationships, in particularly the protective effect to concurrently breast feeding when solids are introduced and the timing of introduction of solids. While this can be assessed in the wider EuroPrevall cohort, it would have to be undertaken with retrospective data collected at 12 months of age. There are concerns about just how accurate these are likely to be given the intervening time. It would therefore be ideal to attempt to replicate these data in a further prospective cohort. A cost effective approach would be to select a group of pregnant women who are at risk of having a child with food allergy to minimise the number that need to be recruited and followed. The cohort could then be followed with electronic internet based diaries and periodic short questionnaires as are being employed in the FSA funded EAT study.

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