The impact of recall bias on the accuracy of dietary information

by
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DECLARATION

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof, that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

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March 2014

ABSTRACT

Background: A number of observational studies where information was obtained retrospectively have been used in the past to inform guidelines regarding allergy prevention. Studies looking at the causative/protective properties of infant dietary factors on diseases that occur later in life also rely on maternal recall many years later. It is unclear however what the effect of the recall bias was on the accuracy/quality of the information obtained.

Objectives: The aim of the study was to determine the impact of recall bias 10 years retrospectively on the accuracy of dietary information in relation to breast feeding, weaning age and introduction of allergenic foods. A literature review was performed into studies assessing the accuracy of data obtained retrospectively and into studies using retrospective data to draw conclusions on the protective/causative factors of infant feeding in relation to food allergy.

Methodology: An infant feeding questionnaire was developed from some of the same questions that were asked by mothers recruited into the FAIR study, a prospective birth cohort on the Isle of Wight. Families had been recruited and followed up since 2001/2002 and data has been gathered when the mothers were 36 weeks pregnant, and then when their child was 3, 6, 9 months and 1 and 2 years old. Mothers were asked in 2012, when their children were 10 years of age, to complete this questionnaire. Agreement of answers was computed using Kappa coefficients, Spearman's correlation and percentage agreement.

Results: One hundred and twenty five mothers completed the questionnaire. There was substantial agreement for recall of whether mothers breast fed, the duration of EBF and breast feeding 10 years earlier ($k = 0.79$, $r = 0.70$ and $r = 0.84$ respectively). Seven per cent ($n = 9$) of mothers however who did breast feed reported not to have. Eighty four per cent ($n = 103$) of mothers recorded correctly whether their child had a bottle of formula milk in hospital. Ninety four per cent ($n = 116$) of mothers recalled accurately that their child had received formula milk at some stage of their infancy. The exact age at which formula milk was first given to their child was answered accurately ($r = 0.63$). The brand of formula milk provided was poorly recalled. Answers to when mothers first introduced solid foods into

their child's diet were not accurate (r = 0.16). The age of introduction of peanuts was the only food allergen that mothers recalled accurately for when they first introduced this into their child's diet (86% correct answers). Recall of whether peanuts were consumed during pregnancy was accurate after two years (k = 0.64) but not after 8 years (k = 0.39).

Conclusion: The study highlights the importance of possible recall bias of infant feeding practices by mothers over a period of 10 years. Recall related to breast feeding and formula feeding were accurately recorded for, but not for age of introduction of solid foods and introduction of allergenic foods. Studies relying on maternal recall of weaning questions need to be cautious.

OPSOMMING

Agtergrond: ’n Aantal waarnemingstudies waarin inligting op retrospektiewe wyse of terugwerkend bekom is, is in die verlede gebruik om riglyne oor die voorkoming van allergie neer te lê. Studies oor die veroorsakende/beskermende kenmerke wat kindervoedingsfaktore op latere siektes het, steun verder op die herinneringe wat die moeder baie jare later kan oproep. Dit is egter onduidelik watter uitwerking hierdie oproepvooroordeel op die akkuraatheid/gehalte van die versamelde inligting het.

Oogmerke: Die oogmerk met die studie was om die impak te bepaal wat oproepvooroordeel met terugwerkende effek van 10 jaar op die akkuraatheid van voedingsinligting oor borsvoeding, speenouderdom en die insluiting van allergeniese voedselsoorte uitoefen. ’n Literatuuroorsig was onderneem van studies wat die akkuraatheid evalueer van data wat retrospektief bekom is, asook studies wat retrospektiewe data gebruik om gevolgtrekkings oor die beskermende/veroorsakende kenmerke van kindervoeding met betrekking tot voedselallergie te maak.

Metodologie: ’n Kindervoedingsvraelys is saamgestel vanaf sommige van die vrae wat aan gewerfde moeders voorheen in die FAIR-studie, ’n voornemende geboortekohort op die eiland Wight, gestel is. Gesinne is in 2001/2002 gewerf en opgevolg, en data is versamel toe die moeders 36 weke swanger was; en weer toe hulle kinders die ouderdom van 3, 6, 9 maande en 1 en 2 jaar bereik het. In 2012, toe hulle kinders 10 jaar oud was, is die moeders weer versoek om hierdie vraelys in te vul. Ooreenstemming tussen antwoorde is bepaal deur Kappa koeffisiënte, Spearman korrelasies en persentasie ooreenstemming.

Resultate: Eenhonderd vyf-en-twintig moeders het die vraelys ingevul. Daar was beduidende ooreenkoms in die moeders se oproep oor die vraag of hulle borsvoeding gegee het, hoe lank eksklusiewe borsvoeding (EBV) geduur het, asook borsvoeding 10 jaar vantevore (k = 0.79, r = 0.70 en r = 0.84 onderskeidelik). Sewe persent (n = 9) van die moeders wat wel borsvoeding gegee het, het egter geantwoord dat hulle dit nie gegee het nie. Vier-en-tagtig persent (n = 103) van die moeders het akkuraat geantwoord op die vraag of hulle kinders bottelvoeding met ’n melkformule in die hospitaal ontvang het. Vier-en-negentig persent (n

=116) van die moeders kon akkuraat oproep dat hulle kinders in ’n sekere stadium van hulle kindertyd melkformule ontvang het. Die vraag oor presies hoe oud die kinders was toe hulle die eerste maal melkformule ontvang het, is akkuraat beantwoord (r = 0.63). Die handelsnaam van die melkformule kon nie goed herroep word nie. Antwoorde oor wanneer moeders die eerste maal vaste voedsel by hulle kinders se dieet ingesluit het, was nie baie akkuraat nie (r = 0.16). Die ouderdom waarop grondboontjies ingesluit is, was die enigste antwoord wat moeders akkuraat kon oproep (86% korrekte antwoorde) op die vraag wanneer hulle die eerste maal ’n voedselallergeen by hulle kinders se dieet ingesluit het. Die antwoord op die vraag of hulle tydens hul swangerskap grondboontjies geëet het, was akkuraat na twee jaar (k = 0.64), maar nie na agt jaar (k = 0.39) nie.

Gevolgtrekking: Die studie onderstreep die belang van moontlike oproepvooroordeel rakende kindervoedingspraktyke by moeders oor ’n tydperk van 10 jaar. Die oproep oor borsvoeding en formulevoeding is korrek aangedui, maar nie vir die ouderdom waarop vaste voedselsoorte en allergeniese voedselsoorte ingesluit is nie. Studies wat op moederoproep oor speningsvrae staatmaak, moet omsigtig gedoen word.

CONTRIBUTIONS BY PRINCIPLE RESEARCHER AND FELLOW RESEARCHERS

The principal researcher, Zoë van Zyl, developed the research question and the protocol. The principal researcher planned the recall study, undertook data collection regarding weaning practices for the 10-11 year follow-up. The principal researcher transferred the weaning and feeding data during the first 3 years of life and family history of allergy data from the original SPSS data bases into an SPSS database specifically developed for the purpose of this thesis and entered the weaning practices data for analyses from the 10-11 year old follow-up also into this database. Data was analysed with the assistance of a statistician, Prof DG Nel. The principal researcher interpreted the data and drafted the thesis. Prof Renée Blaauw and Dr. Carina Venter (Supervisors) provided input at all stages and revised the protocol and thesis.

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LIST OF ABBREVIATIONS

AAP	American Academy of Paediatrics
AD	Atopic Dermatitis
BF	Breast Feeding
CMA	Cow's Milk Allergy
COT	Committee on Toxicity
DBPCFC	Double Blind Placebo Controlled Food Challenge
EAT	Enquiring About Tolerance
EBF	Exclusive Breast Feeding
ESPGHAN	European Society of Pediatric Gastroenterology, Hepatology and Nutrition
EAACI	European Academy of Allergology and Clinical Immunology
FA	Food allergy
FFQ	Food Frequency Questionnaire
FHS	Food Hypersensitivity
FSA	Food Standards Agency
IgE	Immunoglobulin E
MTCT	Mother To Child Transfer
RCT	Randomised Controlled Trial
SPT	Skin Prick Test
UK	United Kingdom

US	United States
WHO	World Health Organisation

LIST OF DEFINITIONS

Allergy	A hypersensitivity reaction initiated by specific I mmunologic mechanisms.[1]
Atopy	A personal and/or familial tendency, usually in childhood or adolescence, to become sensitised and produce IgE antibodies in response to ordinary exposure to allergens, usually proteins.[1]
Exclusive breast feeding	The practice of feeding only breast milk (including expressed breast milk) and allows the baby to receive vitamins, minerals or medicine. Water, breast milk substitutes, other liquids and solid foods are excluded.[2]
Food allergy	An adverse reaction to food when immunological mechanisms have been demonstrated.[1]
Hypersensitivity	Objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons.[1]
IgE-mediated food allergy	Food allergy, where the role of IgE is confirmed in the reaction.[1]
LEAP	Randomised control study that aims to determine the best strategy to prevent peanut allergy in young children, focussing on age of introduction.[3]
Non-IgE mediated food allergy	Inflammation mediated by allergen-specific lymphocytes or by anti-bodies of the IgG isotype.[1]

CHAPTER 1

INTRODUCTION

CHAPTER 1

In this dissertation, Chapter 1 provides an introduction to the research question, and the aims and objectives of the thesis. The research methodology, discussed in Chapter 2, focusses on the comparison of two data sets of exactly the same breast feeding and infant feeding questions, asked 10 years apart to the same participants in a study looking primarily at food allergy prevalence and prevention. Chapter 3 comprises of the literature review with a discussion on recall bias and previous allergy focussed observational studies where recall bias might have played a role. The results of the two data sets from Chapter 2 are presented and discussed in Chapter 4 and 5, along with further studies outside of the area of food allergies that investigated any possible effect of recall bias on data gathered. The conclusion and recommendations are found in Chapter 6.

1.1 Introduction

Prior to conducting any research, the research tools should be well planned as it determines the strength of the evidence that the study generates. The researchers need to consider many factors, such as whether the measurement tools are reliable or valid in order to prevent any biases in the data gathered.[4]

This is particularly important when planning observational studies which are used for hypothesis generation, and in turn inform and direct the interventional studies we perform. One major pitfall in the planning of observational studies however is the issue of bias, which can be influenced specifically by recall bias and non-validated research tools.[5]

The accuracy of data collected retrospectively in comparison to data collected prospectively and the reliability and validity thereof is a very important question for epidemiological research. The retrospective approach of data collection has many advantages. Reduced study duration, relatively easy realisation of results and a potential reduction in cost of resource are some of the reasons why this approach is so popular. Some research that is carried out retrospectively relies on recall over varying periods of time.

One particular area where recall bias might have affected the knowledge pool is in allergy prevention. Some studies that have looked at pregnancy, breast feeding and weaning practices and the potential effect on the development of food allergy (FA) have relied on parents reporting information up to 18 years later. There is no data in the literature regarding the effect of recall bias on infant feeding information obtained retrospectively and how this may affect the development of allergic diseases. Results of these studies have been interpreted without major emphasis on whether recall bias had an impact on the accuracy of the data or not.

Although recall bias may have an effect on the quality of data for allergy prevention, it has been used to inform national and international policies.

It is known that management of allergic disease has a substantial impact on the health economy, and suffering from allergic disease impacts on quality of life.[6] In addition, the potential increase in prevalence of allergic diseases[7], spur experts on to look for effective preventative interventions. One such strategy is looking at breast feeding and weaning practices, particularly weaning age and the age of introduction of allergenic foods. At present, there is no clear evidence to suggest whether early or late introduction of food allergens has an impact on the subsequent development of sensitisation or allergy to certain foods.[8]

This study will investigate the impact of recall bias on the accuracy of information obtained 10 years retrospectively regarding breast feeding and weaning practices. It will also discuss what impact this has on the interpretation of results of studies where recall bias is a potential issue, particularly in the field of allergy.

1.2 Research Question

Does recall bias affect the accuracy of infant feeding practice information obtained 10 years retrospectively?

1.3 Aims and Objectives

Part 1 (Chapter 2, 4, 5): To assess the accuracy of infant feeding information obtained from mothers 10 years retrospectively

In 2001, Venter *et al*[9] looked at the factors associated with maternal dietary intake, feeding and weaning practices, and the development of food hypersensitivity in the infant. Nine hundred and thirty seven mothers completed a Food Frequency Questionnaire (FFQ) at 36 weeks gestation. The majority of these mothers also completed a standardised questionnaire when their child was 3, 6 and 9 months and 1, 2 and 3 years on feeding practices. These answers are the reference data and they are accepted as the 'valid' answers as they were collected at the time of the event and are therefore used to quantify any potential recall bias 10 years later by asking some of the same questions. The aim of the study therefore is to determine the impact of recall bias on the accuracy of dietary information in relation to breast feeding, weaning age and introduction of allergenic foods. Analysis of the comparative data (information obtained during 2001/2002 and in the same group of mothers in 2012) will allow for discussion on the potential impact of recall bias on all studies that have relied on similar recall periods.

Part 2 (Chapter 3): **To investigate studies using retrospective data for pregnancy, breastfeeding and weaning practices by a literature review**

The literature review part of the study discusses what the potential is for recall bias, through assessing the validity and reliability of maternal recall in studies relying on data collected retrospectively. Particular focus was placed on retrospective data collected from mothers during pregnancy, breast feeding (BF) and weaning, with a specific emphasis in relation to

peanut allergy. Food allergy, its prevalence, overall impact and health economic burden is discussed briefly in order to support the understanding of the condition globally. Research carried out on the prevention of food allergy to date is discussed in detail.

1.4 Study Searches

Pubmed and Scopus were used to search for English language journals between 1990 and 2012. If a paper could not be accessed, the librarian at the University of Stellenbosch utilised University resources and scanned a paper copy if required. All types of studies were searched and no search restrictions were in place other than for English, human only studies and within the selected time frames. Full papers were used predominantly, but abstracts were included if they contained sufficient information in order to be referenced appropriately. The following words were used for the Pubmed and Scopus search strings in order to gather the initial collection of papers for the literature review section of this study: *weaning* or *introduction of foods AND practices* or *guidelines* AND *infants* AND *Dietary recall* or *maternal dietary history* AND *food allergy. Recall bias* AND *dietary information. Dietary recall validity* AND *remote dietary recall* AND *Allergy prevention* or *atopic disease prevention.* Hand searching of studies from the reference lists of papers that were searched through Pubmed and Scopus were also included. Some papers were read by the principal investigator for background information, but were not referenced if they were not specifically referred to. Information relating to trials not yet completed or published, for example LEAP, were researched via internet search engines such as google.

CHAPTER 2

METHODOLOGY

CHAPTER 2: METHODOLOGY

2.1 Null Hypothesis

There is no difference in the accuracy, and therefore no recall bias, of dietary information obtained 10 years retrospectively.

2.2 Study Design

The study design is a cross-sectional, descriptive study with a retrospective analytical component (part of a larger study [Referred to as the FAIR study[9]] and the retrospective analytical component will be using historic data from this larger study).

2.3 Baseline FAIR Trial

This study is embedded in a larger study[9] that originated from an unselected birth cohort on the Isle of Wight. Data was obtained from 969 families which was 91% of the total birth population (n = 1063). The FAIR study looked at the prevalence of food allergy in an unselected population of children and factors associated with maternal dietary intake, feeding and weaning practices in relation to the development of food hypersensitivity in the infant. A flow diagram of the study population showing the stages from recruitment to the 10 year follow up is represented below in Figure 2.1

All pregnant mothers with an approximate delivery time between 1st September 2001 and 31st August 2002 were approached at antenatal clinics to participate in the FAIR study. Once consent was obtained, information regarding family history (parent or sibling) of allergy and level of exposure to environmental allergens were obtained using a standardised questionnaire.

Children were SPT (1, 2 and 3 years) to a predefined panel of food allergens including milk, wheat, egg, peanut, cod and sesame. Positive skin test reactions (≥ 3 mm) and reports of

previous adverse reactions to foods regardless of SPT outcome resulted in food challenges being conducted. Double blind placebo controlled food challenges (DBPCFC) were carried out when open food challenges resulted in a positive reaction.

The questionnaires developed for the FAIR study comprised of various questions relating to maternal and infant feeding practices. Specific questions were asked relating to dietary practise when pregnant (using the FFQ[10]); breast feeding practices in terms of exclusivity and duration, age of introduction of formula and specific weaning foods, as well as any dietary avoidance (using study questionnaire). A question about whether peanuts were avoided during pregnancy and if so for what reason was asked at two points in time, namely when the mother was 36 weeks pregnant and then when her child was two years of age. Please see Appendix 8A, 8B, 8C, 8D, 8E and 8F for the questionnaires used at 36 weeks, 3, 6, 9 months and 1, 2 years respectively.

Study participants in the FAIR study were asked to be seen again for further follow up in 2012 (10 years after they first joined the study). For full details of this 10 year FAIR follow up study, please see Appendix 8G for the protocol. All aspects in the FAIR study protocol that are related to this study are highlighted in red.

At the same time that the parents and study subjects attended the 10 year FAIR follow up (2012) for blood tests/saliva samples, parents were also asked to complete a feeding questionnaire. This feeding questionnaire (described in detail below and referred to as the recall questionnaire) was developed by the principal investigator of this study. Selected questions on maternal diet during pregnancy and infant weaning practices which were asked previously in the FAIR study (at 36 weeks gestation; 3, 6 and 9 months as well as 1 and 2 years) were captured in this questionnaire. In order to test recall bias, the questions had to be posed exactly the same as when they were 10 years earlier.

Answers from the original FAIR data from 2001/2002 are now being used as the reference data to quantify the accuracy of the answers from the recall questionnaire, which forms the retrospective analytical component of this study.

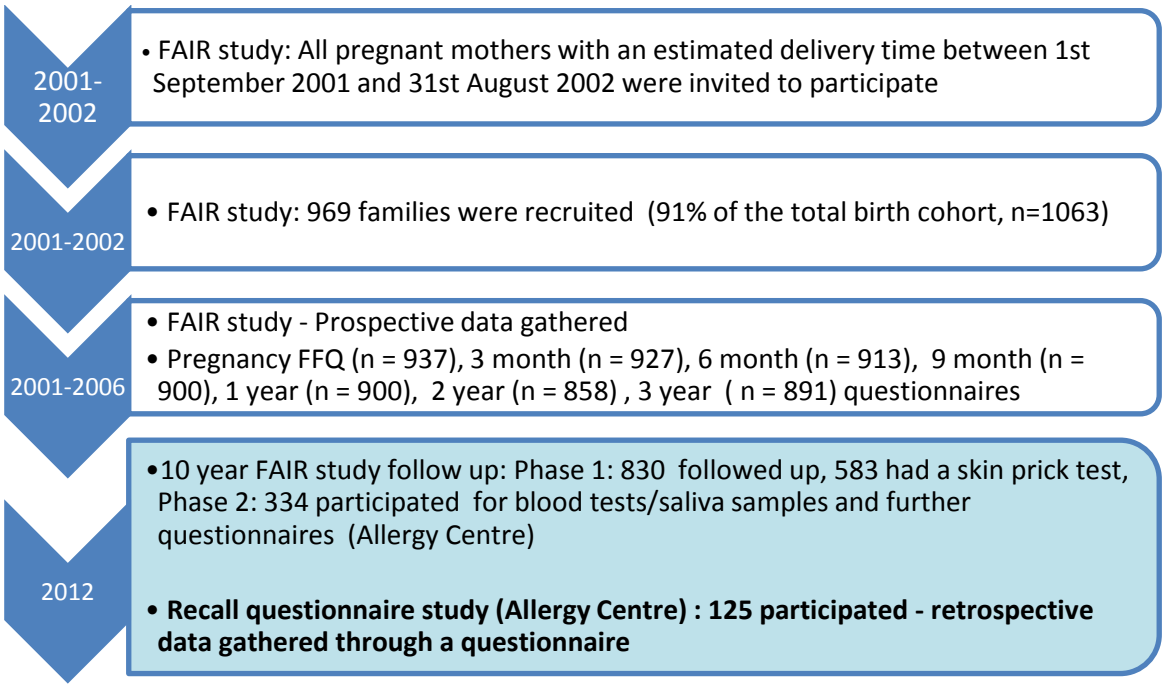

Figure 2.1 Flow diagram of study population from recruitment

2.4 Study Site

The David Hide Asthma and Allergy Research Centre (DHAARC), Isle of Wight, United Kingdom.

2.5 Study Population

Parents of all children (n = 927) who participated in the baseline FAIR study (2001) were asked to participate in this study. The children are now between the ages of 9 and 11 years. The large majority of these parents and their children still reside on the Isle of Wight.

The sample size for this study was calculated using power analyses for repeated measures experiment, which in this case equalled two repetitions. A paired t-test was used for this purpose. Power analyses were done yielding 90% power for different standardised effects, where 0.25 was regarded as “small”, 0.75 was regarded as “medium” and 1.25 as a “large”

standardised effect. In order to detect the smallest standardised effect, a sample size of 121 was set as the minimum for this study.

2.6 Selection of Study Population

2.6.1 Inclusion criteria

All children recruited as part of the FAIR birth cohort and whose parents consented to attending a further 10 year follow up, including those answering the recall questionnaire.

2.6.2 Exclusion criteria

Parents/carers attending the clinic who did not complete the original feeding questionnaires were not included in the study.

2.7 Sampling

Non-random, purposive sampling was used. All parents of the 969 children who participated in the original FAIR study (a non-selective group) and who attended the FAIR clinics during the 10 year follow-up were asked to complete the recall questionnaire.

2.8 Study Procedures

2.8.1 Questionnaire at the Allergy Centre

The David Hide Allergy and Asthma Research Centre (DHAARC) on the Isle of Wight had access to the details and addresses of the children as obtained during the FAIR study and their current addresses were verified on the National Health Service (NHS) care records service. An information sheet about the recall questionnaire (Referred to as the feeding questionnaire for parents) was sent to those families that were happy to come to the Allergy Centre for the 10 year FAIR follow up. (Appendix 8H (adult) and Appendix 8I (child), together

with a reply slip indicating that they were happy to come for an appointment OR happy to be phoned to discuss the study further. On return of these, an appointment letter (Appendix 8J) was sent or the parents were contacted. A consent (Appendix 8K) and assent (Appendix 8L) form for both the FAIR 10 year follow up and recall questionnaire was signed on the day.

2.8.2 Recall questionnaire

2.8.2.1 Validity

The self-administered questionnaire for the recall study (9/10 year recall questionnaire) was developed from a selection of some of the questions used for the FAIR study. The validity of the original FAIR FFQ questionnaire which was given to mothers at 36 weeks gestation, is formally tested and has been published.[10] The original set of the FAIR infant questionnaires (3, 6, 9 and 12 months) were tested for face validity by checking the understanding of the questions with another group of mothers. Criterion-related validity also took place through comparing answers with those charted on the children's red health books, which could be seen as the 'gold standard' answer. Feeding practices on the Isle of Wight are captured in children's 'red books' which health visitors routinely complete with mothers. Face and criterion-related validity tests were carried out on the FAIR infant questionnaires, but due to lack of time and funding, no further validation studies were completed. Mothers were not informed at the time that they would be answering some of these same questions at any point again in the future.

The 9/10 year recall questionnaire in the recall study comprised of 18 selected questions, which had been asked historically from the FAIR questionnaires with the same mothers. The principal investigator selected 18 questions from all of the original FAIR questionnaires based on their suitability for use in allergy prevention. Many of these questions have been asked in some form in other studies[11] looking at the impact of dietary habits or practice on the development of food hypersensitivity.

The specific questions asked in the 9/10 year recall questionnaire included whether the mother breast fed at all, total duration and exclusiveness of breast feeding and reasons for stopping breast feeding. Questions were asked about whether the mother gave formula milk

to her child, when and which formula milk was used. Weaning questions asked included when did the mother first give solid foods? Which were the first 3 foods given? What ages were certain allergenic foods included into the diet? Questions about food avoidances during pregnancy and then when the child was 6 months old were asked. This questionnaire was not validated separately as it had to be designed based on the same questions used in the previous FAIR study in order to test for recall bias, which is the main objective of this study.

The original FAIR questionnaires included all of these questions, some of which were posed slightly differently purely because they were asked prospectively. In order to compare the answers from the original FAIR questionnaires to the answers given in the 9/10 year recall questionnaire, the answer sheet which parents completed (Appendix 8M) for the 9/10 year recall questionnaire was also used as a template for the answers from the previous FAIR questionnaire answers. There was no difference in the answer sheets other than the different appendix numbers at the top. The principal investigator transferred all of the answers given by parents from the selected questions from the FAIR study questionnaires to the answer sheet.

Comparing answers given by mothers in the FAIR study and 9/10 year recall study to assess potential recall bias is the main objective of Part 1 (Chapter 2, 4, 5) of this study.

2.9 Analysis of Data

Data from the answer sheets for both the original FAIR questionnaire as well as the 9/10 year recall questionnaire were entered into SPSS. The data was then exported to MS Excel and STATISTICA (StatSoft Inc. [2012] STATISTICA (data analysis software system), www.statsoft.com version 11) was used to analyse the data. A p-value of $p < 0.05$ represented statistical significance in hypothesis testing. In order to assess whether maternal recall over this period was subject to recall bias, the degree of accuracy of recall had to be determined and quantified. Accuracy or agreement of recall in all cases, unless specified otherwise, was calculated by testing for the agreement of the answer given in the recall questionnaire in 2012 to the reference data given in 2001/2002 in the FAIR study.

Tests that were carried out to assess accuracy of recall and level of agreement were the percentage agreement of answers, Kappa coefficient, Spearman correlation, sensitivity and specificity testing. An explanation of these is given below. All interpretations/cut-off points of 'accurate recall' are based on a p-value < 0.05, meaning that a difference is not statistically different, high coefficient for nominal data (k > 0.61) or for ordinal data (r > 0.61). Statistics where a 'percentage agreement' was computed are discussed at face value and > 85% correct answers were considered accurate.

The percentage agreement was calculated by taking the total number of correctly recalled answers (matched) and dividing this by the total number of responders to the question. These results were described and put into context, depending on the total number of responses. The cut-off point for an accurate answer was >85% correct answers and this was based on clinical judgement as there are no formal guideline to adhere to. This data will be submitted for peer review and opinions on this will be considered if there is disagreement on this cut-off.

The Kappa coefficient was computed to measure the agreement before and later for categorical 2 x 2 responses (E.g. Yes/No). The Kappa coefficient measures the inter-relater agreement and is generally thought to be a more robust measure than simple per cent agreement calculation as it takes into account the agreement occurring by chance.[12] The higher the Kappa coefficient is the more the pre and post answers agree, i.e. the more accurate the post answer (2012) is relative to the reference answer (2001/2002). Although there appears to be a lack of consensus for measures of significance and magnitude with the Kappa coefficient, it is recognised that the higher it is, the more the 'pre' and 'post' agree. For the purpose of reporting and describing the results in this study, the following guidelines by Landis *et al*[13] have been accepted: < 0 = no agreement, 0 – 0.20 = slight agreement, 0.21 – 0.40 = fair agreement, 0.41 – 0.60 = moderate agreement, 0.61 – 0.80 = substantial agreement, 0.81 – 1.0 = almost perfect agreement. These same guidelines were used for the Spearman correlation co-efficient which was used to compute the agreement before and after for the ordinal data.

Sensitivity and specificity tests were used to compute the 'true positive' and 'true negative' for 2 x 2 tables where the answer was dichotomous, i.e. yes/no. The original FAIR answers

were used as the reference data and were considered 'valid' although no formal validity testing was carried out. This recall study assessed recall bias; therefore the exact same questions that were used previously had to be used. The original FAIR answers were given at the time of the event, therefore recall bias due to poor memory is not considered to be significant. The sensitivity was computed by taking the number of correct 'yes' answers and dividing this by the number of correct 'yes' answers added to the number of incorrect 'yes' answers. The specificity was computed by taking the number of correct 'no' answers and dividing this by the number of correct 'no' answers added to the number of incorrect 'no' answers.

Box and Whisker plots as well as histograms were used to display the variation of the results from two sets of non-parametric data.

Answers to some questions, like 'Why did you stop breast feeding?' were allocated to codes that were developed from the 2001/2002 questionnaire. The answer sheet provided did not show this coding as the researcher did not want to prompt mothers, but the answer was entered onto SPSS according to the relevant code that the answer fell into, example 'lack of milk'. This 'blinded' coding allowed for answers to be categorised and interpreted in a clearer way, and allowed for efficient entering of data onto SPSS. Other questions that were coded (single blinded) for categories were: which baby formula did you use, which were the first solid foods introduced, foods that may have been avoided at 6 months and reasons why mothers may have avoided peanuts during pregnancy.

2.10 Ethical and Legal Aspects

Ethics approval was obtained from the National Research Ethics Service (NRES) Committee South Central in Southampton, UK, for the larger FAIR follow-up study with the amendments that include all information/documents related to the recall questionnaire for this study (10/H0504/11)(Appendix 8N). Ethical approval from the Health Research Ethics Committee of Stellenbosch University, South Africa was obtained (S12/01/002) for the study investigating the impact of recall on the accuracy of dietary information (Appendix 8O).

Parents were able to complete their questionnaire in privacy with either the principal investigator or trained allergy nurse on hand to support with any queries if necessary.

Once the data from the original FAIR questionnaires were matched to the 9/10 year recall questionnaires, they were entered into SPSS as anonymous.

CHAPTER 3

LITERATURE STUDY

CHAPTER 3: LITERATURE STUDY

The validity of studies using retrospective data on breastfeeding and infant feeding practises

Evidence-based medicine supports clinicians and health promoters to carry out the best practise and procedures for their patients and community based on the amount and quality of data to support it. The strength of evidence is often determined by the methodology of the relevant study, how valid and reliable the results are and whether bias has affected the results. As there is currently some conflicting evidence available in the area of food allergy prevention, it is particularly important that the strength of evidence generated is weighed up and interpreted accordingly. Validity, reliability and bias and the various types of each will be discussed below.

3.1 Validity, Reliability and Bias

During the assessment of the quality of research, it is important to address validity, reliability and bias as they are all inter-related. Reliability and validity allow us to answer the question of whether the measurement process used in a study produced accurate and consistent results[14] and if bias enters a study in the research design and conduct, this will lead to the results of the study being invalid.

3.1.1 Reliability

Reliability is the extent to which a measurement process gives the same results when repeated under similar circumstances.[15] Yet, it is not enough for a measurement process to be reliable, as repeated measurements can be similar, yet far from the true value. An example of this could be where a question as part of a questionnaire is not posed correctly. The subject may answer the question accurately at different times, but if the question is not posed correctly to extract the answer it is intending, then the answer will not be accurate.

The question may however be reliable at it extracts the same answer each time it is produced.

3.1.2 Validity

Validity is the extent to which a variable or measure captures the underlying concept it is intended to reflect.[15] A question that can be posed to assess the quality of a measure in terms of validity would be "Does the measurement or variable resulting from this process actually reflect what it is intending to reflect?"[14] Different concepts of validity are used to evaluate and improve the validity of a study.

3.1.2.1 Face validity

Face validity refers to the extent to which a measure appears to most observers to capture the concept it is intended to reflect.[14] Questionnaires can be tested for face validity by asking a separate group of subjects to explain their understanding of what the question means. There are no statistical tests to measure if a variable has face validity, as it is a subjective measure.

3.1.2.2 Content validity

Content validity is 'the extent to which a measure covers all dimensions present in the concept it is intended to reflect'.[14] The elements of a concept are best decided by experts in the field, as they would be able to comment on whether the elements provide a representative sample or not. The Delphi technique has been used in a number of studies, as it is regarded as a useful technique to achieve consensus in a specific area where there is lack of empirical evidence and uncertainty.[16] This technique draws on the collective inputs of a group of experts in a particular area and the outputs are influenced by the size of the panel and the qualifications of each expert. This technique has received both positive and negative feedback, as it is a quick and efficient way of combining the knowledge and capabilities of a group of experts[17], yet it represents the opinion of experts rather than indisputable fact.[16]

3.1.2.3 Criterion validity

Criterion-related validity involves evaluating the results against the gold standard i.e. the most valid measurement available.[18] It can be challenging to determine the validity of studies relying on individuals to recall past events many years later, as the 'gold standard answer' may not exist. If there is documentation in health records that describes these specific events at the time, these could be considered the 'gold standard' answer, i.e. a questionnaire on birth weights can be checked against weights recorded in obstetric records.[18] Often the sensitivity and specificity of a measurement are calculated to assess criterion-related validity.

3.1.2.4 Internal and external validity

Internal validity is the extent to which a measure captures the concept it is intended to reflect among the sample of individuals being studied.[14] This cause and effect relationship is based on the measure used and the entire study design. A study looking to determine whether avoidance of a specific food allergen in early weaning has an effect on the development of the specific food allergy would need to consider confounding variables such as potential exposure in utero or genetic predisposition, before a conclusive causal relationship is made.

External validity concerns the extent to which a measure captures the concept it is intended to reflect, not only among the sample of individuals being studied, but also by the broader population represented by that sample.[14] If the study was to take place with another population, would this yield the same results? External validity is challenging to determine in studies involving the potential development of allergic disease, as epidemiological studies in this area show wide variances in prevalence. Sensitisation to the concept of allergic disease also differs considerably between Westernised countries and rural, third world communities.

3.1.3 Bias

Bias is the term commonly used to refer to problems in the design or conduct of studies that lead the study results to be invalid.[19] Random error in a trial results from sampling variability

and it decreases as the sample size increases, however bias is independent of both sample size and statistical significance.[5]

In research, bias is nearly always present and can enter a study at any stage of research, including during study design or data collection, as well as during the analysis of data and publication.[5] At the subject selection stage, if the selected group is not representative of the population that the results are intended for, it is defined as selection bias.

The significance of bias depends on how much it impacts on the validity of the results and conclusions. Bias could create inaccurate outcomes as reality and can ultimately have a negative impact on patients if applied to them.[4]

There are many different types of biases described in the research literature and articles describing ways to minimise bias are available[4], but it is often challenging to avoid some impact from bias. Studies related to food allergy prevention can be prone to recall bias, which will be expanded on in the section below as recall bias is the main aspect of validity discussed in part 1 and part 2 of this study.

3.1.3.1 Recall bias and assessing accuracy of recall

Recall bias is the tendency of subjects to report past events about exposure or outcome in a way that is different between the two study groups[20] and can be intentional and unintentional. This error in recall can lead to misclassification of the related variable among study subjects with a resultant distortion of measure of association in any direction from the null. Recall bias contributes a major threat to the internal validity of studies using self-reported data.[21]

Some studies can be more prone to recall bias than others, for example if the disease/event under investigation is significant or critical such as cancer or the exposure under inquiry is socially undesirable such as illicit drug taking.[22, 23] Thus, recall bias has largely been

associated with case-control studies as cases are more likely to have thought about and to remember past exposures owing to concern about their condition.[19]
Researchers that have looked at the accuracy of maternal recall have found that factors such as the period of recall[24, 26], family size[26, 28], type of information recalled and mother's educational level[26] were implicated.

Recall bias can also enter a study when subjects are asked to recall events many years after they have taken place, likely due to loss of memory. Many epidemiological studies are guilty of a period of recall in obtaining the information; the effect of this is however unclear, particularly in the field of food allergy. Despite suspecting that this period of recall in food allergy prevention studies may have an effect on the reliability of the data, it is still used to inform national policies.[27]

Many food allergy prevention studies focus on infant feeding practices and rely on maternal recall. Studies that looked at the validity and reliability of maternal recall for infant feeding practices over a variation of time periods, starting with the shortest period of recall are summarised below (Table 3.1). Invalid or unreliable recall leads to inaccurate recall, which contributes to recall bias. Despite the focus on the validity of maternal recall in these studies, some of them have been designed poorly themselves.

Bland *et al*[28] studied the accuracy of maternal recall of exclusive breast feeding (EBF) duration, 6-9 months after the birth in 81 mother-infant pairs in a rural health district in South Africa. Prospective data on EBF, which was used as the accurate comparison, was collected weekly from birth. Results showed that 13% (n = 12) of mothers did not provide an answer as they could not remember, 72% (n = 58) did not recall the period of EBF accurately and that 57% (n = 46) overestimated the duration versus 15% (n = 12) that underestimated. The authors concluded that recall at 6-9 months post-delivery was poor, and that inaccuracy was more evident the shorter the period of EBF duration. The authors also looked at factors that could potentially influence recall (educational level of mother, economic advantage and history of breast health problems), but none of these influenced recall significantly. Interestingly, the 48 hour recall method that was also assessed was also not found to be accurate, as it did not reflect EBF history since birth. The WHO definition of EBF was used in

this study; therefore the addition of any water to the child's diet would mark the end of the EBF period. If mothers did not understand the importance of the addition of water, this would explain the degree of over reporting of duration of EBF by mothers.

Agampodi[29] *et al* assessed the validity of maternal recall of EBF duration during infancy. Mother's reported EBF duration was compared to prospective data collected since birth. Prospective data on EBF was gathered through documentation of when any food/liquid item (other than medicine or vitamin/minerals as defined by WHO's definition of EBF) was introduced into a baby's diet. After 9 months follow up, mothers were asked to report EBF duration using one single question ("at what age did you discontinue EBF"?). Results of this study showed that maternal recall method overestimates the duration of EBF and that maternal recall in their study was not a valid method of estimating the duration of EBF ($p < 0.001$). The sensitivity to detect EBF babies at 6 months was 100%, and the specificity was 26%, therefore if mothers were breast feeding exclusively at 6 months, it was very reliable to detect this, however if they weren't, it is highly unreliable. The authors[29] commented that the low validity of results would be more likely due to social desirability bias than recall bias as health care providers collected the data.

Another study that aimed to assess recall accuracy of breast feeding and infant feeding practices among mothers through retrospectively collected data was Gillespie *et al.*[30] Prospective data was collected by interviewing mothers every 3 weeks during the first 3 months after the birth of their child, and mailing a questionnaire at 6 months. A subset was interviewed again by telephone approximately 1.0 - 3.5 years after the birth. Results showed that the age of introduction of solid foods tended to be overestimated in interviews 1.0 – 3.5 years after the birth, compared to those within 3 weeks of the event, by approximately one month for 1.0 – 3.5 year recall and two weeks for 6 –month recall. Even at 6 months, the ages of introduction of solid foods reported were significantly later than the initially reported age. When asked why they stopped breast feeding, mothers who stopped due to mastitis were 100% correct (sensitivity 100%). This study asked the question "When did you stop breast feeding?" in order to assess the date that weaning commenced, which is a major limit as this is not the same question. This factor did not appear to affect the results of how long mother's breast fed for, which is what this question is asking. Another limitation to this

study is the method of data collection at the 1.0 - 3.5 year recall. The gold standard data on breast feeding duration/weaning was collected in weeks, whereas mothers were asked to recall in months which allowed for over-reporting by up to 1 month.

Eaton-Evans and Dugdale[31] investigated the accuracy of maternal recall for infant birth weight, duration of breast feeding and introduction of other milks in 64 mothers. Seventy five children (as mothers with >1 child were included), between the ages of 1 and 10 years (average 3 years) participated in this study. The comparison data used to determine the accuracy of recall was obtained by maternal interview at Child Health Centres, which were attended at least once per month since the birth of the child. Seventy nine per cent of mothers (n = 59) recorded accurately within one month the duration of breast feeding. Ninety five per cent of mothers recalled accurately within two months. Interestingly, the larger differences between recall duration and those recorded from birth were shown for the children who were breast fed for more than 6 months, with an equal amount of over- and underreporting for both. Parity of the mother, education and the present age of the child (i.e. recall period) had no significant effect on the mothers recall accuracy. Fifty eight per cent (n = 46) of mothers recorded within 1 month how old their child was when they first received milk feeds other than breast milk and 77% (n = 61) recalled within a two month period. It was discussed by the authors that the age of introduction of milk feeds other than breast milk could have been poorly recorded initially as mothers may not have mentioned if they were giving milk feeds in addition to breast milk. The type of milk/milk formula first given was also investigated and 73% (n = 58) of mothers answers agreed with those recorded.

Vobecky *et al*[24] examined mother's memory in a retrospective assessment of infant feeding practices and reported that they were generally unreliable. The first set of data (which was used as the gold standard comparison) comprised of prospective questionnaires on a monthly basis including questions on infant feeding practices. The second set of data was obtained ≥ 8 years after, with the same questions to the same mothers. Results from t-tests showed that mothers tended to over-report and underreport the duration of breast feeding and introduction of solid foods. Strong correlation was shown however for duration of breast feeding and duration of BF for EBF (r = 0.95 and r = 0.94 respectively). The age at introduction of solids was recalled very poorly with a correlation of only 0.16 for meat and

0.35 for cereals. The authors concluded that maternal recall on infant feeding practices is not particularly accurate, but this was based on measurement of differences rather than measurements of agreement for breast feeding questions.

Tienboon *et al*[32] compared mothers' recall of infant feeding practices after a period of 14 to 15 years as part of a study looking at the determinants of early risk factors for coronary heart disease in adolescents. Results showed a sensitivity of 82% and specificity of 93% for maternal recall of breast feeding. Less accurate was maternal recall for the timing of the introduction of solids and estimation of duration of BF (this tended to be influenced by recent trends in infant feeding). Interestingly, the agreement was better for first and second born children and for those children who had been breast fed for at least a month.

An earlier study[25] in Israel looked at the validity of maternal reporting of breast feeding history by comparing answers from a questionnaire by mothers of 20 - 22 year olds to their infant child clinic records. The main aims for the study were to ascertain the validity of this approach of obtaining retrospective information and then to make preliminary conclusions of the relation of breast feeding with plasma lipid concentrations. Results showed that duration of breast feeding was well correlated between the two sets of data (r = 0.82). Less well correlated was when formula milk/cow's milk was first introduced into their child's diet (r = 0.16). The authors noted that all of the mothers had breast fed all of their children and that if they maintained similar patterns with each child, it could partly explain the high validity. As the two sets of data were well correlated and recall could be relied on, the authors' recommendations were to investigate a larger group on the relation of breast feeding with plasma lipid concentrations.

Studies of long-term effects of the duration of breastfeeding on the health of both infants later in life and of mothers often relies on reported breastfeeding duration after several decades. Adult intelligence, obesity, serum cholesterol and risk of diabetes have all been investigated in their relationship with breast feeding and breast feeding duration.[33] Promislow *et al*[33] assessed the validity of long term maternal recall of the duration of breastfeeding for elderly US women. Mothers who breastfed a child reported the duration both prospectively in a diary and retrospectively in a questionnaire administered 34 - 50

years later. One hundred and thirty two women out of 140 reported that they had breast fed their child, which was in agreement with their records, giving sensitivity for recall of having breast fed of 94%. Results however showed considerable recall error existed over the range of reported breastfeeding durations. The degree of under- and over-reporting was very similar overall, so there did not appear to be overall recall bias, but there was substantial misclassification for individuals. The trend was for mothers who breast fed for longer durations to underreport and for those who breast fed for shorter durations to over-report. It is important to consider the impact of over-reporting and under-reporting in the pooled results of large studies, as the combined results often lead to inaccurate data.

Table 3.1: Validity of maternal recall of breast feeding history. Adapted from Li *et al*[11]

Study	Population	Method of data collection for recall	Period of recall	Validation method Baseline data)	Comparison between Recall and Validation Standard		
					Breast feeding (ever vs never)	Duration of breast feeding and/or EBF	Age at introduction of other fluids or foods
Bland *et al*[28]	81 mother-infant pairs	Home visit with mother 6-9 months after birth to determine exclusive breast feeding duration	6-9 months	Longitudinal data from birth (7-day recall) at weekly home visit up to 16 wks post delivery	-	Duration of EBF. 72% (n = 58) Recalled inaccurately. 57% (n = 46) overestimated and 15% (n = 12) underestimated duration.	-
Agampodi[29]	103 mother-infant pairs	Mother interview to establish EBF duration	9 months	Prospective data collection with pregnancy record, child health development record & questionnaire	-	Duration of EBF: 77% respondents reported EBF for 6/12, verse 23.9% (n = 27) from prospective data. Sensitivity 100%, specificity 26%	-
Gillespie[30]	184 mothers	Telephone interview	1-3.5 years	Data gathered by telephone interview 3, 6, 9, and 12 wks. Mailed questionnaire at 6 months.	-	Overestimation of duration of breast feeding of one month on average at 1-3.5 year recall period	Overestimation of weaning time. Correlation of recall weaning time was only 0.59 (95% CI [0.46,0.69]
Eaton-Evans and Dugdale[31]	64 mothers, 75-79 children	Maternal face to face interview about infant feeding	1-10 years (average 3 years)	Medical records about infant feeding practices at child health centres (visited at least 1/12)	- -	79% recorded within 1 month (95% within 2 months)	Introduction of milk other than breast milk: 58% recalled within 1 month (76% within 2 months)

Vobecky *et al*[24]	95 mother child pairs	Maternal interview about infant feeding practice	≥8 years	Maternal interviews at monthly intervals from 0-6 months after birth & 3 month intervals 6-36 months (prospective)	Agreement = 85% Sensitivity = 82% Specificity = 93%	r = 0.95 (duration of BF) r = 0.94 ,(duration of BF for EBF, n = 39)	Cereals: r = 0.35 (all) Meats: r = 0.16 (all)
Tienboon *et al*[32]	144 mother-child pairs	Maternal interview about infant feeding practices	14 – 15 years	Infant clinic records	-	37% recalled within 1 month (59% within 2 months) r = 0.7 (breastfed n = 77)	Solid food (<3,3-6,.6 month): Agreement = 65%
Kark *et al*[25]	74 mother-child pairs	Maternal interview	20 – 22 years	Infant child records	Sensitivity = 94%	r = 0.82 (Spearman correlation) (all)	Non-breast milk: r = 0.16 (Spearman correlation)
Promislow[33]	140 elderly women	Self-administered questionnaire	34 – 50 years	Diary data Menstruation and Reproductive history study		26% of women recalled accurately in months, 55% recalled accurately within 1 month and 71% recalled accurately within 2 months.	-

*r = correlation coefficient

Maternal recall of infant feeding practices is particularly important in the field of food allergy where experts seek to understand the relationship between ingestion of a food allergen and developing a food allergy to that particular allergen. Investigations into the method of exposure of potential food allergens (pregnancy, breast feeding and weaning) and timing of ingestion (age of infant) rely heavily on mothers to recall details of these past events.

Before discussing the potential for recall bias in studies relating to the prevention of food allergy, the next few sections provide a background to the prevalence, prognosis, and burden of this disease.

3.2 Prevalence of allergic disease and cost burden

The cumulative prevalence of allergic disease in childhood is high. Although it is difficult to determine true prevalence, studies have shown food allergy to be prevalent in 6% - 8% of children.[34] Food allergy has also been associated with the later development of asthma and atopic rhinitis.[35,36]

Heterogeneity with methodology, diagnostic approaches and study design within existing research impacts on the accuracy of determining true prevalence. Self-reported food allergy is also higher than reports from studies utilising objective measurements.

Genetic factors account for 50-70% of asthma and allergy development. If both parents have allergic disease, their child has a four-fold risk of developing an allergy compared to a child who does not have a parent with allergic disease. The risk of developing allergic disease when one parent is allergic is two-fold.[37]Many children however who develop allergic disease during their first years of life come from families without a history of atopic disease.[38]

Managing allergic disease is a cost burden on health services and specifically specialist allergy services. Gupta *et al*[39] analysed the costs of managing allergic disorders (allergic rhinitis, anaphylaxis, asthma, conjunctivitis, eczema/dermatitis, food allergy and urticarial/angioedema) in the UK and found treatment for these currently accounted for 10% of the prescribing costs of primary care.

With such a cost burden on health services, initiatives to prevent allergic disease are desired and currently being developed.

3.3 Prognosis of Food Allergy

Not all children outgrow food allergy, which means that as long as they are allergic, they are a cost burden to health services. Host and Halken[40], found remission rates for children with cow's milk allergy (CMA) to be 56% children at 1 year, 77% of children at 2 years and 87% at 3 years.

A more recent study by Skripak in the US[41] showed conflicting rates of acquired tolerance, with rates of resolution of CMA being only 19% by 4 years. Although this study is more relevant to tertiary centre populations, these recent results could also suggest that the development of tolerance may take longer than previously thought, particularly with CMA at the more severe end of the spectrum.

With acquisition of tolerance showing to be later in some more recent studies, there is increasing need to focus on preventative strategies for the development of allergic disease.

Although the majority of young children outgrow their food allergies, there is a phenomenon known as the 'atopic march' that can occur, where these children end up developing other allergic disorders such as asthma, rhinitis and inhalant allergy.[42] If there is a causal link between FA and the later development of allergic disease, then prevention of the first stage of the allergic march would appear to be the most effective way to reduce the prevalence of allergic disease overall.[43]

3.4 Trends in Food Allergy over time

There is some evidence that the prevalence of food allergy is increasing[44-50], and it may even be the case that food allergy is increasing in some parts of the world and stabilising in others.[51] There is very little good quality data in the same population (geographical location)

to show that food allergy is increasing. Some authors have referred to this perceived increase as the 'second wave' of the allergy epidemic, with the first wave being the surge in allergic disease asthma and allergic rhinitis which reached peaks in 'Westernised' countries in the 2000's.[7]

The only paper that has looked at the prevalence of food allergy in the same population at a different time found peanut allergy changed very little over time. In three cohorts of 3- to 4-year old children born in the same geographical location (Isle of Wight), peanut sensitization and reported peanut allergy increased from 1994-1996 to 1989, but slightly decreased in 2001 – 2002.[47]

A perceived increase in the prevalence of food allergy and the improved understanding of the impact this has on individuals, communities and health economies has led to increased interest in understanding factors that determine allergy risk and whether influencing these can have an impact in reducing the prevalence of food allergy. Strategies to support prevention of food allergy include mother's diet during pregnancy, breast feeding practice, weaning age and introduction of allergenic foods, all of which will be discussed in detail below.

3.5 Prevention of Food Allergy – Observational Studies

As the burden of food allergy is well recognised, it makes sense to look at ways to prevent the development of food allergy altogether. There is some emerging evidence that has shifted thinking and practice from withholding highly allergenic foods from the infants diet (until the infants immune and digestive systems are more mature) to the questioning if infants should be exposed to allergens early in life.[38]

Numerous studies have also looked at factors that either seem to protect or promote the development of allergies, which include studies focusing on genetics and epigenetics[52], maternal diets during pregnancy and lactation[48,53-55], and feeding practices (breast feeding verse EBF, breast feeding verse formula milk feeding and the introduction of solid foods).[55]

Within the broader 'food allergy spectrum', peanut allergy is the most common cause of fatal and almost-fatal food-induced anaphylaxis.[56,57] This allergy also tends to persist into adulthood. Thus early and aggressive intervention in both prevention and treatment is essential and many of the research studies (observational and interventional) have focussed on peanut allergy specifically.

A prospective study is the ideal study design to observe dietary factors in mothers of infants who develop food allergy, for example peanut allergy. However, due to the relatively low prevalence of the condition, a large birth cohort will be required and needs to be observed for many years in order to provide an adequate number of peanut allergic children and sufficient data. A retrospective study on the other hand allows researchers to include a large number of peanut allergic cases over a much shorter period of time.[58]

The whole purpose of observational studies is to inform regarding possible interventional studies. The data derived from observational studies therefore needs to be valid and free from recall bias for any intervention to be meaningful.

Studies that rely on mothers to recall on infant feeding practices can be subjected to recall bias. In the area of food allergy, studies on dietary intake during pregnancy and infant feeding practices are of immense interest in understanding the etiology of the disease.

3.5.1 Prevention of Food Allergy in pregnancy

Atopic diseases are known to have a strong genetic component and it is well known that maternal allergens cross the placenta from a mother to her child during pregnancy.[59] Some studies have shown that a maternal allergy is a stronger determinant of allergic risk than paternal allergy[60,61] which would also suggest that there are in utero interactions that are implicated. However, Arshad *et al*[58] showed that the effect of maternal versus paternal history of allergy varies with the sex of the child, where maternal history increased the risk of asthma and eczema in girls and paternal allergic history increased the risk in boys. Evidence of maternal allergens crossing the placenta[59] contributed to the recommendations

that pregnant mothers of high risk (parent or sibling with allergy) infants avoid certain food allergens during their pregnancy.

Not all intervention studies are however without risk. Maternal dietary avoidance trials during pregnancy have shown evidence that this can lead to lower mean gestational weight, a non-significantly higher risk of preterm birth, and a non-significant reduction in mean birth rate.[92] The interest of possible sensitisation of food allergens during pregnancy is particularly relevant to peanut allergy because many cases of allergic reactions occur following first known dietary exposure to peanut products, which may indicate exposure during pregnancy or breast feeding.[59] When looking specifically at dietary patterns during pregnancy and the relation to peanut allergy to determine potential *in utero* exposure, it is interesting how evidence has impacted on government advice for atopic mothers over time.

In 1996, Hourihane *et al*[48] looked at the prevalence of peanut allergy and other allergies in the families of people with peanut allergy in their study population of 622. Their results showed that peanut allergy was reported increasingly by successive generations i.e. reports in children and siblings were higher than parents and aunties and increasingly higher than in grandparents. Results looking at dietary patterns showed that the mothers of younger children in the study (0 - 5 years) were more likely to have consumed peanuts often during pregnancy or breast feeding. As a reaction to first known exposure of peanuts was reported in 80% of the subjects under 5 years of age, the authors implied that prior sensitisation could have occurred in utero or via breast milk.

Results of this study led the authors to suggest that recommendations be developed for peanut allergic mothers to avoid peanuts during pregnancy. Supporting factors for this advice is that peanuts are firstly a fairly easily replaced food in the diet and secondly that first allergic reactions to peanuts are severe in nearly 50% of cases.[63] It is important to note here that the results of the Hourihane study[48] on the maternal consumption during breast feeding and lactation may have been subject to recall bias. Mothers of subjects up to the age of 18 years were asked to recall on their consumption of peanuts during pregnancy and lactation, which is a long period of historic recall. The authors were not aware of any evidence to show that maternal recall over a period of up to 18 years is accurate. Although

recall bias was not controlled for, these suggestions were supporting evidence for the development of the 1998 Committee on Toxicity (COT) Report on peanut allergy.[64]

A working group of the Committee on Toxicity of Chemicals in Food, Consumer Products and Environment in the UK was established to advise on the potential association between early exposure of peanuts and the incidence of allergy later in life and on the consumption of peanuts by pregnant and lactating women, infants and children. After reviewing the evidence (including the study from Hourihane *et al*[48]), COT[64] recommended that atopic pregnant women or where another first degree relative of the child is atopic, may wish to avoid eating peanuts and peanut containing products during pregnancy and breast-feeding. It was also advised that during the weaning of these infants and until they were at least 3 years of age, peanuts and peanut products should be avoided. In 1998, the UK government issued this precautionary advice based on COT's recommendations.

In 2003, the Food Standards Agency (FSA) funded Hourihane *et al*[65] and Dean *et al*[66] to investigate the impact of the COT report and subsequent UK government advice on the prevalence of peanut allergy.

Interestingly, results of the Hourihane *et al*[65] study showed that there was no reduction in peanut allergy as a result of this advice. Of the 957 mothers interviewed, 61% of them had recalled hearing about the COT advice, yet only 3.8% reported to have followed the advice by stopping the consumption of peanuts during pregnancy and 5% while breast feeding. The authors concluded that the COT advice to atopic mothers did not appear to affect the prevalence of peanut allergy in children at school entry, but lack of implementation of the advice needs to be considered. The authors of this paper acknowledged the limitation of potential recall bias in this study as mothers where asked to recall their dietary intake of peanuts from 5 -6 years earlier.

Dean *et al*[66] also assessed the compliance and investigated the impact of the government's advice based on the COT report and found that the prevalence of peanut allergy stabilised, but mothers avoided peanuts unnecessarily. Eight hundred and fifty eight mothers of children born 3 years after the COT report was issued were asked specific questions regarding their consumption of peanuts during pregnancy as well as questions specific to the advice at the time. Forty-two per cent of mothers reported to have heard about the

government advice, and half of these made the recommended changes to their diet as a consequence. Sixty-five per cent of the mothers stated that they avoided peanuts during their pregnancy, although this was not linked to whether they were atopic/had an atopic family history or not. This is a significant finding as the advice of avoiding peanuts during pregnancy was intended for atopic mothers/babies with family atopy. Mothers were asked about their dietary intake of peanuts in a questionnaire whilst they were 36 weeks pregnant, which negates the risk of recall bias caused by long term recall.

In December 2008 the COT therefore released a report to change their advice. The FSA then changed their policy and advised that it is no longer appropriate to avoid peanut consumption during pregnancy, breast feeding and infancy irrespective of family atopy.[68]In support of the updated COT recommendations, a European Academy of Allergology and Clinical Immunology (EAACI) Taskforce on Prevention of food allergy has recently reported (in draft) that there is no evidence to recommend that women modify their diet (including peanuts avoidance) during pregnancy to prevent the development of food allergy in their infant/child.[69]

The Food Standards Agency (FSA) also asked the COT to assess whether there was evidence to show an association between early exposure to numerous food allergens (cow's milk, eggs, fish, and nuts) and the occurrence of food allergy (with a particular focus on peanut allergy) in later life. Calvani *et al*[67] reported a statistically significant decrease in risk of sensitization to fish with increased maternal consumption during pregnancy, but mothers had to recall their dietary intake during pregnancy up to a period of 18 years later. Lack *et al*[53] studied the factors associated with the development of peanut allergy in childhood and they did not find a significant association between maternal consumption of peanuts during pregnancy or breast feeding. Mothers in this study were asked about their own consumption of peanuts during pregnancy and lactation when their children were up to 38 months of age.

3.5.2 Prevention of Food Allergy and duration of exclusive and non-exclusive breast feeding

It is widely accepted that breast milk is the best food of choice for babies for many reasons including cost, psychological benefits, prevention of infant disease and safety.[70] Breast milk also provides the ideal nutritional, immunologic and physiologic nourishment for all babies and components of human milk promote maturation of the infants' immune system.[71]

Although advocacy to breast feed will not change, the question of whether breast feeding is effective for the primary prevention of allergic disease remains controversial. The duration of BF, exclusivity and maternal diet are often considered when looking at the association between BF and the development of food allergy. Maternal diet in relation to the development of FA is important as it is well understood that the passage of dietary proteins pass into human breast milk[72-74]and some studies have shown that an exclusion diet of offending allergens by the mother during lactation has resulted in improved symptoms in the infant with atopic eczema.[75,76]

3.5.2.1 Factors affecting validity and reliability of breast feeding studies

The effect of breast feeding on allergy prevention is difficult to study as it is unethical to carry out a randomised control trial (RCT) and assign a group to the 'non breast feeding' category. Due to this, all studies in this field are observational and often subject to confounding factors and biases.[77,78] Recall bias, atopic history, definition of EBF, amount of social pressure and variations in composition of breast milk all influence results looking at breast feeding duration in the development of allergic disease and these will be discussed below.

Recall bias plays a role in many studies that rely on mothers to record retrospectively on feeding practices. Gillespie *et al*[30] studied the recall accuracy of breast feeding variables and hypothesized that as breast feeding often occurs during a time of stress and sleep deprivation; recall of past events might be particularly prone to bias and/or imprecision. One could also hypothesize that recall relating specifically to breast feeding, such as duration and

exclusivity could be less prone to bias as it is emotionally connected time for a mother and her child. Li *et al*[11] however (as discussed in the section on recall bias) found that maternal recall is a valid and a reliable estimate of breast feeding initiation and duration, especially when breast feeding is recalled after a short period (≤ 3 years).

Whether a woman has a personal history or family history of atopic disease could affect her dietary intake and this could also therefore affect the development of allergic disease. Venter *et al*[9] found that women with a family history of allergic disease were more likely to breast feed exclusively at 3 months than those without a personal or family history.

Studies on the effects of breast feeding also rely heavily on definitions used and the method by which data is collected. In assessing the breast feeding situation, the WHO recommends that the 24-hour recall method is used in communities.[79] Bland *et al*[28] found however that 48 hour recall did not accurately reflect EBF since birth. Definitions of EBF also vary considerably from one study to another and this needs to be considered when results are pooled from studies using different definitions. Studies' looking at the validity and reliability of maternal recall for breast feeding need to consider what definition is used and how the question is posed at both points in time.

Another major consideration in the accuracy of reports of duration of breast feeding is the amount of social pressure mothers are exposed to in their environment. Results of recall accuracy cannot be compared in populations where there is a very strong pressure to breast feed verse a population where there is little pressure. Increased social pressure often leads to overestimation of duration of breast feeding, in particular when this information is obtained from a mothers' healthcare provider.[30]

Breast milk composition can vary from mother to mother, particularly in immunomodulatory components such as probiotic content, prebiotic content and fatty acid profile. This makes drawing conclusions of the effect of breast milk on the development of food allergy and other diseases challenging. These variations may also explain some conflicting evidence when looking at EBF duration and its role in the prevention of allergic disease.[80]

3.5.2.2 Evidence of breast feeding and the development of allergy

Observational studies on both unselected and selected populations (e.g. high risk groups) looking at the protective effect of breast feeding have shown conflicting results. Results can be divided into those that showed a protective effect of breast feeding against allergic disease and those that did not show a protective effect (some have even showed an increased effect).

A protective effect of EBF for 4-6 months on the risk of allergic disease (eczema and asthma) in early childhood has been reported, particularly with high risk infants in previous studies[81-83] and in two meta-analyses.[84,85] Other studies showed no protective effect of EBF for 6 months or more on asthma, eczema or atopy at 5 years of age.[86,87] Some studies have shown that the risk of atopy and atopic dermatitis with prolonged breast feeding may even increase, particularly later in life.[88-91]One of these studies, by Sears *et al*[88] included a retrospective component when recording the method of infant feeding, as babies were only recruited at 3 years.

In order to determine the ideal duration of breast feeding or EBF for FA prevention, Kramer and Kakuma[89] carried out a systematic review of 20 independent observational studies. The authors found that there was insufficient evidence for significant reduction in the risk of Atopic Dermatitis (AD), asthma or other atopic outcomes in infants BF exclusively for 6 months in comparison to 3-4 months. None of these studies relied on maternal recall as they were prospective trials.

Some studies looking at evidence for maternal avoidance of allergenic foods whilst breast feeding have shown a reduction in some manifestations of allergies, mainly eczema, however methodological issues in these studies make drawing conclusions from them challenging.[90,91] A recent Cochrane review[92] looked at studies that have researched maternal diet and the effect of maternal dietary allergen avoidance and concluded that advice of allergen avoidance to high risk women during lactation may reduce her child's risk of developing atopic eczema, but referenced that better trials are required.

Hourihane *et al*[48] (referred to in the section on pregnancy) work which was one of the key pieces of research that led to the initial government advice for atopic breast feeding

mothers to avoid eating peanuts and peanut containing foods, reported that the link of peanut allergy presenting earlier in life is possibly related to the increased consumption of peanuts by breast feeding mothers. This conclusion was however based on mothers having to recall their diets whilst breast feeding, up to 18 years earlier, which opens up a potential for recall bias.

3.5.2.3 Current recommendations for breast feeding

Recent guidelines[93] (currently in draft form) on the primary prevention of food allergy have been prepared by the EAACI Taskforce on Prevention and are part of the *EAACI Guidelines for Food Allergy and Anaphylaxis*. These draft guidelines recommend that pregnant and lactating mothers follow a normal diet and breast feed exclusively for 4-6 months. If breast milk (BM) is insufficient for the first 4 months, they recommend that high risk infants are given a hypoallergenic formula as an alternative. In all infants where BM is insufficient after the age of 4 months, it is recommended that a standard cow's milk based formula is introduced, irrespective of whether the child is a high risk infant or not.

Globally, the World Health Organisation (WHO) promotes EBF for the first 6 months of an infants' life.[94] It is however not the WHO's intention to prevent allergies by promoting EBF for this period. There are many health related outcomes, in particular for undeveloped countries which has given weighting to the promotion of EBF for 6 months. The American Academy of Pediatrics (AAP)[95] and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[96] recommend EBF for 4-6 months. Poland is the only country which currently advises specific breast feeding interventions, which is the avoidance of allergenic foods from the mother's diet.[43]

The duration of BF and in particular EBF has a direct impact on when solid foods are introduced into the diet, which forms part of the next section which discusses weaning/age of introduction of solid foods, in relation to food allergy prevention.

3.5.3 Prevention of food allergy and introduction of solid foods

The current evidence base for when to introduce allergens in the diet and whether to introduce these foods in small or large quantities regularly or irregularly is lacking, and this is clear from the lack of evidence-based guidance. The EAACI Taskforce on Prevention draft guidelines has recently assigned the topic of the effect of timing of introduction of different food allergens as a priority 1 for future research due to current knowledge gaps.[93]

Guidance for the introduction of allergenic foods has changed significantly over time. The first consensus document on the introduction of solid foods for the food-allergic infant was published by the American College of Allergy, Asthma and Immunology in 2006[97] which recommended that multiple allergens in solid foods given to the allergic infant be delayed until 6 months of age. The advice also included delaying the introduction of highly allergenic foods even further until after 1 year of age or later, with the recommendation of delaying the introduction of peanuts, tree nuts and fish until 3 years of age.

More recent research has shown that this advice was not supported by evidenced-based research and that adhering to this advice has not been effective. EAACI's current position[93], having reviewed all of the evidence on the introduction of potential food allergens, is that there is insufficient evidence to advise withholding or encouraging exposure to potentially allergenic foods during infancy. This advice is irrespective of atopic heredity and includes foods such as cow's milk, hen's egg and peanuts.

The hypothesis that particularly early consumption of a food allergen can induce oral tolerance[99] is currently of great interest in the allergy world, and there are observational studies that suggest that this hypothesis may be true. In the UK where dietary practise recommendations at the time of the COT report[64] (pre August 2009) were to avoid peanuts in infancy, 25% of allergy clinic patients were peanut allergic.[99] In contrast, in Israel where there is a high infant consumption of peanuts, 2.1% of allergy clinic patients were found to be peanut allergic.[100]These results have led researchers to design and implement long term interventional studies over a period of 5 years (to be discussed in the next section).

It is important to consider the role of family history and potential genetic predisposition when interpreting research that has looked at age of introduction of solids and the

development of allergy. Odijk *et al*[101]looked at the timing of introduction of solids and highly allergenic foods in atopic and non-atopic families and found that there were no differences. Schoetzau *et al*[102] found contrasting results in their study and found that solid food feeding was delayed more frequently past 6 months in mothers with a family risk of eczema than those mothers without a family history. Venter *et al*[9] found that women with a family history of allergic disease were more likely to avoid peanuts from the infant's diet at 6 months.

Current pooled results from studies of early exposure to and avoidance of allergenic foods are conflicting. There are numerous factors that make interpretation of studies on this topic complex, including differences in study designs, effect of a heterogeneous range of exposures and reliance on dietary recall.

Table 2 below comprises of observational studies that have relied on a period of historic recall of dietary factors in relation to food allergy outcomes. The longest recall period of these studies was 3 years. Previous studies that have looked at recall periods of dietary factors (in particular introduction of foods) of periods close to 3 years have shown that information obtained is not particularly accurate.[11,30] The results of these trials therefore need to be interpreted with this flaw within each study.

Table 3.2: Observational studies with recall component on weaning and allergy outcome

Paper	Definition of weaning	Data collection method	Period of Recall	Outcome (e.g. eczema/wheeze)
Koplin *et al*[103]	N/A Specific to introduction of egg	Self-administered questionnaire	11 – 15 months	Introduction of egg at 4 to 6 months was associated with a decreased risk of egg allergy, whereas egg introduction after 10 months was associated with an increased risk of egg allergy. There was no association of egg allergy with duration of breastfeeding (after adjustment for family and personal history of allergy) or age of introduction of other solid foods
Du Toit *et al*[104]	N/A – Specific to introduction of peanuts	Validated Food Frequency Questionnaire (FFQ)	Up to 24 months	Jewish children in the UK have a prevalence of peanut allergy 10-fold higher than that of Jewish children in Israel. Atopy, social class, genetic background and peanut allergenicity did not account for differences. Peanut consumption is high in Israel, whereas consumption in the UK is avoided (During BF and weaning).
Frank *et al*[54]	N/A – Specific to introduction of peanuts	Standardised questionnaire: Mothers of 0-3 year olds were asked to recall weaning history.	Up to 3 years	Peanuts were introduced into the child's diet from a significantly younger age in the peanut-allergic subjects ($p<0.03$). Peanut allergy is more likely to occur if mothers eat peanuts more frequently during pregnancy and introduce it early to the infant's diet.
Gustafsson *et al*[105]	Breast-feeding ended before 6 months of age/ Introduction of cow's milk-based formula before 4 months of age/ Introduction of hen's egg before 12 months of age/ Introduction of fish before 7 months of age	Feeding questionnaire	Up to 35 months	No feeding pattern during infancy was associated with an increased risk of becoming sensitized or developing clinical allergy. No increased risk was seen even in the group of children who were breast-fed less than 1 month.

3.6 Prevention of Food Allergy – Interventional Studies

Results from observational studies allow researchers to plan prospective studies with interventional arms. If the validity of the results from observational trials is poor, these could 'misguide' the researchers that plan the interventional studies. RCTs are seen as the most credible sources of research and therefore if national guidance is released, these need to be based on solid evidence from such RCTs.

3.6.1 Interventional studies for food allergy prevention in pregnancy, during breast feeding and during weaning/introduction of solid foods

Results of interventional studies for food allergy prevention have varied significantly, which has made interpretation and recommendations incredibly challenging. Some of the interventional studies that have been performed to date will be discussed below.

Zeiger *et al*[106] studied the effect of combined maternal and infant food allergen avoidance on the development of atopy of infants with atopic parents. The interventional group had reduced food sensitization and allergy during the first year of life, but this only reached statistical significance for milk. The exact role of delayed solid feeding in the interventional group cannot be explained with the methodology of this study, which involved a number of dietary restrictions both during pregnancy and weaning. This was the largest cohort of selected subjects followed up for the longest duration looking at factors in the development of atopic disease, and would not have been subject to bias from memory due to its prospective design.

In contrast to these results, Arshad *et al*[107] found that reduced exposure of infants to allergens in food and in house dust lowered the risk of the development of allergic disease. In this RCT of 125 infants, the intervention group was assigned to an avoidance diet for lactating mothers, a staggered introduction of allergenic foods up to 12 months as well as household treatments to control for inhaled allergens. These study subjects were followed up for a further few years and the authors concluded that allergic diseases can be reduced for at least the first 8 years of life when following an allergen avoidance diet in infancy and

controlling for house dust mite.[91] An 18 year follow up of the same study population showed that the effect of comprehensive allergen avoidance persists into adulthood.[108]

Intervention studies looking to determine if there is a reduced incidence of CMA with early infant feeding practices have been performed. A prospective study[109] of 6209 healthy infants were enrolled in a birth cohort looking at the risk of exposure to cow's milk for the development of CMA during supplementary feeding. Infants were randomly assigned to three groups, based on the supplement given (liquid cow's milk formula, pasteurised human milk and extensively hydrolysed whey formula). The comparison group was infants who were exclusively breast fed. This study showed that exclusively breast fed infants are not protected against developing CMA and that the use of an extensively hydrolysed whey formula was the most protective. Infants exposed to CM formula in hospital immediately after birth have a higher risk of developing CMA than those in the other supplement groups. In the UK, many mothers are offered CM formula for their babies until breast milk volumes are adequate. One of the questions in this study (Chapter 2) asked whether infants were given some cow's milk formula whilst in hospital. Should results be accurate on recall analysis, this would allow large epidemiological studies to ask this question retrospectively to understand large scale impact of the early exposure of CM formula and the potential impact on the development of CMA.

In 2006, a Cochrane review[89] concluded that an allergen avoidance diet in high risk women during pregnancy is unlikely to significantly reduce the risk of atopic diseases, with the possible exception of atopic dermatitis (AD). All the trials that were considered in this review were interventional trials where an interventional arm of mothers would avoid certain food allergens whilst breast feeding. Previous observational studies like Hourihane *et al*[48] were the basis for setting up these interventional trials.

A recent RCT[110] from Palmer *et al* sought to determine whether early regular egg exposure might reduce the risk of the development of egg allergy. In a DBPC trial infants were allocated to either receive regular whole egg powder or rice powder from 4 months until 8 months, when cooked egg was introduced to both. The group receiving the egg powder showed reduce incidence of egg allergy in comparison to the rice powder group, leading the

authors to suggest that induction of immune tolerance can be achieved through early regular oral egg exposure in infants with eczema.

Long term RCTs are currently underway and the results for the LEAP[111] and EAT[112] studies have yet to be published. Both of these studies are looking at early introduction versus avoidance of some allergenic foods and food allergy outcome. The EAT study (Enquiring About Tolerance) is a prospective study randomly assigning new-borns to one of two groups. The first group will introduce 6 allergenic foods from 3 months of age alongside continued breastfeeding. The second group will follow current UK government weaning advice (aiming for exclusive breastfeeding until 6 months of age) with avoidance of certain allergenic foods before 6 months (cow's milk, peanuts, wheat, eggs and fish). The LEAP study is a long-term RCT in high risk children in the UK and Israel, which aims to identify which practice (avoidance or early introduction), is beneficial to prevent the development of peanut allergy. The results of this study (the comparison of peanut allergy incidence rates at 5 years) will determine the future recommendations/strategy for the prevention of peanut allergy. As much evidence for the development of peanut allergy has relied on long periods of recall, the results of this study are eagerly awaited.

CHAPTER 4

RESULTS

CHAPTER 4: RESULTS

4.1 Demographic Information

4.1.1 Study population

A total of 927 families participating in the FAIR study were approached to participate in the follow up FAIR study with this study embedded. The families were contacted by mail to participate in the trial, with the letter explaining the tests and questionnaire that the children and parents respectively would be asked to participate in. Eight hundred and thirty families (parent and child) responded and participated in the FAIR follow up. Three hundred and thirty four families attended a follow up clinic at the allergy centre for phase 2 of the study. One hundred and twenty five complete questionnaires were obtained from this group of 334, which formed the study population for this study. Figure 4.1 below shows a flow diagram of the study population from initial FAIR study population recruited in 2001 to the follow up numbers obtained for this study in 2012. The reasons why those families who were approached and did not participate were not documented as families were free to withdraw from this birth cohort at any point without having to give a reason.

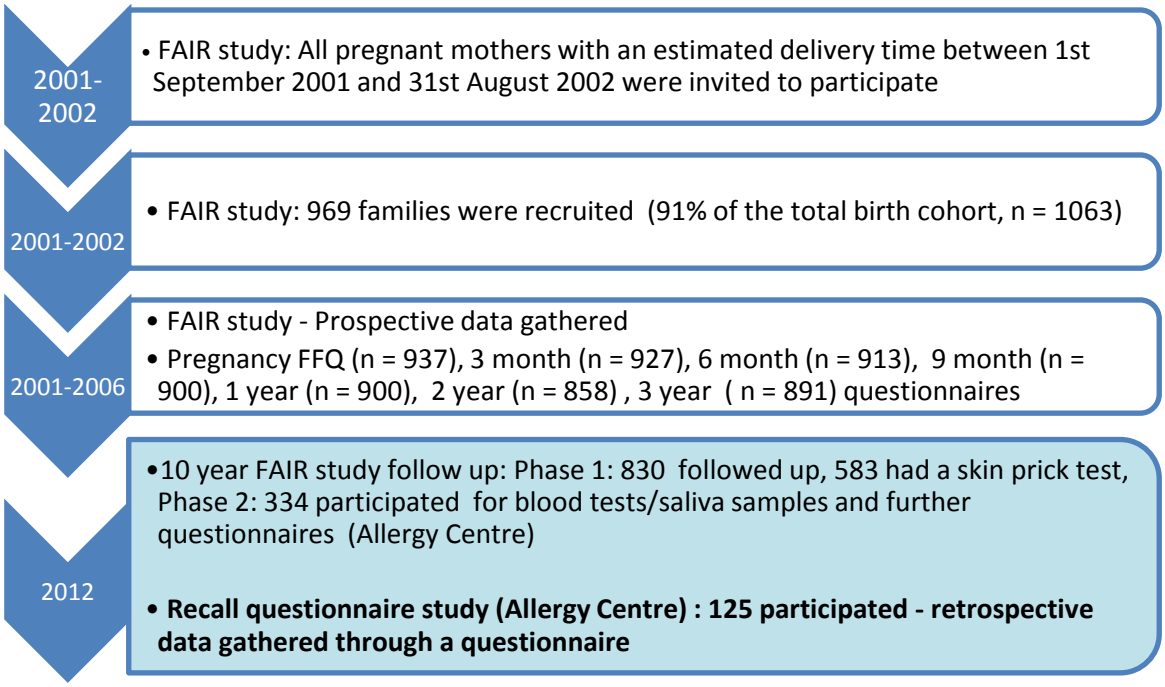

Figure 4.1 Flow diagram of study population from recruitment

For statistical power a sample size of 121 (completed questionnaires) was calculated as the minimum number required in order to detect a small standardised effect. Answers to 125 questionnaires were entered onto SPSS with the matched data from the FAIR questionnaires (36 weeks, 3, 6, 9 and 12 months and 1 and 2 years).

Results will be reported for this study sample of 125 predominantly; however some reporting may include data from the FAIR study if it supports to provide context or clarification.

4.1.1.1 Age and birth order

Families (n = 969) were first recruited onto the FAIR study in 2001/2002 when the mothers were 36 weeks pregnant, and the average age of the pregnant women ranged from 15 to 44 years with a mean age of 27 years and 10 months. Questionnaires were then completed when the children were 3, 6 and 9 months as well as 1, 2 and 3 years.

The next set of results report data on the 125 children only:

The average age of the children (n = 125) in 2002 at the 6 month follow up questionnaire was 6.2 months (SD 0.37, 4.4 – 7.7), which was symmetrically distributed as the median was 6.1 months.

In 2012 the average age of the children (n = 125) at their follow up for this study was 10.5 years (SD 0.32, 9.8 – 11.1) which was also symmetrically distributed as the median was also 10.5 years.

Fifty four per cent (67/125) of the children that mothers recalled feeding practices had an older sibling, whilst forty six per cent (58/125) were firstborns.

4.1.1.2 Gender

Sixty per cent (n = 75) of the study population (n = 125) were boys and 40% (n = 50) were girls. This ratio differed slightly from the initial FAIR study population (n = 969) which comprised of 52% (n = 500) boys and 48% (n = 469) girls.

4.1.1.3 Family History of allergic disease at the age of 12 months

Eighty seven per cent (n = 109) of the study population had at least one family member (mother, father or sibling) with history of/or allergic disease at their 12 month follow up for the FAIR study in 2002/2003. Family history of allergic disease was based on the validated ISAAC questionnaire.[113] This percentage is similar to that of the FAIR study population, where 83% (n = 806) have a family history of allergy.

Nineteen per cent (n = 13) of parents reported that one or more siblings of their child in the study had a food allergy/intolerance at recruitment into the FAIR study in 2001.

4.1.1.4 Incidence of sensitisation and diagnosed Food Allergy (DBPCFC) at 1, 2 and 3 years

Of the 121 children in the study that were skin prick tested at 1 year of age, 2.5% (n = 3) of them were shown to be sensitised to a predefined food allergen. The predefined food allergens that were skin prick tested were milk, egg, wheat, cod, sesame and peanut.

At 1 year of age, 1.6% of the 125 children (n = 2) were diagnosed with FA based on Double Blind Placebo Controlled Food Challenge (DBPCFC), SPT and history.

Two of the 115 children (1.7%) who were skin prick tested were found to be sensitised to a predefined food allergen (milk, egg, wheat, cod, sesame and peanut) at 2 years of age.

Food allergy was diagnosed based on two variations of methods. The first method was with an Oral Food Challenge (OFC), SPT and history which resulted in an incidence of 2.4% (n = 3) and the second method was with DBPCFC, SPT and history and the incidence was 0.8% (n = 1).

Of the 114 children, 4% (n = 5) that were skin prick tested at 3 years showed positive SPT.

Food allergy was diagnosed at 3 years based on Oral Food Challenge (OFC), SPT and history and then DBPCFC, SPT and history and the incidence was 2.5% (n = 3) and 1.7% (n = 2) respectively.

4.2 Accuracy of Recall

4.2.1 Recall regarding breast feeding questions

4.2.1.1 Breast feeding versus not breast feeding

Mothers were asked whether they breast fed their infants in 2001/2002 and again 10 years later in 2012. Ninety three per cent (114/123) mothers reported accurately that they had breast fed. The Kappa coefficient was computed to measure the agreement from 2001/2002 to 2012 as it is generally thought to be a more robust measure than simple per cent agreement calculation since it takes into account the agreement occurring by chance. The kappa coefficient for agreement of the answer to whether a mother breast fed her child 10 years earlier or not is 0.79, which is considered substantial. The 95% confidence interval for the Kappa coefficient is 0.63 – 0.90.

Table 4.1 below shows both the specificity and sensitivity of the reported answers. The specificity of the answers from the mothers in 2012 is 100%. Mothers who therefore reported 'No' were 100% accurate in the pre and post questionnaire, i.e. if mothers did not breast feed, they reported this accurately and none reported to have breast fed if they did not. The sensitivity was computed to be 91%, therefore a very high percentage of mothers who said they did breast feed actually did. Very surprisingly 9% of mothers who did breast feed reported not to have breast fed.

Table 4.1 Breast feeding: specificity and sensitivity

Did you breast feed at all?				
	Breast fed NO (2012)	**Breast fed YES (2012)**	**Row totals**	
Breast fed NO (2001/2002)	22	0	22	100.0%
Row %	100.00%	0.00%		(Specificity)
Breast fed YES (2001/2002)	9	92	101	91.1%
Row %	8.91%	91.09%		(Sensitivity)
Totals	31	92	123	
	71.0%	100.0%		
	(Negative predictive value	(Positive predictive value)		

4.2.1.2 Duration of exclusive breast feeding

The World Health Organisation (WHO) defines exclusive breast feeding (EBF) as the practice of feeding only breast milk (including expressed breast milk) and allows the baby to receive vitamins, minerals or medicine. Water, breast milk substitutes, other liquids and solid foods are excluded.[79] For simplification of this term for parents in this study, EBF was defined as breast feeding without adding in drinks (other than water), formulas or food. As the outcomes for the initial FAIR study were to investigate dietary factors on the development of food hypersensitivity, the addition of water to breast milk would not have any effect on allergenic load to the infant. The aim of the recall study was to test for potential recall bias between the FAIR answers and the answers 10 years later. The exact same question therefore had to be used.

Mothers were asked how long they breast fed exclusively for, and were provided with a selection of timeframes, e.g. Up to 1 month and more than 6 months. Spearman correlation tests were computed to measure the agreement between the answers reported by the mothers in 2001/2002 and then again in 2012. A substantial correlation was found between the answers over 10 years ($r = 0.70$, $p < 0.05$), which means that asking mothers to recall how long they breast fed exclusively for over a 10 year period was found to be accurate.

Figure 4.2 below shows the distribution of answers in 2001/2002 and 2012. These answers are not matched; they are simply a representation of the distribution of answers at both time points. Although there is substantial agreement between the answers over this period of time, this histogram shows that some mothers recalled breast feeding their baby for longer periods i.e. more than 6 months, than they actually did. The distribution also shows that the majority of mothers who breast fed, breast fed exclusively for up to 1 month.

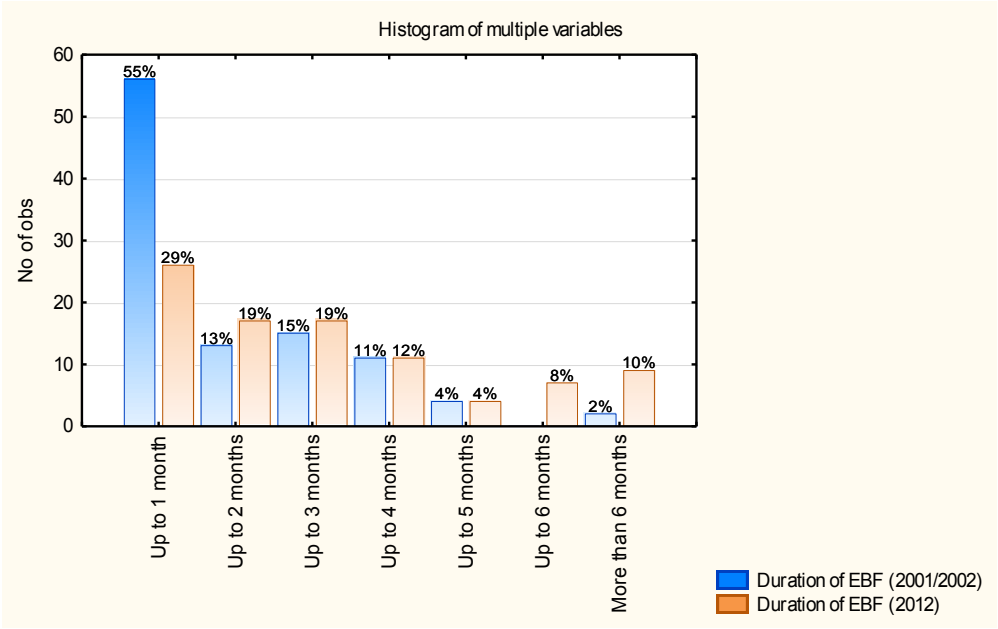

Figure 4.2 Duration of exclusive breast feeding

4.2.1.3 Duration of any breast feeding

Mothers were asked how long they breast fed for and the ranges of timeframes provided for selection were up to 1 month, 2 months, 3 months, 4 months, and 5 months, up to 6 months, then up to 9 months, up to 12 months, until 12 months or more than 12 months.

There was substantial agreement between the answers reported in 2012 and those reported 10 years earlier ($r = 0.84$, $p < 0.05$). There appears to be very little recall bias with mothers reporting how long they breast fed for in total. Figure 4.3 below is a scatterplot illustrating the strong correlation between the answers reported.

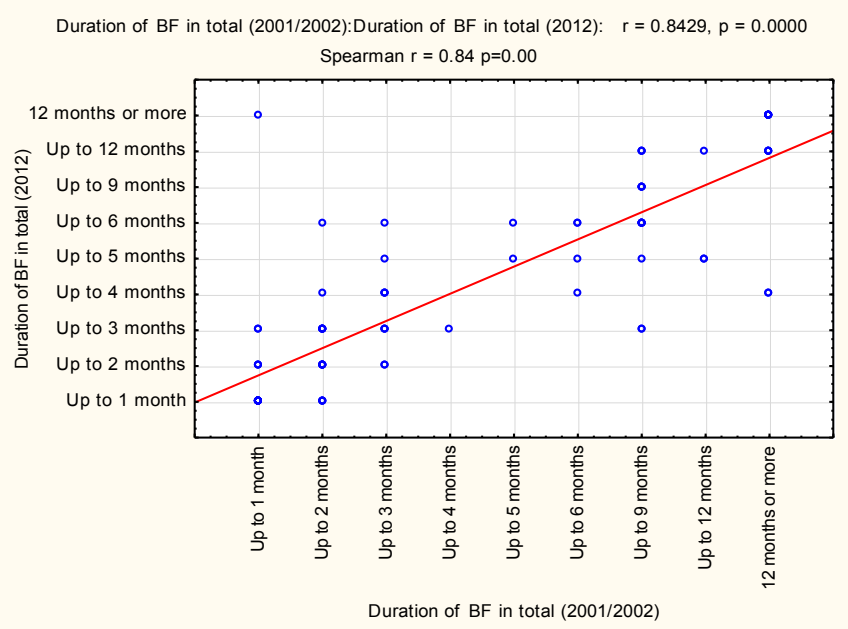

Figure 4.3 Correlation between duration of breast feeding answers in 2001/2002 and 2012

4.2.1.4 Reason for cessation of breast feeding

All mothers who breast fed at all were asked throughout each follow up questionnaire why they stopped breast feeding. Forty three per cent (36/83) gave the same reasons in 2012 as they did in 2003. The most common and accurately reported reason given for cessation of breast feeding in this study was baby's age (12/83)

4.2.2 Recall regarding formula feeding questions

4.2.2.1 Formula milk in hospital

Mothers were asked if their baby received any formula milk whilst in hospital. In the UK, some babies are offered a bottle of milk within the first 1 - 2 days in hospital (primarily if the baby's blood sugar is low), until breast feeding is established. Mothers were initially asked this question through a questionnaire when their baby was 3 months of age (FAIR 3 month questionnaire), and using this answer as the valid answer, 41.6% (52/125) of babies had a bottle of formula milk within the first 1-2 days, irrespective of whether mothers breast fed or not.

The percentage of accurate answers to whether a child had a bottle of formula milk whilst in hospital was computed and 84% (103/123) of mothers recalled this correctly.

The Kappa coefficient (See Figure 4.4 below) was computed to measure the agreement of the answer from 2001/2002 to 2012. The kappa coefficient for agreement of the answer from 10 years earlier is 0.67 (CI 0.54 – 0.80), which is considered substantial agreement.

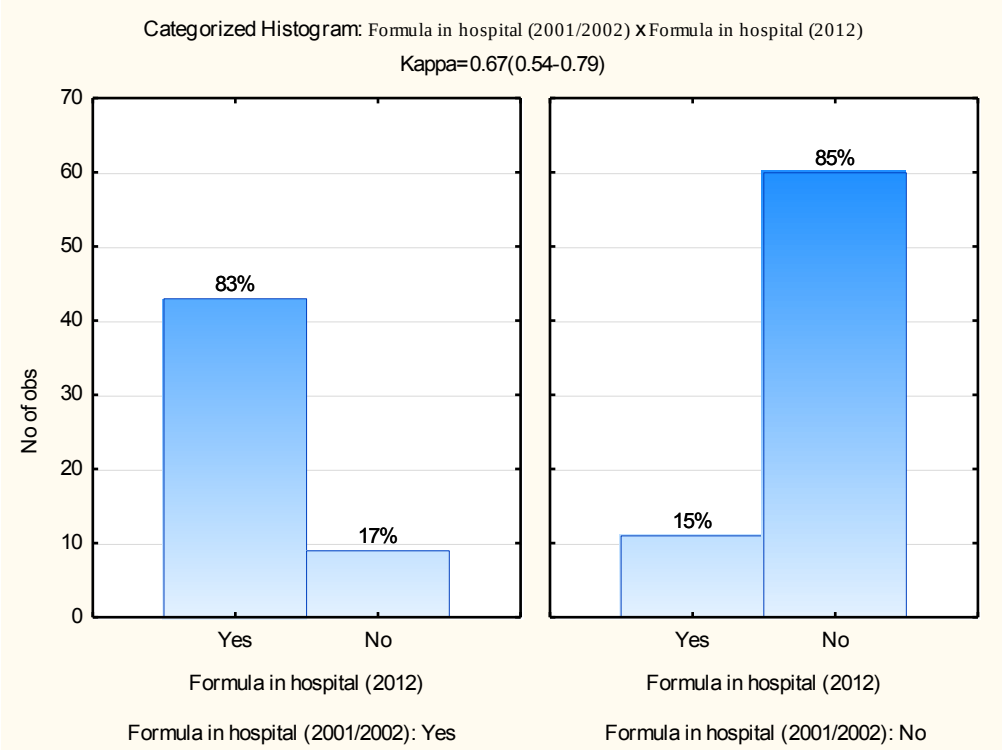

Figure 4.4 Formula milk in hospital: Measurement of agreement for answers in 2012 compared to 2001/2002.

The specificity and sensitivity of the reported answers were computed. The specificity of the answers over this time period of recall is 84.5%. Therefore, if formula milk was not given to their child in hospital in 2001/2002, 84.5% of mothers reported this in 2012. The sensitivity was computed to be 82.7%; therefore a very high percentage of mothers recalled that their children had formula milk in hospital if they did 10 years earlier.

The results of different statistical tests show that asking a mother if her child received a bottle of formula milk in hospital over a period of 10 years is not subject to significant recall bias.

4.2.2.2 Formula milk given at all during infancy

The FAIR study asked parents about their infant feeding practise (breast milk, formula milk or mixed) within each questionnaire up to the 12 month follow up. Mothers were asked in the 2012 recall questionnaire whether formula milk was given to their child at some point during their infancy, irrespective of when and how much.

Table 4.2 below shows the number of mothers who reported whether formula milk was given to their child at some point during their infancy in 2001/2002 and 2012, and the final column shows the number of matched answers and the percentage that were correct over this 10 year recall period. Ninety four per cent (116/124) of mothers recalled accurately in the 9/10 year recall questionnaire that their child had received formula milk at some stage of their infancy, irrespective of when and how much.

Table: 4.2 Numbers of reports and correct % of recall for the introduction of formula milk

Did you give your baby formula at any point (i.e. either as a top up drink or as the baby's main drink)			
Answer options	**2001/2002 (n)**	**2012 (n)**	**Correct answers % (n)**
Yes	n = 117	n = 114	89.5% (n = 111)
No	n = 8	n = 10	4% (n = 5)
Total answers	n = 125	n = 124	**93.6% (116/124)**

Table 4.3 below shows both the specificity and sensitivity of the reported answers. The specificity of the answers over this time period of recall is 95.7%. Therefore, if formula milk was not given to their child at all in 2001/2002, 95.7% of mothers reported this in 2012. Very few mothers therefore reported to have given formula milk to their child if they did not give formula milk 10 years earlier. The sensitivity was computed to be 62.5%; therefore 37.5% of mothers recalled that their child had some formula milk even if they did not 10 years earlier. There were a small number of mothers that did not give any formula milk to their child at any time, which explains the lower sensitivity as the ratio of 'incorrect' answers appears so much higher.

Table 4.3 Formula milk given at all: Specificity and sensitivity

Did you give your baby formula milk at any point (i.e. either as a top up drink or as the baby's main drink)				
	Formula at all YES (2012)	**Formula at all NO (2012)**	**Row totals**	
Formula at all YES (2001/2002)	111	5	116	95.7% (specificity)
Row %	95.69%	4.31%		
Formula at all NO (2001/2002)	3	5	8	62.5% (sensitivity)
Row %	37.50%	62.50%		
Totals	114	10	124	
	97.4%	50.0%		
	(Negative predictive value	(Positive predictive value)		

4.2.2.3 Age at which formula milk was first introduced

Mothers were asked at which age they first gave formula milk to their child and options were given from up to 1 month, each month to up to 9 months, and then after 12 months. Spearman correlation tests were used to test for agreement between the 2001/2002 and 2012 answer and computed that there was a substantial agreement in the reported age at which mothers introduced formula milk ($r = 0.63$, $p < 0.05$).

Figure 4.5 below shows the distribution of answers in 2001/2002 (Blue column) and 2012 (red column). This histogram shows that the majority of mothers introduced some formula milk into their baby's diet within 1 month of birth. The trend for both the reference answer in 2001/2002 and the reported answer in 2012 was for fewer mothers to introduce formula

milk as time went on. It also shows that some mothers recalled introducing formula milk after their child was a year old, although this was not the case 10 years earlier.

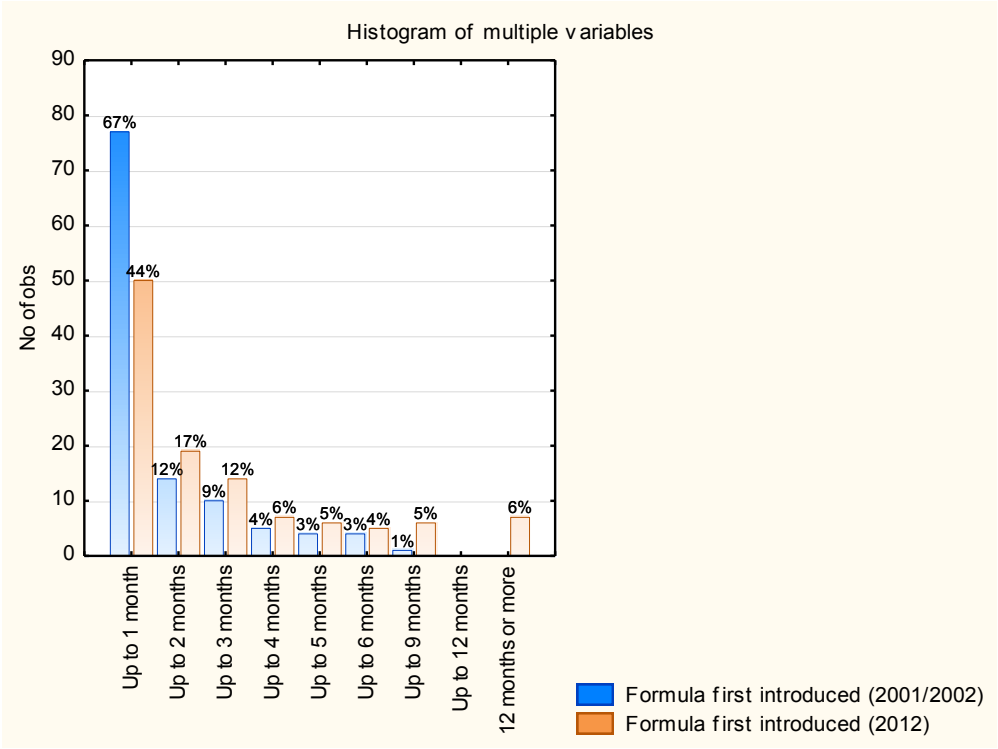

Figure 4.5 Distribution of recall for when formula milk was first introduced

4.2.2.4 Brand and variant of formula milk given

Mothers who had given formula milk to their baby were asked to recall which formula milk was given. Ninety four per cent (117/125) of mothers gave formula milk to their child at some point in their infancy. Only 17/125 (13.6%) mothers answered this question of which formula milk they gave, which in itself shows poor memory for this detail. Fifty nine percent (11/17) recalled the exact brand name over this 10 year period. Forty one per cent (7/17) of mothers recalled accurately the exact variant of the brand of formula milk. Neither of these results are statistically significant due to low numbers.

4.2.3 Recall with age of introduction of solid foods

4.2.3.1 Age of introduction of solid foods

Mothers were asked an open question (age categories were not given) about how old (weeks) their child was when they first gave solid foods. In the initial FAIR questionnaire at 3 months, parents were asked if they had given their baby any food or drinks other than breast milk/infant formula in the past 3 months, and they were asked to list these and give the age of their child in weeks for when each food/drink was introduced. The 6 month questionnaire for the FAIR study then asked parents when (child's age in weeks) they first introduced solid foods into their baby's diet.

Spearman correlation tests were used to compute the agreement between the ages reported in 2001/2002 and 2012. There was a slight agreement between the two periods of reporting, meaning that asking mothers to recall how old their child was when they first gave solid foods (in many cases this would be classified as weaning), is not reliable ($r = 0.16$).

Figure 4.6 below is a box and whisker plot which shows the distribution of answers from the mothers in 2001/2002 and 2012. The average age answered was 14.93 (SD = 2.48) weeks and 15.56 (SD = 4.57) weeks for 2001/2002 and 2012 respectively, showing that the answers in 2012 varied more than those in 2001/2002. More mothers recalled to have weaned earlier than they actually did.

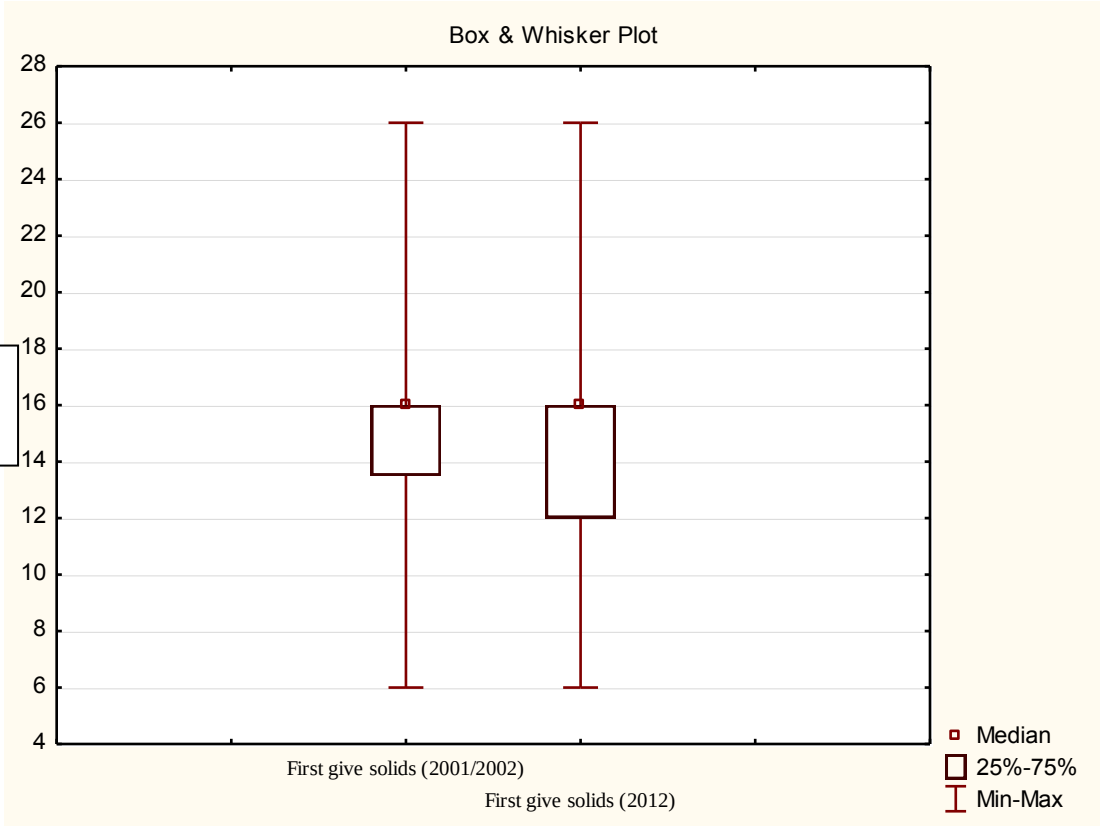

Figure 4.6 Recall of when solid foods were first introduced

4.2.3.2 Recall of age of introduction of solid foods within 4 weeks of the reference answer

Some previous studies looking at the accuracy of recall of infant feeding practices in weeks have also considered accuracy within a four week period. Calculations for this group of mothers for accuracy of recall within a 4 week period showed that 76% of mothers could accurately remember when they first gave solid foods to their child. Considering this test for accuracy is allowing a 4 week margin, it would not be particularly useful to ask mothers to recall when they first introduced solid foods over a 10 year recall period. Figure 4.7 below shows this result graphically in a histogram.

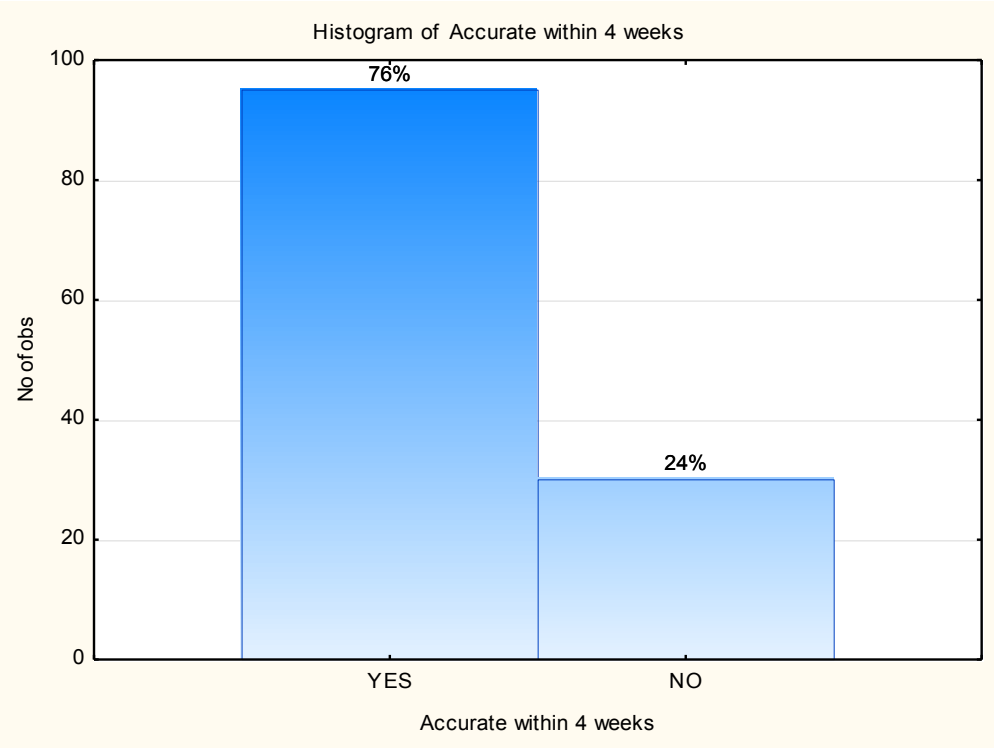

Figure 4.7 Accuracy of recall of weaning age within 4 weeks

4.2.3.3 Accuracy of recall of first 3 foods introduced

Mothers were asked an open question to determine which first 3 baby foods were introduced at weaning. With 125 mothers, there were therefore 375 opportunities (3 x 125) for mothers to recall a food/food group from 10 years earlier. A food was either categorised as a standalone food item or a food group, based on the categories set for the FAIR trial. Fifty three per cent (n = 66) of mothers were able to recall two or more of the foods/food groups accurately, leaving 47% who recalled one or no foods/food groups accurately. The distribution of the 178 accounts of accurate recall is shown below in table 4.4. Rice, non-citrus fruit/juice and vegetables (not potato or tomato) were the most common foods/food groups that were accurately recalled.

Table 4.4 Distribution of correct answers by food group

Which were the first 3 baby foods used?	
	Correct % (n)
Rice	55% (69)
Wheat	6.4% (8)
Oats	3.2% (4)
Potato	3.2% (4)
Vegetable (not potato or tomato)	34.4% (43)
Milk and dairy	2.4% (3)
Eggs	0% (0)
Poultry	0% (0)
Meat	0% (0)
Non-citrus fruit/juice	36% (45)
Citrus fruit/juice	1.6% (2)
Strawberry	0% (0)
Total number of correct answers	100% (178)

4.2.3.4. Commercial baby foods

Mothers were asked whether they gave their child commercial baby food during infancy in 2001/2002 and then again in 2012. Using the reference answer from 2001/2002, 94% of mothers (112/119) did give commercial baby food at some point. In 2012, 87% (101/116) of mothers recalled correctly whether they had given their child commercial baby foods 10 years earlier. This result shows that asking mothers if they have given commercial baby food to their child up to 10 years earlier results in a large majority of correct answers (> 85% correct answers accepted as accurate).

Table 4.4 below shows the number of mothers that recalled answers to this question in 2001/2002 and 2012 and the final column shows the number of matched answers and the percentage that were correct over this 10 year recall period.

Table 4.5 Numbers of reports and correct % of recall for the use of commercial baby food

Did you use commercial baby food?			
Answer options	**2001/2002 (n)**	**2012 (n)**	**Correct answers % (n)**
Yes	n = 112	n = 105	83.6% (n = 97)
No	n = 107	n = 17	3.45% (n = 4)
Total answers	n = 119	n = 122	**87% (101/116)**

Figure 4.8 below shows the distribution of answers in 2001/2002 and 2012. This figure does not show the number of matched answers and agreement of recall, but shows the total distribution of data and how the vast majority of mothers did provide commercial baby food to their child.

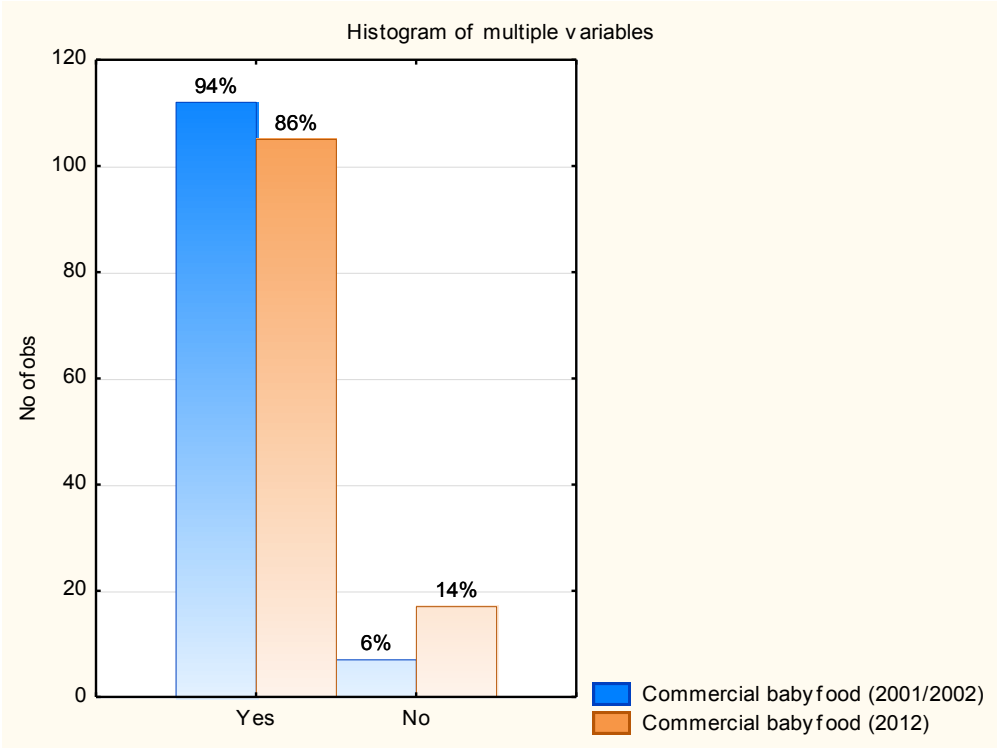

Figure 4.8 Commercial baby food: Distribution of answers in 2001/2002 and 2012

Both the specificity and sensitivity of the reported answers were computed. The specificity of the answers over this time period of recall is 88.2%. Therefore, if commercial baby food was not given to their child at all in 2001/2002, 88.2% of mothers reported this in 2012. The sensitivity was computed to be 66.7%; therefore 33.3% of mothers recalled that their child had some commercial baby food if they did not 10 years earlier. There were only a small number of mothers that did not give any commercial baby food to their child, which explains the lower sensitivity as the ratio of 'incorrect' answers appears so much higher.

4.2.4 Accuracy of recall of age of introduction of major food allergens

The age at which certain food allergens are introduced during infancy has shown to have an impact on the development of food allergies. Mothers were asked the age of their child when they first introduced some major food allergen groups into their diet. Each major food allergen group was listed with an option for mothers to select a categorical age range of introduction (< 3 months, < 6 months, < 9 months and > 9 months). Table 4.6 below shows the number and percentage of mothers that recalled correctly when they first introduced certain allergenic foods into their child's diet. Most foods were poorly recalled for, apart from peanuts which showed 86% accuracy. This results shows that asking mothers to recall when they first introduced peanuts or peanut containing foods into their child's diet is accurate over a 10 year period (If we accept > 85% as an accurate figure). All other allergenic food groups are not accurately recalled over a 10 year period.

Table 4.6 Number and percentage of correct answers for introduction of allergenic foods/food groups in 2001/2002 and 2012

At what age did you introduce the following foods into your child's diet?	
Allergenic food group options	**% accurate (n)**
Wheat containing foods (e.g. baby rusk, baby cereals, cereals, pasta, bread, cakes, biscuits)	44.8 (52/116)
Dairy foods (e.g. yoghurt, fromage frais, custard, ice cream, butter, margarine, cow's milk in food, cheese)	50.9 (59/116)
Fish	34.5 (30/87)
Whole egg	30.8 (28/91)
Soya	34.5 (10/29)
Tree nuts – almonds, brazil nuts, pecan nuts, hazel nuts, walnuts etc. (e.g. in chocolate, crunchy nut cornflakes, choc chip cookies, pesto sauce, vegetarian meals)	66 (51/77)
Peanuts (e.g. Bombay mix, peanut butter, peanut	85.7 (72/84)

The distribution of answers to the age of introduction of some of the major food allergen groups (wheat, dairy, fish, whole egg, soya, tree nut and peanuts) in 2001/2002 and 2012 are represented graphically below in histograms and box and whisker plots.

Figure 4.9 below shows that over a third of mothers (n = 39) recalled that they had introduced wheat containing foods within the first 3 months, which is a lot higher than the four per cent (n = 5) mothers that actually did introduce wheat within 3 months in 2001/2002.

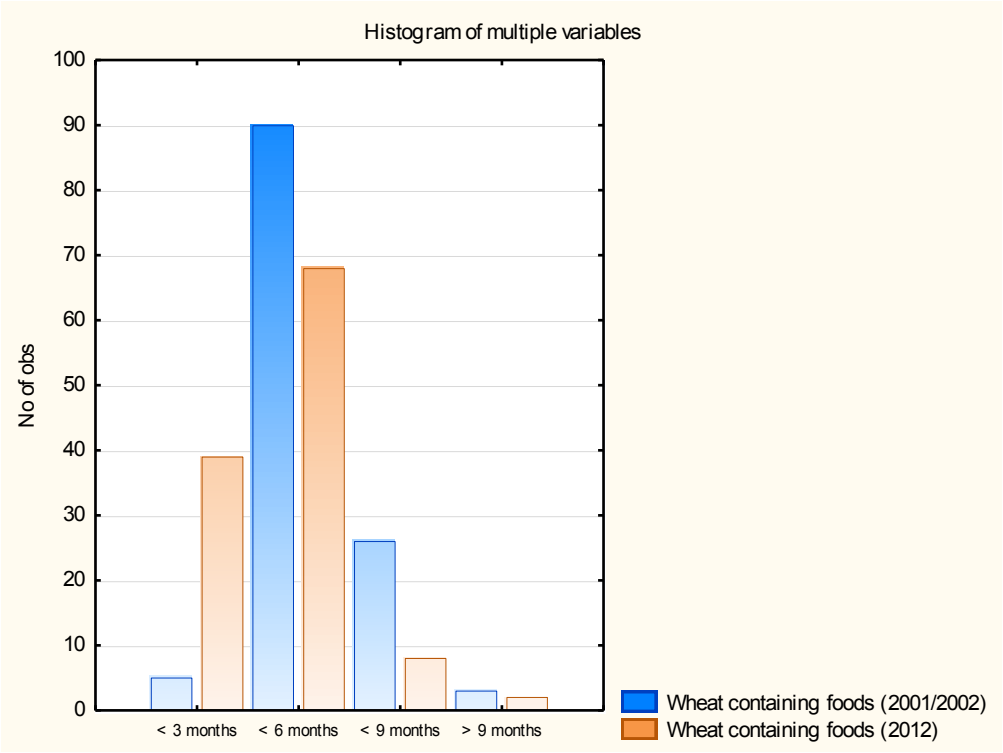

Figure 4.9: Age of introduction of wheat

Figure 4.10 below shows the distribution of mothers' answers given to when diary was first introduced into their child's diet in 2001/2002 and 2012. There is a large difference in the number of mothers (n = 36 versus n = 3) that recalled introducing dairy into their baby's diet within 3 months in 2001/2002 and 2012 respectively. Eighty three per cent (n = 104)) of mothers introduced dairy foods when their child was less than 6 months of age, yet only 55% (n = 64) recalled to have included dairy at this age.

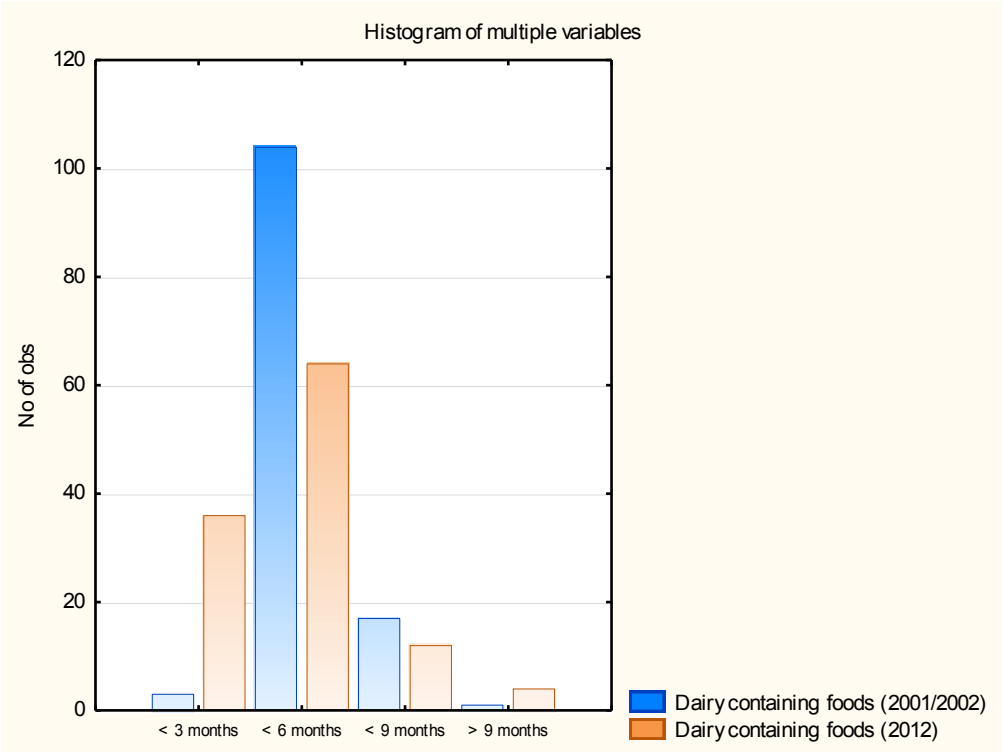

Figure 4.10 Age of introduction of dairy

The introduction of fish is represented in box and whisker plots below in Figure 4.11. There were some reports of mothers introducing fish into their children's diets at < 3 months, which was not the case at the time.

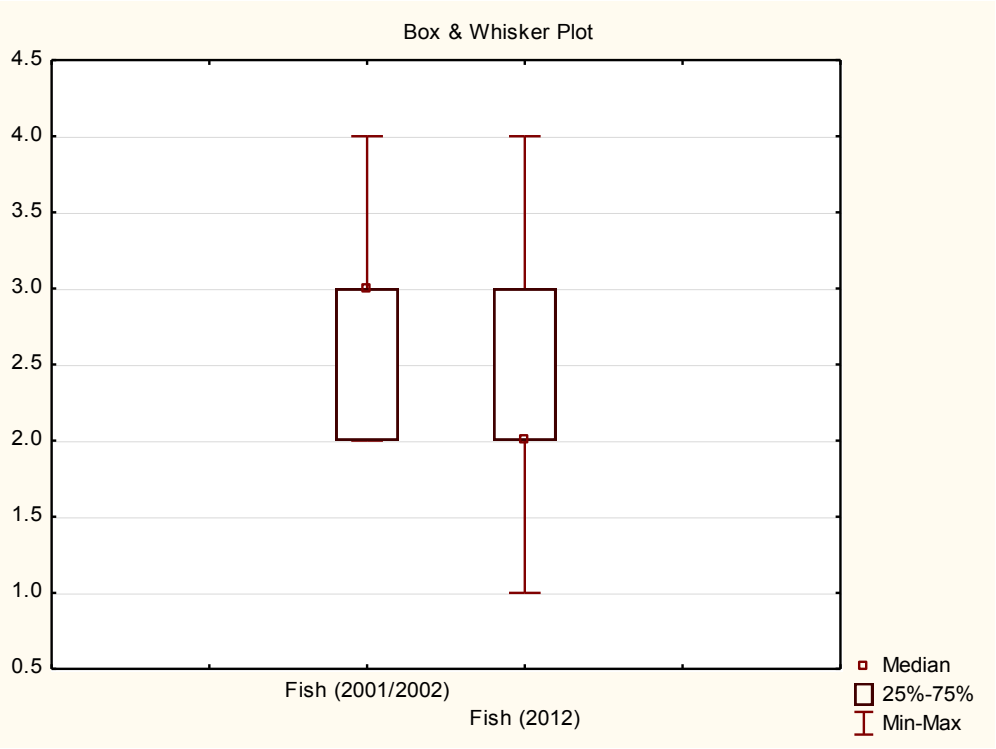

Figure 4.11 Accuracy of recall of introduction of fish

The box and whisker plot for recall of introduction of peanuts (Figure 4.12 below) shows that all mothers reported introducing this food group after 9 months of age, both in 2001/2002 and 2012.

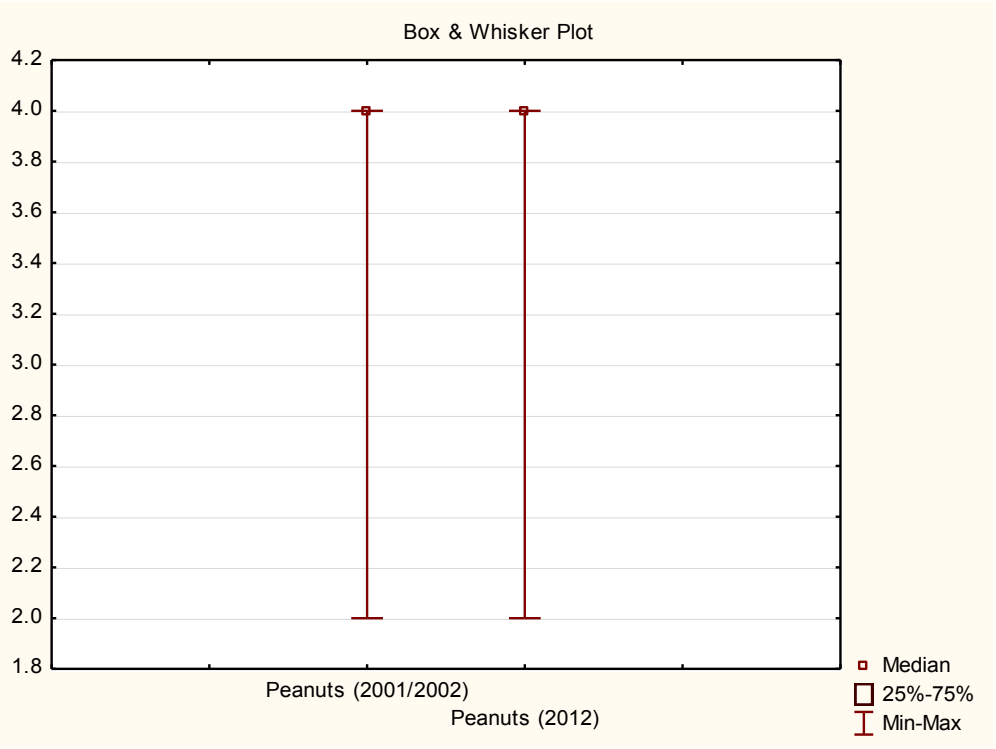

Figure 4.12 Accuracy of recall of introduction of peanuts

The distribution of answers to when soya was introduced both in 2001/2002 and 2012 is shown in Figure 4.13 below. It is noticeable that the majority of mothers recalled introducing soya in 2001/2002 when their child was more than 9 months of age. Only 39 mothers in total answered this question in 2012, which in itself suggests that mothers could not remember.

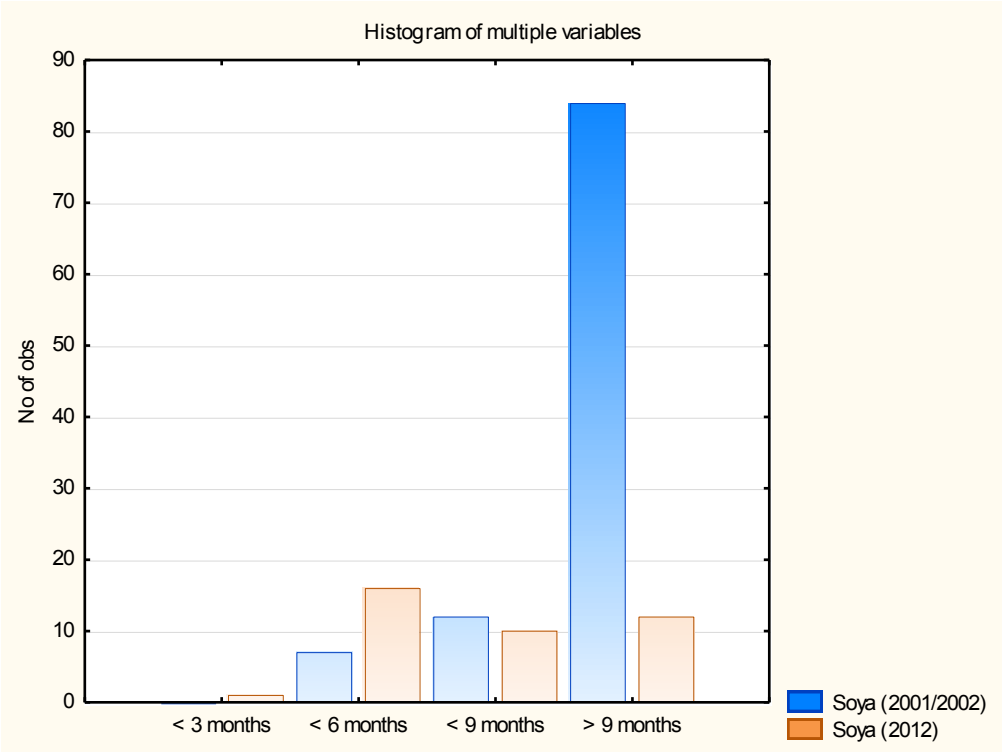

Figure 4.13 Age of introduction of soya

The distribution of recall for when mothers first introduced tree nuts into their child's diet is shown in Figure 4.14 below. Nearly all mothers (97%) had introduced tree nuts after 9 months (2001/2002 answers), whereas some mothers (n = 10) recalled in 2012 that they introduced them earlier.

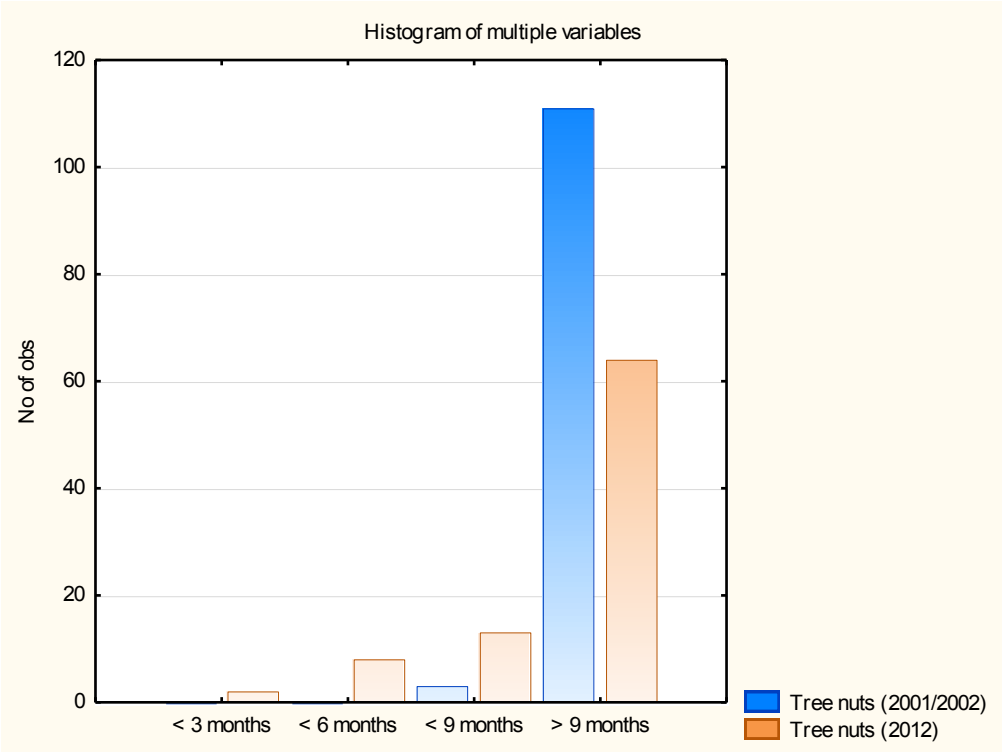

Figure 4.14 Age of introduction of tree nuts

The distribution of answers to when mothers introduced peanuts into their child's diet is represented graphically in Figure 4.15 below. The majority of mothers recalled both in 2001/2002 and 2012 that they introduced peanuts after their child was 9 months old. No mothers introduced peanuts before 6 months of age.

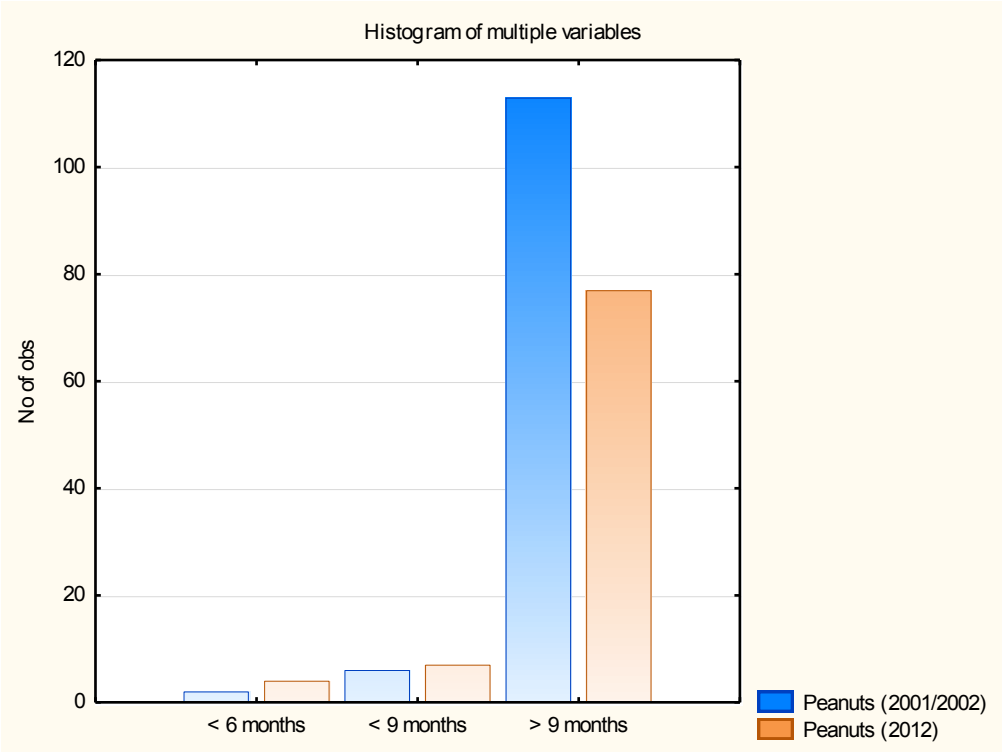

Figure 4.15 Age of introduction of peanuts

4.2.5 Accuracy of recall of food avoidance at 6 months

Mothers were asked if they were consciously avoiding any foods from their child's diet at 6 months of age. The Kappa coefficient was computed to measure the agreement from 2001/2002 to 2012 as it is generally thought to be a more robust measure than simple per cent agreement calculation since it takes into account the agreement occurring by chance. The kappa coefficient for agreement of the answer to whether a mother was avoiding food in her 6 month old child's diet 10 years earlier or not is 0.09 (CI -0.07 – 0.27), which is considered no agreement. This shows that asking mothers to recall up to 10 years later whether they were avoiding any foods in their child's diet when their child was 6 months is not at all accurate.

Table 4.7 below shows both the specificity and sensitivity of the reported answers, which reinforce the poor agreement between answers 10 years apart. The specificity of the answers from the mothers in 2012 is 54.5%. Nearly half of mothers who therefore reported 'No' to avoiding food items were incorrect. The sensitivity was computed to be 55.4%;

therefore just under half of mothers who reported that they did avoid food items 10 years earlier did not.

Table 4.7 Consciously avoiding foods at 6 months: Specificity and sensitivity

When your baby was 6 months old, were you consciously avoiding any food items from their diet?				
	Avoiding food items at 6 months NO (2012)	**Avoiding food items at 6 months YES (2012)**	**Row totals**	
Avoiding food items at 6 months NO (2001/2002)	24	20	44	**54.5% (specificity)**
Row %	54.55%	45.45%		
Avoiding food items at 6 months YES (2001/2002)	33	41	74	**55.4% (sensitivity)**
Row %	44.59%	55.41%		
Totals	57	61	118	
	42.1%	67.2%		
	(Negative predictive value	(Positive predictive value)		

From those mothers that were avoiding any foods, they were asked again which specific foods were avoided. Out of the seventy nine accounts of avoidance (could be > 1 per mother, as mothers could list more than one food item), 40.5 % (32/79) of the recalled food/food group matched the answers given 10 years earlier. Each parent had an opportunity to list up to 5 foods that they could have avoided from their child's diet when they were 6 months old. This result is reported here as the percentage accurate over the total number of accounts (i.e. one mother could list up to 5). Due to the poor agreement for

whether mothers were avoiding any foods from their child's diet at 6 months, no detail on what specific foods is significant.

4.2.6 Recall of peanut consumption during pregnancy

Mothers were asked whether they excluded peanuts during their pregnancy at 36 weeks, when their child was 2 years of age (FAIR) and with this study when their child was 10 years of age. Both the 2 year questionnaire from the FAIR study and this 10 year recall questionnaire allowed for parents to provide an answer of why they avoided peanuts. The option for 'never eat peanuts' was included in the 2012 recall questionnaire so that the group who were not consciously trying to avoid peanuts for any reason other than not liking them, were included. Answers from the question of peanut avoidance during pregnancy at the 2 year point included 'never eat peanuts', which allowed analyses against the 2012 answers. Due to how this question was asked at these three time points, the analysis on accuracy/agreement of recall could be assessed from the 36 weeks pregnant to the 2 year time period (Yes/No) and from the 2 year and 10 year time period (Yes/No/Never eat peanuts). No tests were carried out directly from the 36 weeks pregnant to the 10 year point as we would not be comparing like with like.

The Kappa coefficient was computed to measure the agreement from the 36 week pregnancy questionnaire in 2001/2002 and the 2 year questionnaire in 2003/2004. The answers recalled by mothers over this two year period were shown to be substantially agreeable (k = 0.64 CI 0.50 – 0.77), meaning that asking mothers whether they avoided peanuts during pregnancy when their child was two years of age was shown to be accurate.

The agreement between mother's answers in 2012 from 8 years earlier in 2003/2004 is k = 0.39, which is considered fair agreement, and therefore not high enough to be considered accurate. The 95% confidence interval for the Kappa coefficient is 0.25 – 0.53. Figure 4.16 below shows the percentage of answers given for each category, .i.e. No, Yes and Never eat peanuts. Below each graph is a legend which shows what the answer was in 2003/2004, which is considered the 'valid', reference answer, and the bars show the answers that

mothers provided at the 8/9 year follow up in 2012. Correct answers for no, yes and never eat were 63%, 69% and 47% respectively.

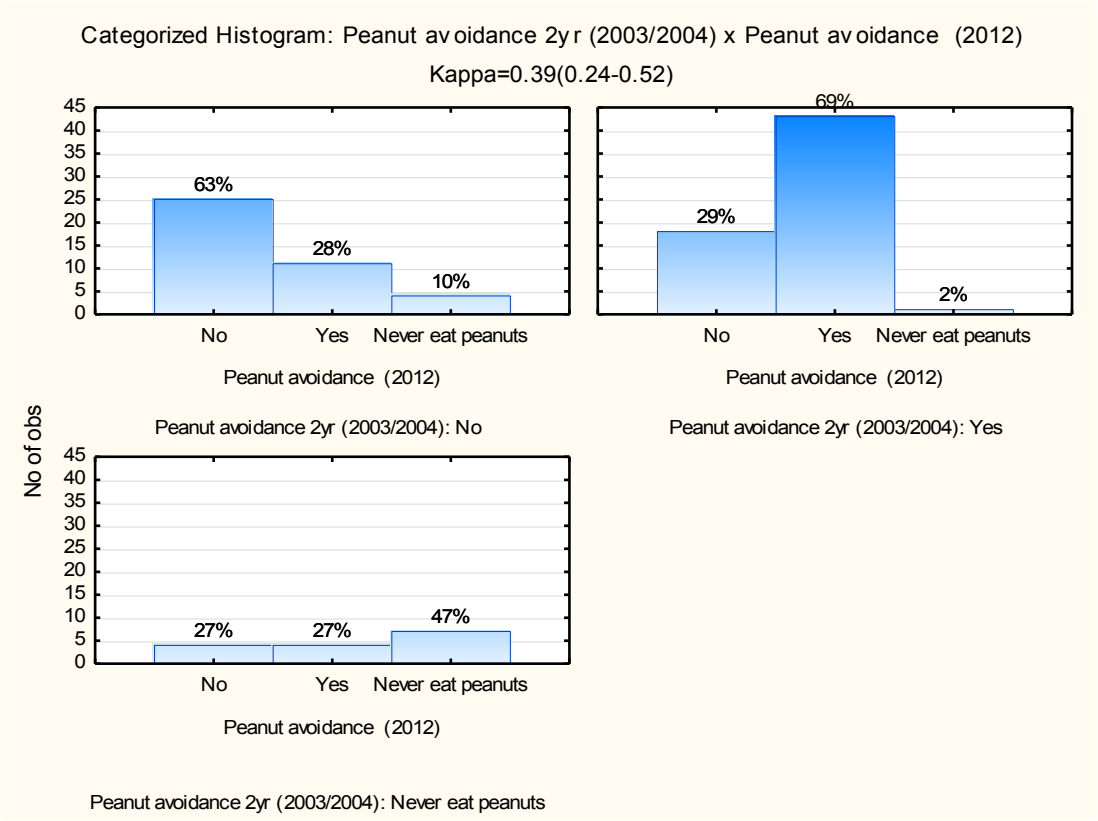

Figure 4.16 Avoidance of peanuts during pregnancy: Measurement of agreement for answers in 2012 compared to 2003/2004.

Mothers who avoided peanuts during their pregnancy were asked the reason why. This question was asked as an open question and all answers fell into two categories, either a known allergy in the family or because it was the recommendation at the time. The Kappa coefficient was computed to measure the agreement of the mother's answer from 2003/2004 to 2012. The kappa coefficient for agreement of the answer from 8 years earlier is k = 0.70, which is considered substantial agreement (95% CI 0.39 - 0.92).The question about why mothers avoided peanuts in their diet is therefore a reliable question over an 8 year period.

Figure 4.17 below shows the distribution of answers given by mothers both in 2003/2004 and 2012.

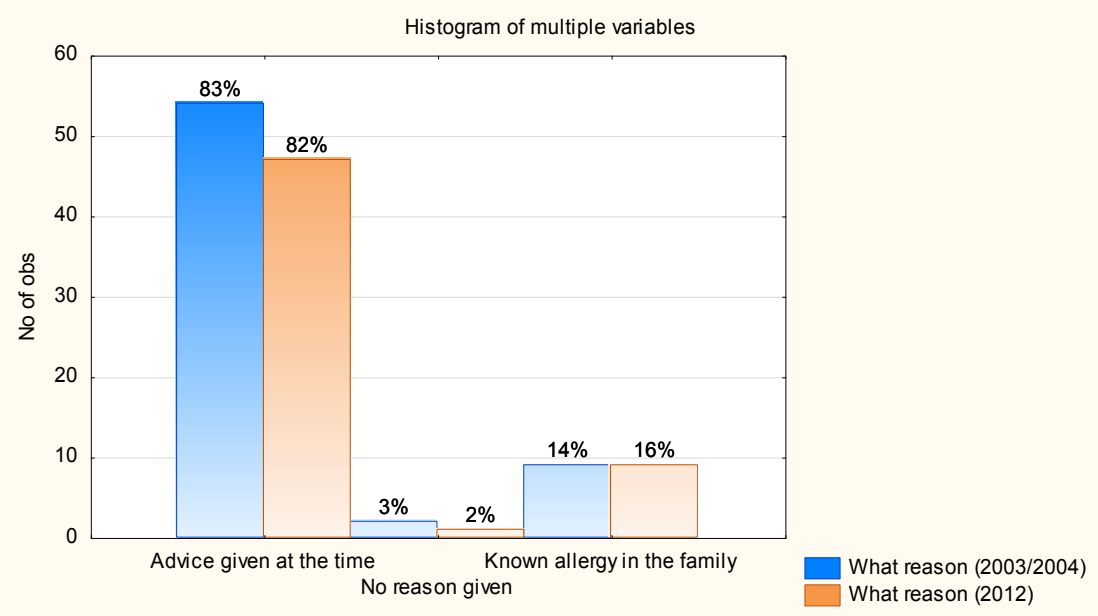

Figure 4.17 Reason for avoiding peanuts: Distribution of answers given in 2003/2004 and 2012

4.3 Potential factors that may have influenced accuracy of recall

Some studies that have previously looked at accuracy of recall over long periods of time have also looked at factors that may influence accuracy/lack of accuracy of recall. These have included the birth order of a child and level of education of the parent. In this recall study; birth order, family history of allergy and diagnosis of food allergy were factors that were investigated in order to determine any possible influence of these on accuracy of recall.

4.3.1 Birth order and accuracy of recall

Previous studies have discussed birth order as a factor that can influence recall of events in infancy.[24,25,32,33] The birth order of the study population was obtained from initial FAIR data captured in 2001/2002 and was reported as either 'first born' or '2nd and later'. Accuracy of

recall in relation to whether breast fed or not, duration of BF as well as when formula was first introduced were compared according to the birth order of the child.

4.3.1.1. Birth order and breast feeding at all

Kappa coefficient tests were computed to measure the agreement of the answers given by mothers of first born children as well as mothers of children born second or later.

There was a stronger agreement for recall of whether they breast fed or not for mothers of children who were born second or later compared to those for first born children (r = 0.85 versus r = 0.62 respectively). The agreement for both groups however was substantial. It is therefore reliable to ask mothers whether they breast fed 10 years after the event, however it is even more reliable to ask a mother of a child who was born second or later.

4.3.1.2 Birth order and duration of any breast feeding

There was substantial agreement for the reported duration of BF in all groups, irrespective of whether mothers were recalling for firstborn's or children born second or later. Agreement of answers over the 10 years showed slightly higher agreement for mothers of children born second or later compared to firstborns' (r = 0.87 versus r = 0.82 respectively).

4.3.1.3 Birth order and introduction of formula milk

Spearman correlation tests were used to measure the level of agreement between the answers from mothers of firstborns' and those of children born second or later. Mothers of children who were born second or later tended to have more reliable answers than those of first born children (r = 0.69 versus r = 0.58 respectively). According to guidelines from Landis *et al*[13], answers from mothers of second born or later are substantially agreeable, whereas recall from mothers of firstborn's are moderately agreeable.

Table 4.8 below shows the percentage of accurately recorded information for the 'firstborn', '2nd or later' and the total group. These results show that recall for a child born second or later are slightly more accurately than those recalled for a firstborn child.

Table 4.8 Percentage of accurate answers for birth order

Birth order and accuracy of recall						
	Firstborn % (n)	**r**	**2nd or later % (n)**	**r**	**All groups % (n)**	**r**
Breast fed at all	91.4% (53/58)	0.62	93.8% (61/65)	0.85	92.7% (114/123)	0.79
Breast fed in total (duration)	46.8% (22/47)	0.82	44.2% (19/43)	0.87	45.6% (41/90)	0.84
When formula was first introduced	46.2% (24/52)	0.58	53.5% (31/58)	0.69	50% (55/110)	0.63

*r = Correlation co-efficient

4.3.2 Family history of allergy and accuracy of recall

It is known that an immediate family history of a food allergy (parent or sibling) can lead to the development of a food allergy in a child. Therefore, it can be considered that if there is a known family history of a food allergy, that there is a potential impact on the emphasis that is placed on when this particular food item is introduced into the diet of other younger family members.

Eighty seven per cent (109/123) of this study population had a family history of allergy. All comparisons made therefore, between the accuracy of recall for mothers with a family history or not, are not significant because the numbers in the group without a family history of allergy are too small.

4.3.3 Food allergy diagnosis and accuracy of recall

There were an inadequate number of children with diagnosed food allergy in this study to make comparisons between the accuracy of recall of mothers of children with food allergy compared to those mothers of children without a food allergy.

4.4 Summary of Results

The results of this study show that the accuracy of maternal recall over a 10 year period varies considerably according to the specific aspect of infant feeding being recalled. Recall of answers related to breast feeding (breast fed at all, duration of EBF and BF), and formula feeding (formula in hospital, formula at all and age of introduction of formula) agree substantially over these two time points. The brand of formula given to a child is not well remembered. Whether commercial baby food was provided and the age of introduction of peanuts into a child's diet 10 years earlier is well recalled, however other aspects of introduction of solid foods is poorly recalled (age of introduction of solid foods, age of introduction of other allergenic foods and whether foods were avoided at 6 months of age). Whether mothers avoided peanuts during pregnancy is well recalled over a two year period after birth, however over an 8 year period it is not well recalled. In this study, accuracy of answers was better from mothers' of children born second or later. The influence of family history or food allergy diagnosis on the accuracy of recall would need a larger study population to be determined.

CHAPTER 5

DISCUSSION

CHAPTER 5 DISCUSSION

A cross-sectional, descriptive study with a retrospective analytical component was performed to assess the accuracy of information provided regarding infant feeding practices 9-10 years retrospectively. Data on breast feeding and infant feeding practices were collected prospectively from mothers in the FAIR[9] trial and this study tested the accuracy of recall over this period by asking some of the same questions 10 years later. The results of this study showed that mother's answers to questions related to breast and formula feeding over a 10 year period are accurate. Less accurate is recall relating to introduction of solid and allergenic foods and whether certain foods were avoided in a child's diet during weaning.

The results of this study and of other studies that investigated the reliability and validity of maternal recall of infant feeding data collected retrospectively will be discussed below. The potential impact these findings have on current evidence and future trials in the area of food allergy and other diseases are also discussed.

5.1 Demographic information and accuracy of recall

The study population are a group of mothers that are living on the Isle of Wight, UK. As the UK is a westernised country, it is likely that they are more sensitised to the concept of allergy in comparison for example to rural, third world communities. Accuracy of recall related to, for example, the consumption/avoidance of peanuts during pregnancy, should be interpreted with caution in vastly different communities.

The average age of the children when mothers completed the recall questionnaires was 10.5 years, which is therefore the recall period of this study. The length of the recall period has shown to have an impact on the accuracy of the results obtained.[24,25,28-33]

Just over half (54%) of the children that mothers recalled infant feeding practices for had an older sibling. There was substantial agreement for mothers recalling for all three questions (breast fed at all, duration of BF, and when formula milk was first introduced) with a child that was born second or later ($p < 0.05$). Reports 10 years later from mothers of firstborns

agreed substantially for whether they breast fed at all and for what duration, but there was only moderate agreement for when they first introduced formula milk. The results of this study show that there was better agreement of recall over a 10 year period for mothers recalling for whether they breast fed, how long they breast fed for and for when formula was first introduced and for a child that had an older sibling. Tienboon *et al*[32] grouped first- and second-born together, and investigated the accuracy of maternal recall against those with more siblings. This group found better agreement with questions related to breast feeding for mothers of first- and second-born. Another study[25] found no difference between the accuracy of answers over a period of up to 10 years when parity was investigated.

Results of the larger FAIR[9] study showed that a family history of allergy was associated with an increased likelihood to breast feed exclusively for any duration (eighty eight mothers with a family history versus thirteen who did not have a family history). Eighty seven per cent (n = 109) of the study population had at least one family member (mother, father or sibling) with a history of/or allergic disease. There are no studies that the principal investigator is aware of that have looked at the impact of family history of allergy on the accuracy of recall of dietary information. Due to the low numbers of subjects that did not have a family history of allergy in this study, it was not possible to draw any significant conclusions as to whether a family history of allergy has any impact on the accuracy of recall over a 10 year period. If there is a family member with a food allergy, one would expect that the family are more sensitised to food allergies. Recall related to food allergy could therefore be impacted differently to other populations (for e.g. if a child has a peanut allergy, a mother is more likely to have thought about when peanuts were first introduced into the child's diet).

There are discussions in the literature regarding case-control studies and the risk of recall bias entering due to the cases being more likely to have thought about and remembered past exposures owing to concern about their condition.[19] Cow's milk allergy often presents when a mother introduces formula milk into her child's diet as the 'allergenic load' of formula milk is higher than that of breast milk. An assumption could be made therefore that mothers of cow's milk allergic children are more likely to accurately recall when they first introduced formula milk into their child's diet compared to mothers of children who are not allergic to milk. The principal investigator is not aware of any studies that have looked at whether accuracy of recall of infant feeding practices is affected by a diagnosis of allergy in

the child the recall is based upon. Unfortunately, due to low numbers of food allergic children, no significant conclusions could be drawn from this study.

5.2 Recall regarding breast feeding questions

Results of this study showed that asking a mother whether she breast fed her child after 10 years results in accurate answers. Surprisingly though, results showed a sensitivity of 91%, therefore there were some mothers who breast fed that did not recall breast feeding. As the majority of mothers in the study breast fed for up to 1 month, it could be explained that some mothers didn't feel that the short duration of breast feeding justified a 'yes' answer. Other potential reasons for poor recall of breast feeding events could be, through speculation, factors such as post natal depression or severe tiredness over this period. If results of the comparative data showed that more mothers recalled to have breast fed than actually did, one could speculate that potential recall bias was introduced because mothers gave answers that they felt their health care professionals wanted to hear.

Studies that have looked at the accuracy of recall of breast feeding questions when children were 15 and 22 years old have found a significant correlation in answers given over this period[25,32]. This study therefore emphasises the accuracy of recall over long periods. Studies that investigate the benefits of breast feeding on other health outcomes can therefore rely on mothers' recalling after substantially long periods of time.

The need for accurate breast feeding data is great in HIV transmission research. The WHO rely heavily on consistent and accurate documentation of early infant feeding practices in order to make infant feeding recommendations to address the HIV pandemic. There is evidence that EBF presents a significantly lower risk than mixed feeding, and minimal additional risk than exclusive replacement feeding in mother to child transfer (MTCT).[28]The addition of any water alongside breast milk ends the period of EBF according to the WHO definition. If the importance of the addition of water is not clearly communicated to mothers, they may over report the duration of EBF. Over reporting of breast feeding duration has been found in studies[29, 30]. Valid data is required in order to attribute postnatal transmission to a particular feeding pattern (for example, EBF).

A study[114] looking at the effect of breast feeding on children's educational test scores relied on mothers to recall breast feeding initiation and duration over a 9 year period. The authors reported from results that any amount of breastfeeding was associated with significantly higher test scores than no exposure, but that the evidence of the dose-response relationship was weak. Based on the substantial agreement for breast feeding initiation that the present study found, and results of some other studies mentioned above, the authors from this study investigating educational test scores could be quite confident that recall over the nine year period is accurate.

The influence of the duration of breast feeding has been investigated for many health outcomes such adult intelligence[115, 116], obesity[117, 118], diabetes risk[119], serum cholesterol[120], and blood pressure[121]. Breast feeding duration has also been investigated for maternal health, for example risk of breast[122]/ovarian cancers[123] as well as for osteoporosis[124]. Most of these infant and maternal diseases present years and often decades later, therefore breast feeding history often has to be assessed by maternal recall over long periods. It is therefore important to assess the validity of studies investigating the accuracy of recall over long periods. If the measures of association are well understood, health policies and recommendations can be developed for the benefit of communities.

The results of this recall study found that it is highly reliable to ask a mother to recall over 10 years how long she breast fed for and whether exclusively or not. Other studies in the literature had mixed findings. Some long term recall studies found strong accuracy in recall[224,25], yet some studies with shorter recall did not find this question as reliable[28-30]. Interestingly, the latter acknowledged some validation issues, for e.g. Agampodi[29] where recall for weaning was assessed by asking mothers when they stopped EBF. EBF could be stopped when introducing formula milk, which is not the introduction of solid foods

It has been discussed previously that there are a number of factors that can affect the accuracy of reported answers from mothers regarding the duration of breast feeding and EBF.

How a question is posed can impact the validity of the answer it is trying to seek. The definition of EBF would need to be explained clearly at all assessment opportunities, and most importantly be consistent between the two assessment periods, before recall can be

assessed accurately. Exclusive breast feeding was defined the same in both the FAIR study questionnaire and the recall questionnaire. As the FAIR study is focused on the epidemiology of food allergy, the definition of EBF was not strictly the WHO definition as water was not considered. The question of the duration of EBF for purpose of the FAIR study was therefore valid for the intention to understand when the child could have been exposed to other potential allergens. A key learning from Gillespie *et al*[30] is that the same measures need to be used at the different time points of asking the question when assessing recall, i.e. if you ask a mother how long she breast fed for in weeks the initial time, it would only be valid to ask mothers to report in weeks in the follow up. Results in their study showed significant over-reporting, which is believed to be attributed to, if only partly, the 'rounding up' of answers by parents.

The effects of breast feeding duration on teenage (17 year old) plasma lipid concentrations were investigated in 1984[22]. Results showed an inverse relationship of cholesterol with duration of breastfeeding in girls and no consistent finding in boys. Mothers were interviewed and asked about their breast feeding duration 20 - 22 years after their child was born. This data was compared to child health clinic charts. The study also determined the validity of reports over this period and found that reports were well correlated over this lengthy period (r = 0.82).

5.3 Recall regarding infant formula feeding questions

Eighty four per cent (n = 103) of mothers in this present study recalled accurately about whether their child received a bottle of milk formula within the first 1 - 2 days of birth. The level of agreement between the answers over this period was substantial (r = 0.67 CI 0.54 – 0.80). Previous interventional studies looking at supplementary feeding and the risk of cow's milk allergy found that infants exposed to cow's formula in hospital immediately after birth have a higher risk of developing CMA than those in the other supplement groups (pasteurised human milk, whey hydrolysate formula and exclusive breast feeding)[81]. This means that larger trials with a retrospective component of a significant period (up to 10 years recall) can investigate if the introduction of cow's milk formula during a child's first 1-2

days of life has an impact on the potential development of CMA, without a concern about recall bias being a major flaw.

This present study found that 94% of mothers recalled accurately whether they gave any formula milk to their child 10 years before (irrespective if just in hospital or not). The sensitivity was 95.7%, and the specificity was 62.5%. There were so few mothers that did not provide some amount of formula milk, that this affected the specificity and resulted in a kappa coefficient of a moderate agreement (k = 0.52) due to such low numbers not giving formula milk. Our results therefore showed that it is highly reliable to ask a mother whether she gave formula milk to her child 10 years earlier.

The age at which formula feeding is introduced into an infant's diet can determine the duration of EBF as well as when a higher allergenic load is introduced. The impact of this time on for example HIV and MTCT as well as on the development of potential cow's milk allergy have been discussed previously.

Kark *et al*[25] found a poor correlation between answers to the question of when non-breast milk was first introduced over a 20 - 22 year recall period. Another older study[31] over a recall period of 1 - 10 years measured accuracy based on 'percentage accurate' and found that 58% and 75% of mothers recalled accurately the introduction of non-breast milk within 1 and 2 months respectively. The 'percentage accurate' was calculated by matching the answers of recall to the answers of the original valid answer and working out what percentage of these were accurate. Although a small amount of 'percentage accurate' calculations were computed for this recall study, most results were computed for level of agreement rather than 'percentage accurate', and we did not look at 'percentage accurate' outside of the exact month of the initial answer. The results of this recall study found a substantial agreement in the reported age at which mothers introduced formula milk. This is not surprising based on the fact that there was accurate reporting of breast feeding questions.

Very few studies investigated the type of formula milk mothers gave to their child, but one study found that 73% (n = 58) of mothers recalled this question accurately over up to 10 years later[31]. This present study showed, due to lack of answers provided, that mothers do not remember this detail 10 years after the event.

5.4 Recall regarding introduction of solid and allergenic foods

A big question in the allergy field and general population is "When should we wean and introduce certain allergenic foods?" Advice for parents/carers has changed over time as research in this area has been conflicting. The EAACI Taskforce on Prevention draft guidelines has assigned this topic of the effect of timing of introduction of different food allergens as a priority one for future research.

Other studies that have looked into the accuracy of recall of the introduction of certain foods in an infant's diet have found poor accuracy rates.[24, 25, 30] These studies investigated recall of periods from 1 – 22 years.

One study[30] acknowledged that they used a poorly constructed question, "When did you stop breast feeding" as the measurement for duration of breast feeding and time point when weaning commenced. This question has poor face validity and the answer to this will not accurately determine when weaning commenced. This is a good example of the importance of constructing a question appropriately to ensure that it extracts the answer it is intending to.

Mothers in this recall study were asked a few questions related to the introduction of solid foods. They were asked when they first gave solid foods, what first 3 foods they introduced, whether they gave their child commercial baby foods and when they introduced various allergenic foods into their infants' diets.

The age at which solid foods were introduced into their infant's diets was weakly recorded (moderate correlation) by the mothers. There was a tendency for mothers to report that they weaned earlier than they did a decade earlier, although there were also some mothers that reported to wean much later too. Accuracy of recall improved when calculations were made to within a '4 week period' of the previous FAIR answer. One study[30] that looked specifically at the accuracy of recall of age of weaning found that mothers overestimated the age of weaning significantly over a 1 - 3.5 year period.

Gustafsson *et al*[105] studied the impact of age of weaning and the age of introduction of certain food allergens on the risk of the development of sensitisation and clinical allergy.

Results of this study relied on a recall period of up to 3 years. Based on the studies reviewed and the results of this study, the outcomes should be interpreted with caution.

Infants can be exposed to certain allergens, unbeknown to the parent, by consuming commercial baby foods. Ninety four per cent of mothers in this study gave commercial baby food to their infant at some point. Eighty seven per cent of these mothers recorded this correctly. Asking mothers this question after a 10 year period has not been shown to be subject to recall bias. Further detail regarding the variant of commercial baby food was not investigated in this study.

Mothers were asked when they introduced wheat, dairy, fish, whole egg, soya, tree nut and peanut containing foods into their child's diet. The timing of the introduction of whole egg, fish and soya was particularly poorly recalled for (31%, 35% and 35% accurate respectively). Only 29/125 mothers recalled when they introduced soya into their child's diet, which in itself shows that their memory of this event was poor. Wheat containing foods, dairy and tree nuts were not accurately recalled for at 45%, 51% and 66% accurate answers. A third of mothers (n = 36) thought that had given wheat/wheat containing foods within the first 3 months, whereas in reality, only three mothers had. Ninety seven per cent (n = 112) of mothers recalled that they introduced tree nuts after their child was 9 months of age. This suggests, in comparison to reporting earlier introduction of other allergens, that mothers may have been avoiding introducing tree nuts specifically. Peanuts were the only allergenic food/food group accurately recalled for, where 86% (n = 72). The majority of mothers also reported to have introduced peanuts after 9 months of age, again showing that mothers avoided introducing peanuts in the early stages of weaning.

In Westernised countries like the UK, a lot of emphasis of allergy prevention is focussed on peanut allergy. The COT report[64], which was commissioned by the Food Standards Agency in the UK, clearly highlighted peanuts as the allergen to be avoided at the time. Mothers residing in the UK therefore are more likely to be sensitised to the concept of peanut allergy, and results from maternal recall cannot be extrapolated to communities that are vastly different, e.g. rural, third world countries.This may also explain the poor recall for other food allergens. Two studies[54, 104] that investigated the relationship between the timing of the introduction of peanuts and the development of peanut allergy relied on mothers to recall

details up to 2 and 3 years later. Results of this recall study showed accuracy of maternal recall of when peanuts were first introduced into their child's diet over an assessment period of 10 years.

5.4.1 Accuracy of recall of foods avoided at 6 months

WHO recommend weaning to commence at six months. Historic advice has been to delay weaning of certain allergenic foods until later in infancy and childhood to prevent the development of any food allergy. It is therefore interesting to assess whether mothers accurately remember whether any food items were avoided, and specifically which ones. There was a very poor agreement for answers from mothers as to whether any foods were avoided when their child was 6 months old ($r = 0.09$). There are no significant outcomes when investigating further detail around which foods due to this and the low number of answers to this question. The author is not aware of any other study that has looked at recall of avoided foods.

5.5 Recall of consumption of peanuts during pregnancy

Maternal allergens cross the placenta from a mother to her child during pregnancy[59], which is why maternal diet during pregnancy is of great interest in the field of allergy. Possible sensitisation of food allergens during pregnancy is particularly relevant to peanut allergy as many cases of allergic reactions are on the severe end of the spectrum and often occur following first known exposure to peanut products.

Results of a study that investigated the exposure of peanuts during pregnancy and the prevalence of peanut allergy[48] contributed to the development of national guidelines for pregnant mothers of high risk infants to avoid peanuts during their pregnancy[64]. This study relied on mothers to report whether they consumed peanuts during pregnancy when their children were up to 18 years of age.

Further studies by Dean *et al*[66] and Hourihane *et al*[65] were commissioned by the Food Standards Agency (FSA) in order to investigate whether the guidance on peanuts avoidance was being followed by the target group and whether it was having an impact on the prevalence of peanut allergy in the UK. Hourihane *et al*[65] found that there was no reduction in the prevalence of peanut allergy and only 3.8% of the mothers interviewed had followed the advice of stopping the consumption of peanuts during pregnancy. This study relied on mothers to recall from 5 - 6 years earlier whether they avoided peanuts or not.

Evidence that contributed to the development of the national guidelines as well as evidence to review impact of them therefore both relied on periods of extended recall (5/6 year and 18 years respectively). It is therefore interesting to look at the results of this recall study, which is the only known study that looked at the accuracy of maternal recall of peanut avoidance in pregnancy.

In the FAIR study, mothers were asked at 36 weeks pregnant and when their child was 2 years of age whether they avoided peanuts during pregnancy. Over the two year recall period, mother's answers to whether they avoided peanuts during pregnancy were accurate. This is interesting and useful data for researchers in the field of food allergy, where there is often reliance on such retrospective data. According to this study, trials looking at the association between maternal consumption of peanuts and the development of peanut allergy can rely on mother's recall up to 2 years post pregnancy.

Recall of maternal peanut consumption over a period of 8 years was shown to be subject to recall bias. There is a limitation to this result however, as the valid answer used for comparison of recall was when the mothers' child was 2 years of age. Although results showed that answers up to 2 years are accurate, the level of agreement ($r = 0.70$) was substantial but not perfect. The 'valid' answer that the 8-year recall answer is assessed against is therefore not 100% accurate.

There are mothers that do not eat peanuts when they are pregnant purely for the reason that they don't like them. These mothers therefore avoid peanuts, but not because they are concerned about the potential development of peanut allergy in their child. This point is important when we consider that the FSA in the UK previously commissioned investigations to look into whether government advice on peanut avoidance had been followed. The

results of this present study assessing accuracy of recall found that it is reliable to ask those mothers that did not eat peanuts during pregnancy why this was the case. All answers fell into two categories, either because it was the advice given to them at the time or because there was a family history of peanut allergy.

Final conclusions of this study and recommendations are discussed in Chapter 6.

CHAPTER 6

CONCLUSION AND RECOMMENDATIONS

CHAPTER 6 CONCLUSION AND RECOMMENDATION:

6.1 Conclusion

The study gathered data from 125 mothers who answered questions related to infant feeding practices that were asked 10 years earlier. Questions were asked about peanut avoidance during pregnancy, breast feeding, formula feeding, and the introduction of solid and allergenic foods. Levels of agreement between these answers were computed in order to assess whether maternal recall over this period is accurate and therefore void of significant recall bias.

The study concludes that the accuracy of recall for infant feeding practices over a 10-year period is dependent on the specific question that is asked.

Previous studies that have investigated the effect of breast feeding on other health outcomes and relied on a lengthy period of recall (up to 10 years) can be confident that any initiation of breast feeding is accurately recalled .The duration of breast feeding in the present study was accurately recalled, but this outcome is not consistent across all studies.

The use of an accurate and consistent definition for EBF is of paramount importance when drawing any conclusions from studies that rely on maternal recall for EBF. Many studies that have aimed to validate accuracy of recall for the duration of EBF have implemented weak methodology through the use of inaccurate and inconsistent definitions.

Just over 40 per cent of the children in this study received some formula milk soon after birth whilst in hospital and the large majority of mothers remembered this. Based on results from this recall study, future studies in the field of food allergy can rely on maternal recall for a period up to 10 years to investigate the impact of the consumption of formula during the first few days of life.

Recall for weaning age has shown to be consistently inaccurate, particularly when relying on a recall period of more than 3 years. Inaccurate definitions used to determine weaning age are shown in the literature, leading to invalid results and misleading classifications for exposure.

Peanut allergy is of immense interest in the field of allergy, which is why the principal investigator included the assessment of recall for dietary practices related to peanuts. Previous studies relied on maternal recall of when peanuts were introduced into their child's diet up to 18 years earlier. The results of this study showed that it is reliable to ask a mother when she first introduced peanuts 10 years earlier. The majority of studies that have investigated the impact of late verse early introduction of peanuts have relied on maternal recall over 3 - 5 years, therefore the results of those studies should be valid with regard to recall accuracy/insignificant recall bias.

This recall study and others discussed found that asking mothers to recall on when they introduced any other food allergens/foods into their child's diets is not accurate. We are waiting for results from prospective trials on the early versus late introduction of food allergens, which will give us the answers we need to make recommendations to parents to prevent the development of food allergies.

Current advice for pregnant mothers is not to avoid any food allergens in their diet unless they have a food allergy themselves. This advice has changed, as previously pregnant women who had a family history of allergy were recommended to avoid peanuts. The advice to avoid peanuts during pregnancy was based on research, including an investigation that relied on mothers to recall if they consumed peanuts during pregnancy when their children were up to 18 years old. Based on this present study, where answers after a recall period of 8 years was not accurate, a 18 year recall period would be subject to recall bias.

Asking mothers whether they avoided peanuts during pregnancy after a period of 2 years has been shown to be accurately recalled for and if mothers did avoid peanuts during pregnancy it is also shown to be free from significant recall bias to ask them why after a period of 8 years.

Recall on breast and formula feeding for children who were born second or later was more accurate than recall for firstborns. From the evidence available, it is difficult to say whether parity definitely affects accuracy of recall over a period of time as there have been mixed results. The results of studies looking at parity have also not all used the same categories, for example some studies separate firstborn from second and older and others have grouped firstborn and second born and compared accuracy of recall against that for older children. It

was not possible to assess whether a family history of food allergy or a clinical allergy in the child had any impact on the accuracy of maternal recall.

As this study population are based in the UK, which is a Westernised country that is likely to be more sensitised to the concept of food allergy than for example a rural, third world country, the results cannot automatically be extrapolated to vastly different communities.

Most research in the field of food allergy would be reliant on a period of maternal recall shorter than 10 years. It has been discussed however that previous research has relied on maternal recall of up to 18 years. The results of this study support with the interpretation of previous research that has relied on lengthy recall periods, and helps inform the planning of future research.

6.2 Recommendations

In order for future research designs to provide quality information on which to base national and international guidance, information from the study can be applied. From the results of this study and the review of the literature; recommendations are discussed below.

1. For future trials looking at the accuracy of recall or interpreting recall with breast feeding practices, it is recommended that definitions for EBF in particular are valid and consistent across the two time points where data is collected. Many studies in the literature have not validated their questions and/or have not used the same question at the latter recall point. This practise leads to results that are not valid, and interpretation of data that is potentially misleading.
2. Units of measurement, for example weeks or months, should be the same at both data collection points. This practise can lead to over or underreporting and is not truly validating whether mothers can recall certain detail over a period. When assessing accuracy of recall, measures should be accurately aligned.
3. If researchers want to investigate the impact of ANY breast feeding on health outcomes, and are relying on maternal recall, the principal researcher recommends the researchers select a ‘minimum duration’ i.e. 1 week. This study found that some

mothers said that they did not breast feed when they had reported to breast feed 10 years earlier, and therefore may not have considered a small amount of breast feeding as sufficient to justify saying that they did.

4. In this study 40 per cent of children received some formula milk in hospital within the first days after birth. Future research in infant feeding practices and relation to food allergy, HIV and baby friendly initiatives should consider this point in their planning.
5. Large epidemiological studies could ask mothers retrospectively whether formula milk was provided to their child in the first few days of life to understand large scale impact of the early exposure of CM formula and the potential impact on the development of CMA
6. To investigate when weaning commenced, it is important that the accurate definition of weaning is clearly communicated. Stopping EBF is not a definition of weaning as a mother could transition from EBF onto a hydrolysed formula and this would not be defined as when weaning commenced.
7. To determine whether a family history of allergy or a food allergy diagnosis has an impact on the accuracy of recall over a specific time frame, future researchers need to recruit a larger population size for statistical significance.

6.3 Limitations of Study

This study search comprised of studies published in the English language only, therefore any data published in a different language was not considered in this study.

Mothers were asked to recall previous infant feeding practises from 9-10 years earlier. Much of the research in food allergy relies on maternal recall over a shorter period, i.e. 3 - 5 years. Where poor accuracy of specific questions was shown in this recall study, this can not be interpreted for a shorter recall period. Accuracy of recall over the very short term (24 hour, 7 day diary) was outside of the scope of this present study.

Although the population on the Isle of Wight is reflective of the population in the South of England, the results of this study need to be interpreted with caution in populations that are dissimilar.

6.4 Further areas for research

Some prospective research in the field of allergy is currently waiting to be published and this will hopefully provide recommendations as to whether early or delayed introduction of allergenic foods protects against the development of a specific food allergy.

It would be interesting to investigate the accuracy of recall of these exact infant feeding questions after a period of 3 - 5 years.

CHAPTER 7

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CHAPTER 8

APPENDICES

Appendix 8A

Please complete this form when you are 36 WEEKS PREGNANT by ticking the appropriate boxes and send back to the David Hide Asthma and Allergy Centre in the enclosed pre-paid envelope. Please answer every question. If you have any queries, please phone the Dietitian: Carina Venter on 534193

Name & Address	Date questionnaire completed	/ /
Hospital Number		
Date of Birth		

Tel No: (Home)	Other contact:
(Work)	
(Mobile)	

1. How are you planning to feed your baby?

Breast[1]		Bottle[2]		Undecided[3]		Both[4]	

2. Please tick all of the following statements that are applicable to you:

I am following a normal diet	Yes[1]		No[2]	
I am following a vegetarian diet	Yes[1]		No[2]	
I am following a vegan diet	Yes[1]		No[2]	
I am excluding raw eggs, unpasteurised soft cheese, liver etc. due to my pregnancy	Yes[1]		No[2]	
I am excluding peanuts due to my pregnancy	Yes[1]		No[2]	
I am following a special diet due to medical reasons (please state medical condition)	Yes[1]		No[2]	
I am excluding certain foods due to personal choice (please list foods)	Yes[1]		No[2]	

3. Have you taken any medication during pregnancy e.g. antibiotics, aspirin, paracetamol etc.
IF 'NO' GO TO Q. 5

Yes[1]		No[2]	

4. If yes, what?

5. Have you taken any of the following supplements during this pregnancy?

	Yes[1]	No[2]	
Multivitamin			
Multi mineral			
Calcium			
Iron			
Folic acid			
Other			What?

Appendix 8A

6. On average, how often have you eaten these foods during pregnancy?

	Never[1]	Rarely (1-2 per month or less)[2]	Occasionally (1-3 per week)[3]	4 times per week or more[4]	Uncertain[5]
Milk and milk products (e.g. custard, yoghurt, ice cream, chocolate, butter, margarines, cheese – pizza, cheese sauce, lasagne, cheezy biscuits)					
Egg (e.g. omelettes, flans, meringues, cakes, cookies, batter mixes, egg pasta, quorn, mayonnaise, quiches)					
Wheat (e.g. bread, cereals, pasta, pizza, cakes, pies, pastry)					
White fish (e.g. tuna, fish cakes, battered fish,fish fingers)					
Shellfish (e.g. crab, prawns, shrimps, lobster, crayfish)					
Oily fish (e.g. mackerel, salmon, sardines, pilchards, herring, kipper, white bait, trout, crab, FRESH tuna)					
Peanuts (e.g. Bombay mix, peanut butter, peanut brittle, peanut cookies, sate, some vegetarian meals)					
Tree nuts - almonds, brazil nuts, pecan nuts, hazel nuts, walnuts etc. (e.g. in chocolate, crunchy nut cornflakes, stuffing mix, sweet mincemeat, choc chip cookies, almond slice, marzipan, pesto sauce. vegetarian meals, Greek desserts like bakklava)					
Seeds e.g. sesame, poppy, sunflower (on bread rolls, tahini paste)					
Citrus fruits (eg orange, tangerine, grapefruit, lemon, lime)					

7. How many helpings/portions of fruit and vegetables do you eat daily? (1 portion is: 1 fruit, 1 bowl of salad, 2-3 tablespoons of vegetables, 1 bowl of fruit salad, large slice of melon or other large fruit, a handful of dried fruit or a cupful of berries or grapes)

1 portion[1]		2 portions[2]		3 portions[3]		4 portions[4]		5 portions[5]		More than 5 portions[6]	
Less than 1 portion[7]											

8. Have you deliberately excluded soya from your diet during pregnancy? Yes[1] ☐ No[2] ☐

9. Have you deliberately excluded any additives from your diet during pregnancy? Yes[1] ☐ No[2] ☐

10. Do you normally smoke? Yes[1] ☐ No[2] ☐
IF 'NO' GO TO Q.12

11. If yes:
Have you cut down during this pregnancy? Yes[1] ☐ No[2] ☐
Have you stopped smoking during this pregnancy? Yes[1] ☐ No[2] ☐
How many cigarettes do you smoke daily on average? ☐

12. Have you regularly been exposed to cigarette smoke elsewhere?

At home	Yes[1]	☐	No[2]	☐		
At work	Yes[1]	☐	No[2]	☐	N/A[3]	☐

Comments

Thank you for taking the time to complete this questionnaire

Appendix 8B

Breastfeeding only (3 months)

1. Are you currently excluding any foods from your diet? Yes[1] ☐ No[2] ☐
   IF 'NO' GO TO Q. 3

2. If yes, why?

Vegetarian	Yes[1]	☐	No[2]	☐	Eat Fish	Yes[1]	☐	No[2]	☐
Vegan	Yes[1]	☐	No[2]	☐					
Dislike certain foods	Yes[1]	☐	No[2]	☐	Food				
Due to babies allergy/intolerance	Yes[1]	☐	No[2]	☐	Food				
Due to own allergy/intolerance	Yes[1]	☐	No[2]	☐	Food				
Due to lactation	Yes[1]	☐	No[2]	☐	Food				
Other reason	Yes[1]	☐	No[2]	☐	Food				

3. Have you identified any foods in your diet that affected your baby after breast feeding? Yes[1] ☐ No[2] ☐
   IF 'NO'GO TO Q. 5

4. If yes, what foods and what effect did they have?

Food	code	Effect	code

5. Have you taken any medication (e.g. antibiotics, paracetamol or aspirin) since your baby's birth? Yes[1] ☐ No[2] ☐
   IF 'NO' GO TO Q. 7

6. If yes, what? (If no tick assume answer to be NO)

Antibiotics	Yes[1]	☐	No[2]	☐		
Paracetamol	Yes[1]	☐	No[2]	☐		
Aspirin	Yes[1]	☐	No[2]	☐		
Other medication	Yes[1]	☐	No[2]	☐	Please specify	

7. Has your baby ever had an infant formula (bottle)? Yes[1] ☐ No[2] ☐ D/K[3] ☐
   IF 'NO' OR D/K END OF QUESTIONNAIRE

8. If yes, which formula?

Comments

e.g. fortified / TPN / tube feed

For Office Use Only

		Food	code
Possible Intolerance / Allergy			
Definite Intolerance / Allergy			
No Intolerance / Allergy			

Appendix 8B

Formula + Breast milk (3 months)

1. Are you currently excluding any foods from your diet? Yes[1] ☐ No[2] ☐
   IF 'NO' GO TO Q. 3

2. If yes, why?

Vegetarian	Yes[1]	☐	No[2]	☐	Eat Fish	Yes[1]	☐	No[2]	☐
Vegan	Yes[1]	☐	No[2]	☐					
Dislike certain foods	Yes[1]	☐	No[2]	☐	Food				
Due to baby's allergy/intolerance	Yes[1]	☐	No[2]	☐	Food				
Due to own allergy/intolerance	Yes[1]	☐	No[2]	☐	Food				
Due to lactation	Yes[1]	☐	No[2]	☐	Food				
Other	Yes[1]	☐	No[2]	☐	Food				

3. Have you identified any foods in your diet that affected your baby after breast feeding? Yes[1] ☐ No[2] ☐
   IF 'NO' GO Q. 5

4. If yes, what foods and what effect did they have?

Food	code	Effect	code

5. Have you taken any medication (e.g. antibiotics, paracetamol or aspirin) since your baby's birth? Yes[1] ☐ No[2] ☐
   IF 'NO' GO TO Q. 7

6. If yes, what? (If no tick assume answer to be NO)

Antibiotics	Yes[1]	☐	No[2]	☐		
Paracetamol	Yes[1]	☐	No[2]	☐		
Aspirin	Yes[1]	☐	No[2]	☐		
Other medication	Yes[1]	☐	No[2]	☐	Please specify	

7. When did you introduce bottle feeding? Age (weeks) ☐

8. Which formula are you using at present? ☐ ☐

9. Why have you chosen this formula? (If no tick assume answer to be NO)

	Formula 1				Formula 2				
Treatment of allergy/intolerance	Yes[1]		No[2]		Yes[1]		No[2]		
Prevention of allergy	Yes[1]		No[2]		Yes[1]		No[2]		
Other child was allergic to milk	Yes[1]		No[2]		Yes[1]		No[2]		
One that was given in hospital	Yes[1]		No[2]		Yes[1]		No[2]		
Advised to do so	Yes[1]		No[2]		Yes[1]		No[2]		By whom
Own preference	Yes[1]		No[2]		Yes[1]		No[2]		
Available in Baby Clinic	Yes[1]		No[2]		Yes[1]		No[2]		
Other	Yes[1]		No[2]		Yes[1]		No[2]		

10. Have you ever used any formula other than the one you are using at the moment? Yes[1] | No[2]

IF 'NO' GO TO Q. 12

11. If yes, what formula and why did you change?

Formula	code	Age when you changed	How long used	Reason for change	code

12. Do you feed your baby breast/bottle equally, more breast or more bottle?

Breast > half[1]		Equal[2]		Bottle > half[3]		Breast + top up[4]	

Comments

e.g. fortified / TPN / tube feed

For Office Use Only

		Food	code
Possible Intolerance / Allergy			
Definite Intolerance / Allergy			
No Intolerance / Allergy			

Appendix 8B

Formula feeding only (3 months)

1. Have you ever breast fed your baby?
IF 'NO' GO TO Q. 10

Yes[1]		No[2]	

2. If Yes, for how long?

1 feed[1]		1 day[4]		1 week[10]		7 weeks[16]	
2 feeds[2]		2 days[5]		2 weeks[11]		8 weeks[17]	
3 feeds[3]		3 days[6]		3 weeks[12]		9 weeks[18]	
		4 days[7]		4 weeks[13]		10 weeks[19]	
		5 days[8]		5 weeks[14]		11 weeks[20]	
		6 days[9]		6 weeks[15]		12 weeks[21]	

3. Why did you stop breast feeding your baby?

Reason	code

If Mum breast feeding > 1 week

4. During the time you were breast feeding, did you exclude any foods from your diet?
IF 'NO' 'D/K' OR 'N/A' GO TO Q. 6

Yes[1]		No[2]	
D/K[3]		N/A[-100]	

5. If yes, why?

Vegetarian	Yes[1]		No[2]		Eat Fish	Yes[1]		No[2]	
Vegan	Yes[1]		No[2]						
Dislike certain foods	Yes[1]		No[2]		Food				
Due to baby's allergy/intolerance	Yes[1]		No[2]		Food				
Due to own allergy/intolerance	Yes[1]		No[2]		Food				
Due to lactation	Yes[1]		No[2]		Food				
Other	Yes[1]		No[2]		Food				

6. Have you identified any foods in your diet that affected your baby after breast feeding?
IF 'NO' 'D/K' OR 'N/A'GO TO Q. 8

Yes[1]		No[2]	
D/K[3]		N/A[4]	

7. If yes, what foods and what effect did they have?

Food	code	Effect	code

8. If breast feeding at all, have you taken any medication (e.g. antibiotics, paracetamol or aspirin) since your baby's birth? Yes[1] | | No[2] | |
IF 'NO' GO TO Q. 10

9. If yes, what

Antibiotics	Yes[1]		No[2]			
Paracetamol	Yes[1]		No[2]			
Aspirin	Yes[1]		No[2]			
Other medication	Yes[1]		No[2]		Please specify	

10. When did you first introduce formula bottle feeding? Age | | days | | weeks

11. Which formula are you using at present? | | | |

12. Why have you chosen this formula? (If no tick assu me answer to be NO)

	Formula 1				Formula 2				
Treatment of allergy/intolerance	Yes[1]		No[2]		Yes[1]		No[2]		
Prevention of allergy	Yes[1]		No[2]		Yes[1]		No[2]		
Other child was allergic to milk	Yes[1]		No[2]		Yes[1]		No[2]		
One that was given in hospital	Yes[1]		No[2]		Yes[1]		No[2]		
Advised to do so	Yes[1]		No[2]		Yes[1]		No[2]		By whom
Own preference	Yes[1]		No[2]		Yes[1]		No[2]		
Available in Baby Clinic	Yes[1]		No[2]		Yes[1]		No[2]		
Other	Yes[1]		No[2]		Yes[1]		No[2]		

13. Have you ever used any formula other than the one you are using at the moment? Yes[1] | | No[2] | |
IF 'NO' END OF QUESTIONNAIRE

14. If yes, what formula and why did you change?

Formula	code	Age when you changed	How long used	Reason for change	code

Comments

e.g. fortified / TPN / tube feed

For Office Use Only

		Food	code
Possible Intolerance / Allergy			
Definite Intolerance / Allergy			
No Intolerance / Allergy			

Appendix 8C

FAIR Study

Six month Questionnaire

Child's Name & Address		Date of questionnaire	/ /
		Sex	Male[1] Female[2]
		GP	
		HV	
	Length ins cms	Date	D/K
	Weight lbs oz kgs	Date	D/K
Child's date of birth:			
Mother's Name	Mother's IW number		
Telephone No.	E-mail address:		

Intolerance / Allergy from three month questionnaire

		Food	code
Possible Intolerance / Allergy			
Definite Intolerance / Allergy			
No Intolerance / Allergy			

1. Who completed questionnaire?

Mother[1]	Father[2]	Grandparent[3]	Guardian[4]	Other[5]	Who

2. Has the child had 1st and 2nd immunisations at three months? (3/12 Q)

1st Imm				2nd Imm			
Yes[1]		No[2]		Yes[1]		No[2]	

3. Has your child had the following immunisations in the last three months?

	1st Immunisation						2nd Immunisation					
Polio	Yes[1]		No[2]		D/K[3]		Yes[1]		No[2]		D/K[3]	
HIB, Diptheria, Tetanus	Yes[1]		No[2]		D/K[3]		Yes[1]		No[2]		D/K[3]	
Whooping Cough	Yes[1]		No[2]		D/K[3]		Yes[1]		No[2]		D/K[3]	
Meningitis C	Yes[1]		No[2]		D/K[3]		Yes[1]		No[2]		D/K[3]	

	3rd Immunisation						
Polio	Yes 1		No[2]		D/K 3		
HIB, Diptheria, Tetanus	Yes 1		No[2]		D/K 3		
Whooping Cough	Yes 1		No[2]		D/K 3		
Meningitis C	Yes 1		No[2]		D/K 3		
Other	Yes 1		No[2]		D/K 3		What

4. Has your child ever had wheezing or whistling in the chest in the past three months?

Yes[1]		No[2]		D/K[3]	

5. In the last three months, has your child had a dry cough at night, apart from the cough associated with a cold or a chest infection?

Yes[1]		No[2]		D/K[3]	

6. In the last three months, has your child suffered from an itchy, stuffy Or runny nose when they did not have a cold or flu?

Yes[1]		No[2]		D/K[3]	

7. Has your child ever suffered from an itchy skin that looks like nettle rash /hives?

Yes[1]		No[2]		D/K[3]	

8. Has your child ever had an itchy dry flaky skin/eczema that was coming and going over the last three months?
IF 'NO' OR 'D/K' GO TO Q. 10

Yes[1]		No[2]		D/K[3]	

9. If yes, where does your child get the itchy dry flaky skin/eczema?

Place	code	Place	code

10 Has your child ever suffered from vomiting (>1 tbsp) in the last three months?

Yes[1]		No[2]		D/K[3]	

11 Has your child ever suffered from diarrhoea in the last three months?

Yes[1]		No[2]		D/K[3]	

12 Has your child ever suffered from constipation in the last three months?

Yes[1]		No[2]		D/K[3]	

13 Has your child ever suffered swelling of the eyes, lips, tongue or throat in the last three months?

Yes[1]		No[2]		D/K[3]	

14 Has your child ever suffered from colic/tummy ache in the last three months?

Yes[1]		No[2]		D/K[3]	

15 Has your child suffered from any food related problems in the last three months?

Yes[1]		No[2]		D/K[3]	

16 If yes, what?

Symptom	code	Food	code	Temp Rel	code	Frequency	code	Age (wks)	Still present			
									Yes[1]		No[2]	
									Yes[1]		No[2]	
									Yes[1]		No[2]	
									Yes[1]		No[2]	

17 Have you consulted your GP/Paediatrician regarding any of the above symptoms in the last six months?

GP	Yes[1]		No[2]		Paediatrician	Yes[1]		No[2]	

IF 'NO' GO TO Q. 19

18 If yes, what symptoms?

Symptom	code	Symptom	code

19 Which method of feeding are you using <u>at the moment</u>?

Breast milk only[1]		Bottle only[2]		Both[3]	

IF BREAST ONLY OR BOTTLE ONLY GO TO Q. 21

20 If both, do you feed your baby breast/bottle equally, more breast or more bottle?

Breast >half[1]		Equal[2]		Bottle >half[3]		Breast + top up[4]		Breast + occasional bottle [5]	

21 In the last three months, have you given your baby any water?

Yes[1]		No[2]	

22 When did you first introduce solids into your baby's diet? ____ weeks

23 Have you given your baby any of the following foods and at what age?

Rice or baby rice		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Wheat containing foods (e.g. baby rusk, baby cereals, cereals, pasta, bread, cakes, biscuits)		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Oats or oat cereal		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Non-citrus fruit (e.g. banana)		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Citrus fruit (e.g. orange, orange juice, mandarin, clementine, lemon, lime, tangerine, grapefruit)		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Strawberry		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Vegetables (not tomato or potato)		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Tomato		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Potato		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Dairy foods (e.g. yoghurt, fromage frais, custard, ice cream, butter, margarine, cow's milk in food, cheese)		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Chicken or turkey		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Lamb		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Beef		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Pork		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Fish		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Whole egg		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Pulses (e.g. lentils, peas, baked beans)		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Soya		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Tree nuts – almonds, brazil nuts, pecan nuts, hazel nuts, walnuts etc. (e.g. in chocolate, crunchy nut cornflakes, choc chip cookies, pesto sauce, vegetarian meals)		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Peanuts (e.g. Bombay mix, peanut butter, peanut brittle, peanut cookies, Snickers bar, some vegetarian meals)		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Sesame (e.g. humous, tahini, seed rolls, cereal bars)		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Other food (specify)		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
		<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	

24 Which three foods have you introduced first?

Food	code	Food	code	Food	code

25 Have you given your baby any baby cereals, packet foods or jars yet? Yes[1] ___ No[2] ___

26 Are you consciously avoiding any foods from your baby's diet at present? Yes[1] ___ No[2] ___
IF 'NO' GO TO Q. 28

27 If yes, what?

Food	code	Food	code

28 Have you given your baby any of the following drinks and at what age?

Fruit squash –citrus	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Fruit squash – non-citrus	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Diet fruit squash – citrus	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Diet fruit squash – non-citrus	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	

Fruit juice – citrus	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Fruit juice – non-citrus	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Fruit juice – prune	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Herbal drinks	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	

Tea/coffee	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Cold flavoured milk drinks	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Fizzy drinks	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Cow's milk	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Flavoured water	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	
Other drinks (specify)	<3 mths[1]		3-6 mths[2]		No[3]		D/K[4]	

29 Has your baby taken any medication (e.g. gripe water, antibiotics etc) or used any medicated creams in the last three months? Yes[1] No[2]
IF 'NO' GO TO Q. 31

30 If yes what?

Gripe water	Yes[1]		No[2]			
Calpol	Yes[1]		No[2]			
Colief	Yes[1]		No[2]			
Infacol	Yes[1]		No[2]			
Antibiotics	Yes[1]		No[2]			
Other medication	Yes[1]		No[2]		Please specify	

31 Has your baby had a temperature/fever in the last six months? Yes[1] No[2]

32 If yes, how many times?

1		2		3		4		5		6		>6						

33 What was the reason for this temperature/fever?

Immunisation		Gastro-enteritis		Teething		Chest infection		cold			
Flu		Other		specify				Don't know			

34 Do you normally smoke? Yes[1] No[2]

35 If yes, how many cigarettes do you smoke daily on average?

36 Has your baby regularly been exposed to cigarette smoke? Yes[1] No[2]

37 Is your baby exposed to pets at home?

Cat	Yes[1]		No[2]			
Dog	Yes[1]		No[2]			
Other	Yes[1]		No[2]		What?	

38 Is your baby regularly exposed to pets elsewhere?

Cat	Yes[1]		No[2]			
Dog	Yes[1]		No[2]			
Other	Yes[1]		No[2]		What?	

IF STILL BREAST FEEDING (Breast only / Breast + Bottle)

39 Mum reverted back to breast feeding only after a period of bottle feeding? Yes[1] No[2]

40 Has your baby ever had an infant formula? Yes[1] No[2] D/K[3]
IF 'NO' OR 'D/K' END OF QUESTIONNAIRE

41 If yes, which formula?
IF BREAST FEEDING ONLY END OF QUESTIONNAIRE

IF BOTTLE FEEDING AT ALL (Get info from 3 month questionnaire)

42 When did you first introduce bottle feeding? ____ Days ____ Weeks

43 When did you stop breast feeding? | Days | | Weeks

44 Why did you stop breast feeding your baby?

Reason	code

45 Which bottle feed are you using at present? ____

46 In the last three months have you used any formula other than the one you are using at the moment? Yes[1] | | No[2] |

IF 'NO' END OF QUESTIONNAIRE

47 If yes, what formula and why did you change?

Formula	code	Age when you changed	How long used	Reason for change	code

For Office Use Only

		Food	code
Possible Intolerance / Allergy			
Definite Intolerance / Allergy			
No Intolerance / Allergy			

Appendix 8D

FAIR Study

Nine month Questionnaire

Child's Name & Address	Date of questionnaire / /
	Sex: Male[1] Female[2]
	GP
	HV
	Length: ins cms Date D/K
	Weight: lbs oz kgs Date D/K
Child's date of birth:	
Mother's Name	Mother's IW number
Telephone No.	E-mail address:

Intolerance / Allergy from six month questionnaire

		Food	code
Possible Intolerance / Allergy			
Definite Intolerance / Allergy			
No Intolerance / Allergy			

1. Who completed questionnaire?

Mother[1] Father[2] Grandparent[3] Guardian[4] Other[5] Who

2. Has the child had 1st and 2nd immunisations at three months? (6/12 Q)

	1st Imm		2nd Imm	
	Y[1]	N[2]	Y[1]	N[2]

3. Has your child had the following immunisations in the last three months?

	1st Immunisation			2nd Immunisation		
Polio	Yes[1]	No[2]	D/K[3]	Yes[1]	No[2]	D/K[3]
HIB, Diptheria, Tetanus	Yes[1]	No[2]	D/K[3]	Yes[1]	No[2]	D/K[3]
Whooping Cough	Yes[1]	No[2]	D/K[3]	Yes[1]	No[2]	D/K[3]
Meningitis C	Yes[1]	No[2]	D/K[3]	Yes[1]	No[2]	D/K[3]

	3rd Immunisation			
Polio	Yes[1]	No[2]	D/K[3]	
HIB, Diptheria, Tetanus	Yes[1]	No[2]	D/K[3]	
Whooping Cough	Yes[1]	No[2]	D/K[3]	
Meningitis C	Yes[1]	No[2]	D/K[3]	
Other	Yes[1]	No[2]	D/K[3]	What

4. Declined all immunisations: Yes[1] No[2] N/A[-100] Reason

5. Has your child ever had wheezing or whistling in the chest in the past three months? Yes[1] No[2] D/K[3]

6. In the last three months, has your child had a dry cough at night, apart from the cough associated with a cold or a chest infection? Yes[1] No[2] D/K[3]

7. In the last three months, has your child suffered from an itchy, stuffy Or runny nose when they did not have a cold or flu? Yes[1] No[2] D/K[3]

8. Has your child ever suffered from an itchy skin that looks like nettle rash /hives? Yes[1] No[2] D/K[3]

9. Has your child ever had an itchy dry flaky skin/eczema that was coming and going over the last three months?
IF 'NO' OR 'D/K' GO TO Q. 11

Yes[1]		No[2]		D/K[3]	

10 If yes, where does your child get the itchy dry flaky skin/eczema?

Place	code	Place	code

11 Has your child ever suffered from vomiting (>1 tbsp) in the last three months?

Yes[1]		No[2]		D/K[3]	

12 Has your child ever suffered from diarrhoea in the last three months?

Yes[1]		No[2]		D/K[3]	

13 Has your child ever suffered from constipation in the last three months?

Yes[1]		No[2]		D/K[3]	

14 Has your child ever suffered swelling of the eyes, lips, tongue or throat in the last three months?

Yes[1]		No[2]		D/K[3]	

15 Has your child ever suffered from colic/tummy ache in the last three months?

Yes[1]		No[2]		D/K[3]	

16 Has your child suffered from any food related problems in the last three months?

Yes[1]		No[2]		D/K[3]	

17 If yes, what?

Symptom	code	Food	code	Temp Rel	code	Frequency	code	Age (wks)	Still present			
									Yes[1]		No[2]	
									Yes[1]		No[2]	
									Yes[1]		No[2]	
									Yes[1]		No[2]	

18 Have you consulted your GP/Paediatrician regarding any of the above symptoms in the last six months?

GP	Yes[1]		No[2]		Paediatrician	Yes[1]		No[2]	

IF 'NO' GO TO Q. 20

19 If yes, what symptoms?

Symptom	code	Symptom	code

20 Which method of feeding are you using <u>at the moment</u>?

Breast milk only[1]		Bottle/Beaker only[2]		Both[3]	

IF BREAST ONLY OR BOTTLE ONLY GO TO Q. 22

21 If both, do you feed your baby breast/bottle equally, more breast or more bottle?

Breast >half[1]		Equal[2]		Bottle >half[3]		Breast + top up[4]		Breast + occasional bottle [5]	

22 In the last three months, have you given your baby any water?

Yes[1]		No[2]	

23 In the last three months have you introduced any of the following foods?

Rice or baby rice	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Wheat containing foods (e.g. baby rusk, baby cereals, cereals, pasta, bread, cakes, biscuits)	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Oats or oat cereal	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Non-citrus fruit (e.g. banana)	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Citrus fruit (e.g. orange, orange juice, mandarin, clementine, lemon, lime, tangerine, grapefruit)	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Strawberry	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Vegetables (not tomato or potato)	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Tomato	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Potato	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Dairy foods (e.g. yoghurt, fromage frais, custard, ice cream, butter, margarine, cow's milk in food, cheese)	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Chicken or turkey	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Lamb	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Beef	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Pork	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Fish	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Whole egg	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Pulses (e.g. lentils, peas, baked beans)	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Soya	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Tree nuts – almonds, brazil nuts, pecan nuts, hazel nuts, walnuts etc. (e.g. in chocolate, crunchy nut cornflakes, choc chip cookies, pesto sauce, vegetarian meals)	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Peanuts (e.g. Bombay mix, peanut butter, peanut brittle, peanut cookies, Snickers bar, some vegetarian meals)	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Sesame (e.g. humous, tahini, seed rolls, cereal bars)	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Other food (specify)	Yes[1]		No[2]		D/K[3]		N/A[-100]	
	Yes[1]		No[2]		D/K[3]		N/A[-100]	
	Yes[1]		No[2]		D/K[3]		N/A[-100]	

Yes[1]		No[2]	

24 Are you consciously avoiding any foods from your baby's diet at present?
IF 'NO' GO TO Q. 26

25 If yes, what?

Food	code	Food	code

26 In the last three months have you given your baby any of the following drinks?

Fruit squash	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Fruit juice	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Tea/coffee	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Fizzy drinks	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Cow's milk / flavoured milk drinks	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Flavoured water	Yes[1]		No[2]		D/K[3]		N/A[-100]	
Other drinks (specify)	Yes[1]		No[2]		D/K[3]		N/A[-100]	

27 Has your baby taken any medication (e.g. gripe water, antibiotics etc) or used any medicated creams in the last three months?
IF 'NO' GO TO Q. 29

Yes[1]		No[2]	

28 If yes what?

Gripe water	Yes[1]		No[2]			
Calpol	Yes[1]		No[2]			
Colief	Yes[1]		No[2]			
Infacol	Yes[1]		No[2]			
Antibiotics	Yes[1]		No[2]			
Neurofen	Yes[1]		No[2]			
Other medication	Yes[1]		No[2]		Please specify	

29 Do you normally smoke? Yes[1] | | No[2] | |

30 If yes, how many cigarettes do you smoke daily on average? |

31 Has your baby regularly been exposed to cigarette smoke? Yes[1] | | No[2] | |

32 Is your baby exposed to pets at home?

Cat	Yes[1]		No[2]		
Dog	Yes[1]		No[2]		
Other	Yes[1]		No[2]		What?

33 Is your baby regularly exposed to pets elsewhere?

Cat	Yes[1]		No[2]		
Dog	Yes[1]		No[2]		
Other	Yes[1]		No[2]		What?

IF BOTTLE FEEDING AT ALL (Get info from 3/6 month questionnaire)

34 When did you first introduce bottle feeding? | Days | Weeks

35 When did you stop breast feeding? | Days | Weeks

36 Why did you stop breast feeding your baby?

Reason	code

37 Which bottle/beaker feed are you using at present? |

38 In the last three months have you used any formula other than the one you are using at the moment? Yes[1] | | No[2] |
IF 'NO' END OF QUESTIONNAIRE

39 If yes, what formula and why did you change?

Formula	code	Age when you changed	How long used	Reason for change	code

For Office Use Only

		Food	code
Possible Intolerance / Allergy			
Definite Intolerance / Allergy			
No Intolerance / Allergy			

Appendix 8E

FAIR Study

Twelve month Questionnaire

Child's Name & Address	Date of questionnaire / /
	Sex: Male[1] Female[2]
	GP
	HV
	Height: ins / cms
Child's date of birth:	
Mother's Name	Mother's IW number
Telephone No.	E-mail address

1. Have you, your partner or children suffered with the following

	Mother	Father	Siblings					
			M	F	M	F	M	F
Asthma								
Hayfever								
Eczema								
Urticaria								
Food Allergy								

2. Parental smoking

Mother	Yes[1]		No[2]	
Father/Partner	Yes[1]		No[2]	

3. Is your baby regularly exposed to pets?

Cat	Yes[1]		No[2]		
Dog	Yes[1]		No[2]		
Other	Yes[1]		No[2]		What?

4. Birth weight

Type of delivery	NVD		EmCS		ElCS		Forceps		Ventouse	
Breast fed	days		weeks		months					
Weaning age	weeks		months							

5. Has your child ever had wheeze/whistling in the chest in the last 3 months Yes[1] No[2]
IF 'NO' GO TO Q. 15

6. If yes, how many times in the last year? 0[1] 1-3[2] 4-12[3] >12[4]

7. Did it cause sleep disturbance? 0[1] <1 night a weeek[2] >1 night a week[3]

8. Did your child require hospitalisation for this at any time? Yes[1] No[2]

9. Has your child ever had wheeze/whistling with a chest infection or cold? Yes[1] No[2]

10 Has your child ever had wheeze/whistling when he/she did not have a chest infection or cold? Yes[1] No[2]

11 Has your child ever had asthma | Yes[1] | No[2] |

12 Has your child ever had treatment for wheeze/asthma? | Yes[1] | No[2] |

13 Have you identified a cause for the wheeze or asthma? | Yes[1] | No[2] |
IF 'NO' GO TO Q. 15

14 If yes, what?

Pollen[1]	Dust[2]	Smoke[3]	Animal[4]	Infections[5]
Food[6] (specify)				
Other[7] (specify)				

15 Has your child ever had a dry cough at night apart from that associated with a cold or flu in the last 3 months? | Yes[1] | No[2] |
IF 'NO' GO TO Q. 21

16 If yes, does he/she usually have a cough only with a cold or flu? | Yes[1] | No[2] |

17 Does he/she usually have a cough without a cold or flu? | Yes[1] | No[2] |

18 How many episodes has he/she had in the last 12 months? | 0[1] | 1-3[2] | 4-6[3] | 7 or more[4] |

19 Have you identified a cause for the cough? | Yes[1] | No[2] |
IF 'NO' GO TO Q. 21

20 If yes what?

Pollen[1]	Dust[2]	Smoke[3]	Animal[4]	Infections[5]
Food[6] (specify)				
Other[7] (specify)				

21 Has your child ever had a dry scaly rash coming and going (for more than 6 months)? | Yes[1] | No[2] |
IF 'NO' GO TO Q. 28

22 If yes, has your child ever been diagnosed with eczema? | Yes[1] | No[2] |

23 Has your child ever been treated for rash/eczema | Yes[1] | No[2] |
IF 'NO' GO TO Q. 25

24 If yes, with what?

25 Where is the rash/eczema?

Face[1]	Trunk[2]	Arms[3]	Legs[4]	Folds of skin[5]
Other[6] (specify)				

26 Have you identified a cause for the eczema? | Yes[1] | No[2] |
IF 'NO' GO TO Q. 28

27 If yes, what?

Pollen[1]	Dust[2]	Smoke[3]	Animal[4]	Infections[5]
Food[6] (specify)				

Other[7] (specify)			

28 Has your child had a runny or stuffy nose in the last 3 months? Yes[1] | No[2]
IF 'NO' GO TO Q. 34

29 If yes, how often? <1/month | 1-3/month | >1/week

30 Have you identified a cause for this? Yes[1] | No[2]
IF 'NO' GO TO Q 32

31 If yes, what?

Pollen[1]		Dust[2]		Smoke[3]		Animal[4]		Infections[5]	
Food[6] (specify)									
Other[7] (specify)									

32 Has your child ever been treated for this? Yes[1] | No[2]

33 If yes, with what?

34 Has your child had diarrhoea in the last 3 months? Yes[1] | No[2]
IF 'NO' GO TO Q 38

35 If yes, how often? <1/month | 1-3/month | >1/week

36 Have you identified a cause for this? Yes[1] | No[2]

37 If yes, what?

Infection[1]		Drug[2]		Food[3] (specify)					
				Other[4] (specify)					

38 Has your child had vomiting in the last 3 months? Yes[1] | No[2]
IF 'NO' GO TO Q 42

39 If yes, how often? <1/month | 1-3/month | >1/week

40 Have you identified a cause for this? Yes[1] | No[2]

41 If yes, what?

Infection[1]		Drug[2]		Food[3] (specify)					
				Other[4] (specify)					

42 Has your child had food related problems in the last 3 months? Yes[1] | No[2]
IF 'NO' GO TO Q. 46

43 If yes, what?

Symptom	code	Food	code	Temp Rel	code	Frequency	code

44 Have you avoided any of these foods from your baby's diet? Yes[1] | No[2]

Appendix 8E

IF ‘NO’ GO TO Q. 46

45 If yes what?

Food	code	Reason	code	Improvement in symptoms				Diagnosis confirmed			
				Yes[1]		No[2]		Yes[1]		No[2]	
				Yes[1]		No[2]		Yes[1]		No[2]	
				Yes[1]		No[2]		Yes[1]		No[2]	
				Yes[1]		No[2]		Yes[1]		No[2]	

46 Has your child had any of the following in the last 3 months?

		Yes[1]	No[2]	No. of Episodes
Urticaria				
Swelling of:	Lip			
	Lip and face			
	Tongue/throat			
Collapse				
Loss of consciousness				
Difficulty breathing				

47 Have you identified a cause for the above?

Yes[1]		No[2]	

48 If yes, what?

Drug[1]		Insect sting[2]		Food[3] (specify)			
				Other[4] (specify)			

49 Has your child required any medication in the last 3 months?

Yes[1]		No[2]	

50 If yes, what

	Yes[1]	No[2]					
Lotions / creams / ointments							
Inhalers							
Eye drops							
Suspensions							
Other							

Appendix 8E

Medical Examination

Eyes	redness[1]		swollen eyelids[2]		other[3]		

Skin

dry[1]		erythema[2]		excoriation[3]		lichenification[4]		vesicles[5]		other[6]		

Nose

rhinorrhoea[1]		crusting[2]		congestion/blockage[3]		polyps[4]		other[5]		

Respiratory System

chest deformity[1]		wheeze[2]		crackles[3]		other[4]		

Other

Skin Prick Tests

Aeroallergens			Size	Food Allergens			Size
HDM				Milk			
Grass				Wheat			
Cat				Egg			
Dog				Fish			
Cladosp				Sesame			
Alternaria				Other			
Other							

Other Investigations

Food Challenge

Appendix 8F

FAIR Study

Two Year Questionnaire

Child's Name & Address	Date of questionnaire / /
	Sex: Male[1] Female[2]
	GP
	HV
	Height: ins cms
	Weight: lbs oz kgs
Child's date of birth:	

Mother's Name	Mother's IW number
Telephone No.	E-mail address

1. Do you, your partner or children suffer with or have you, your partner or children suffered with the following

	Mother	Father	Sibling1		Sibling2		Sibling3		Sibling4		Sibling5	
			M[1]	F[2]	M[1]	F[2]	M[1]	F[2]	M[1]	F[2]	M[1]	F[2]
	Y[1]/N[2]	Y[1]/N[2]	Y[1]/N[2]	Y[1]/N[2]	Y[1]/N[2]	Y[1]/N[2]	Y[1]/N[2]	Y[1]/N[2]	Y[1]/N[2]	Y[1]/N[2]	Y[1]/N[2]	Y[1]/N[2]
Asthma												
Nocturnal/recurrent cough												
Hayfever												
Eczema												
Urticaria												
Food Allergy												

2. Parental **smoking** Smoke during pregnancy Yes[1] No[2]

3. Does anyone in the house smoke now?

						In house				How many
Mother	Yes[1]		No[2]		N/A	Yes[1]		No[2]		/day
Father/Partner	Yes[1]		No[2]		N/A	Yes[1]		No[2]		/day
Other	Yes[1]		No[2]		N/A	Yes[1]		No[2]		/day

4. Do any of the above smoke outside the house Yes[1] No[2] N/A

5. **Pets** in the house in the last year

Cat	Yes[1]		No[2]		
Dog	Yes[1]		No[2]		
Other	Yes[1]		No[2]		What?

6. Baby regularly exposed to pets elsewhere in the last year

Cat	Yes[1]		No[2]		
Dog	Yes[1]		No[2]		
Other	Yes[1]		No[2]		What?

7. Has your child been immunised to

DPT	Yes[1]		No[2]	
DT (without pertussis)	Yes[1]		No[2]	
Polio	Yes[1]		No[2]	
Hib	Yes[1]		No[2]	
Meningococcal Group C	Yes[1]		No[2]	
BCG	Yes[1]		No[2]	
MMR	Yes[1]		No[2]	

Other	Yes[1]		No[2]		What?	

8. Has your child ever had wheeze/whistling in the chest at any time in the past? Yes[1] No[2]
IF 'NO' GO TO Q. 20

9. Any wheeze/whistling in the last 12 months? Yes[1] No[2]

10 If yes, how many times in the last year? 0[1] 1-3[2] 4-12[3] >12[4]

11 Average sleep disturbance it caused in 12 months? 0[1] <1 night a weeek[2] >1 night a week[3]

12 Did your child require hospitalisation for this at any time? Yes[1] No[2]

13 Has your child ever had wheeze/whistling with a chest infection or cold? Yes[1] No[2]

14 Has your child ever had wheeze/whistling when he/she did not have a chest infection or cold? Yes[1] No[2]

15 Has your child ever been diagnosed with asthma? Yes[1] No[2]

16 Has your child ever had treatment for wheeze/asthma? Yes[1] No[2]

17 If yes, what?

18 Have you identified a cause for the wheeze or asthma? Yes[1] No[2]
IF 'NO' GO TO Q. 20

19 If yes, what?

Pollen[1]	Dust[2]	Smoke[3]	Animal[4]	Infections[5]
Food[6] (specify)				
Other[7] (specify)				

20 Has your child ever had a dry cough at night apart from that associated with a cold or chest infection? Yes[1] No[2]
IF 'NO' GO TO Q. 28

21 Has your child ever had a dry cough at night in the last 12 months? Yes[1] No[2]

22 If yes, does he/she usually have a cough only with a cold or chest infection? Yes[1] No[2]

23 Does he/she usually have a cough without a cold or chest infection? Yes[1] No[2]

24 How many episodes has he/she had in the last 12 months? 0[1] 1-3[2] 4-12[3] >12[4]

25 Average sleep disturbance it caused in 12 months 0[1] <1 night a week[2] >1 night a week[3]

26 Have you identified a cause for the cough? Yes[1] No[2]
IF 'NO' GO TO Q. 28

27 If yes what?

Pollen[1]	Dust[2]	Smoke[3]	Animal[4]	Infections[5]
Food[6] (specify)				

Other[7] (specify)			

28 Has your child ever had a dry itchy rash coming and going (for at least 6 months)? Yes[1] No[2]
IF 'NO' GO TO Q. 38

29 At what age did it first occur? days weeks months

30 Has your child had a dry itchy rash at any time in the last 12 months? Yes[1] No[2]

31 In the last 12 months on average has your child been kept awake by this itchy rash? 0[1] <1 night/week[2] > 1 night/week[3]

32 If yes, has your child ever been diagnosed with eczema? Yes[1] No[2]

33 Has your child ever been treated for rash/eczema Yes[1] No[2]
IF 'NO' GO TO Q. 38

34 If yes, with what?

35 Where is the rash/eczema?

Face[1]	Trunk[2]	Arms[3]	Legs[4]	Folds of skin[5]
Other[6] (specify)				

36 Have you identified a cause for the eczema? Yes[1] No[2]
IF 'NO' GO TO Q. 38

37 If yes, what?

Pollen[1]	Dust[2]	Smoke[3]	Animal[4]	Infections[5]
Food[6] (specify)				
Other[7] (specify)				

38 Has your child had a problem with sneezing or a runny or blocked nose in the last 12 months? Yes[1] No[2]
IF 'NO' GO TO Q. 44

39 If yes, how often? <1/month[1] 1-3/month[2] >1/week[3]

40 Have you identified a cause for this? Yes[1] No[2]
IF 'NO' GO TO Q 44

41 If yes, what?

Pollen[1]	Dust[2]	Smoke[3]	Animal[4]	Infections[5]
Food[6] (specify)				
Other[7] (specify)				

42 Has your child ever been treated for this? Yes[1] No[2]

43 If yes, with what?

44 Has your child had diarrhoea in the last 12 months? Yes[1] No[2]

Appendix 8F

IF 'NO' GO TO Q 48

45 If yes, how often?

<1/month[1]		1-3/month[2]		>1/week[3]	

46 Have you identified a cause for this?

Yes[1]		No[2]	

47 If yes, what?

Infection[1]		Drug[2]		Food[3] (specify)		
				Other[4] (specify)		

48 Has your child had vomiting in the last 12 months?
IF 'NO' GO TO Q 52

Yes[1]		No[2]	

49 If yes, how often?

<1/month[1]		1-3/month[2]		>1/week[3]	

50 Have you identified a cause for this?

Yes[1]		No[2]	

51 If yes, what?

Infection[1]		Drug[2]		Food[3] (specify)		
				Other[4] (specify)		

52 Has your child had food related problems in the last 12 months?
IF 'NO' GO TO Q. 56

Yes[1]		No[2]	

53 If yes, what?

Symptom	code	Food	code	Temp Rel	code	Frequency	code

54 Have you avoided any of these foods from your baby's diet?
IF 'NO' GO TO Q. 56

Yes[1]		No[2]	

55 If yes what?

Food	code	Reason	code	Improvement in symptoms				Diagnosis confirmed			
				Yes[1]		No[2]		Yes[1]		No[2]	
				Yes[1]		No[2]		Yes[1]		No[2]	
				Yes[1]		No[2]		Yes[1]		No[2]	
				Yes[1]		No[2]		Yes[1]		No[2]	

56 Has your child had any of the following in the last 12 months?

		Yes[1]	No[2]	No. of Episodes
Urticaria				
Swelling of:	Lip			
	Eyes			
	Lip and face			
	Tongue/throat			
Other rash				
Collapse				
Loss of consciousness				

Appendix 8F

Difficulty breathing			

57 Have you identified a cause for the above?

Yes[1]		No[2]	

58 If yes, what?

Drug[1]		Insect sting[2]		Food[3] (specify)			
				Other[4] (specify)			

59 Has your child required any medication in the last 12 months?

Yes[1]		No[2]	

60 If yes, what

	Yes[1]	No[2]						
Lotions / creams / ointments								
Inhalers								
Eye drops								
Suspensions								
Other								

61 Are you consciously avoiding any foods from your baby's diet at present?

Yes[1]		No[2]	

62 If yes, what?

Food	code	Food	code

63 Did you avoid peanuts during pregnancy?

Yes[1]		No[2]		N/A[-100]	

64 If yes, for what reason?

65 The government issued advice in 1998 about eating peanuts whilst pregnant and breastfeeding. Do you remember hearing about that at the time?

Yes[1]		No[2]		Don't remember[3]	

66 Did any of the following people speak to you or give you information about eating peanuts and peanut containing foods **during your pregnancy**?

	N/A[-100]					
GP	Yes[1]		No[2]		Don't remember[3]	
Midwife	Yes[1]		No[2]		Don't remember[3]	
Health Visitor	Yes[1]		No[2]		Don't remember[3]	
Dietitian	Yes[1]		No[2]		Don't remember[3]	
Other	Yes[1]		No[2]		Don't remember[3]	
Media	Yes[1]		No[2]		Don't remember[3]	

IF 'NO' OR 'DON'T REMEMBER' GO TO Q. 69

67 Did you change your diet on the basis of this advice?

Yes[1]		No[2]		Don't remember[3]	

68 If you changed your diet did you

Stop eating peanuts completely?[1]	
Stop eating obvious peanuts but continue eating foods that 'may contain peanut?[2]	
Increase your consumption of peanut?[3]	

Don't remember[4]	

69 Breast fed

days	weeks	months

IF NOT BREAST FED END OF QUESTIONNAIRE

70 Did any of the following people speak to you or give you information about eating peanuts and peanut containing foods **whilst breastfeeding**?

	N/A[-100]		Yes[1]		No[2]		Don't remember[3]	
GP			Yes[1]		No[2]		Don't remember[3]	
Midwife			Yes[1]		No[2]		Don't remember[3]	
Health Visitor			Yes[1]		No[2]		Don't remember[3]	
Dietitian			Yes[1]		No[2]		Don't remember[3]	
Other			Yes[1]		No[2]		Don't remember[3]	
Media			Yes[1]		No[2]		Don't remember[3]	

IF 'NO' OR 'DON'T REMEMBER' END OF QUESTIONNAIRE

71 Did you change your diet on the basis of this advice? Yes[1] No[2] Don't remember[3]

72 If you changed your diet did you

Stop eating peanuts completely?[1]	
Stop eating obvious peanuts but continue eating foods that 'may contain peanut?[2]	
Increase your consumption of peanut?[3]	
Don't remember[4]	

		Food	code
Possible Intolerance / Allergy			
Definite Intolerance / Allergy			
No Intolerance / Allergy			

Appendix 8F

Medical Examination (Not done[10])

Eyes	redness[1]		swollen eyelids[2]		other[3]		normal[9]		

Skin

dry[1]		erythema[2]		excoriation[3]		lichenification[4]		vesicles[5]		other[6]		normal[9]	
Eczema[17]													

Nose

rhinorrhoea[1]		crusting[2]		congestion/blockage[3]		polyps[4]		other[5]		normal[9]	

Respiratory System

chest deformity[1]		wheeze[2]		crackles[3]		other[4]		normal[9]		

Other

Skin Prick Tests Not done[-103]

Food allergens	Size	Positive[1]	Negative[2]	Aeroallergens	Size	Positive[1]	Negative[2]
Histamine				HDM			
Saline				Cat			
Milk				Grass			
Egg				Other			
Wheat							
Fish							
Peanut							
Sesame							
Other							

Food Challenge

University of Portsmouth

Research Proposal

An indepth investigation of Food Hypersensitivity in 8-10 year old children: Its natural history, incidence after infancy and its impact on health related quality of life

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Table of Contents

Title

An indepth investigation of Food Hypersensitivity in older children: Its natural history, incidence after infancy and its impact on health related quality of life

Background

Definitions

A European Academy of Allergy and Clinical Immunology task force [1] has suggested that any adverse reaction to food should be called food hypersensitivity (FHS). When immunological mechanisms have been demonstrated, they suggest that the appropriate term is food allergy. Where the role of IgE is confirmed, it is suggested that it is known as IgE-mediated food allergy. They suggest that other reactions, previously sometimes referred to as 'food intolerance' should be referred to as non-allergic food hypersensitivity. Severe, generalised allergic reactions to food are classified as anaphylaxis. FHS can therefore present as a wide range of reactions varying from non-fatal food intolerance to more severe reactions such as anaphylaxis.

Prevalence of FHS

It is important to have accurate national data on the rate of FHS in order to meet the needs of the allergic community; particularly as the prevalence of food allergies vary depending on the diet and exposure to food allergens. Geographical variance in prevalence of self-reported food hypersensitivity and differences in the foods reported to cause hypersensitivity has been well documented [2]. It is well know that reported prevalence of FHS overestimates FHS diagnosed by food challenges and other tests. Very few population-based studies looking at FHS in children based on food challenges are available in the literature.

In the USA, 480 consecutive children born into a paediatric clinic were recruited at a routine two-week appointment. The researchers determined that 8% (cumulative incidence) of the children (0-3 years) out of the 28%, who presented with possible symptoms of food allergy, were truly food allergic as assessed by food challenges [3]. Osterballe et al. [4] estimated the prevalence of FHS to the most common allergenic foods in an unselected population of children (111 children <3 yr of age, 486 children 3 yr of age and 301 children older than 3 yr of age) by questionnaire, skin prick test, histamine release test and specific IgE followed by oral challenge to the most common allergenic foods. The prevalence of FHS was 2.3% in the children 3 yr of age and 1% in children older than 3 yr of age. The most common allergenic

food was hen's egg affecting 1.6% of the children 3 yr of age. In a German study [5], 4.2% of children (0 – 17 years) were found to suffer from FHS as assessed by double blind placebo controlled food challenges (DBPCFC). In this study questionnaires were sent to 2 354 children and 739 responded. The foods most commonly implicated were apple, kiwi, soy, hazelnut, and wheat, although challenges were performed to a much wider range of foods.

We have recently shown that in a birth cohort of children on the Isle of Wight, 7.2% of parents report adverse reactions to food at 12 months of age, 8.9% at two years and 9.2% at three years[6;7]. Of the 807 children seen at one, two and three years, 272 (33.7%) reported a food related problem. Based on open food challenges (OFC) and a good clinical history, the prevalence of FHS was 4% at one year[6], 2.5% at two years and 3.0% at three years[7]. Based on DBPCFC and a good clinical history, the prevalence of FHS was 3.2% at one year, 2.1% at two years and 2.9% at three years[7]. Cumulative, by 3 years of age, 6.0% of children were diagnosed with FHS based on OFC and history and 5.0% children based on DBPCFC and history. Overall the foods implicated in this study were milk, egg, peanut, corn, potato, tomato, salicylates and wheat[7].

There are no data available regarding the natural history of food allergies and intolerances in a birth cohort of children beyond the age of 3 years in this information is very much needed for improved patient care. Following-up the FAIR children at the age of 8-10 years will give us an ideal opportunity of filling the gap in the information pool.

Diagnosis

Central to any study looking at prevalence is the use of valid diagnostic tools. Diagnosis of FHS requires a detailed clinical history, which provides important information and may involve a SPT and/or sIgE blood test. These tests may be followed by a trial period on an exclusion diet, followed by food re-introduction, or a food challenge.

The clinical history provides important information, but cannot correctly identify FHS as despite careful history taking, the correlation between reported FHS and FHS as confirmed by a double-blind, placebo-controlled food challenge (DBPCFC) is between 12 - 21% of patients[8-10].

Skin prick test measures specific IgE attached to mast cells in the skin and specific IgE test measures levels of circulating specific IgE to allergen in the circulation. However, the presence of IgE in the skin or in the blood only indicates that an individual is sensitised to an allergen, but not necessarily clinically allergic. In general, a SPT is considered positive if the

wheal is ≥ 3mm bigger than the negative control [11]. A positive SPT indicates a 50% possibility having IgE mediated FHS. A negative SPT indicates a 95% possibility of not have IgE mediated FHS. There are now more specific clinical decision points available in the literature which indicates to clinicians if a food challenge is needed and how likely the challenge is to be positive [12-16].

Specific IgE is measured as fluorescent enzyme-labelled IgE (CAP-RAST FEIA). Specific IgE levels is considered "positive" if levels are above 0.35 kU_A/l. In general, the higher the level of specific IgE the more likely the child is to be allergic, but there is no clear cut-off point between being allergic or not. Specific IgE levels of >15 kU_A/L for milk, >7 kU_A/L for egg and >14 kU_A/L for peanut is considered highly indicative that the person is truly suffering from a food allergy[12;17-20]. As with the SPT, these decision points should be viewed as guidelines rather than set diagnostic points.

Identification of the particular food protein being sensitised to, could give additional information regarding the likelihood of suffering from a true food allergy. A number of allergenic proteins in peanut have been described and the relative importance of these allergens in the diagnosis of peanut and other nut allergies are being still being studied. In peanut allergy, sensitisation to Ara H2 seems to be more indicative of a true allergy, than sensitisation to Ara H1 and Ara H3[21] . Hazelnut allergy can vary between mild oral symptoms and potentially dangerous anaphylaxis. Sensitisation to Cor a 1 (Bet v 1) and Cor a 2 (profilin) account for relatively mild symptoms. However, subjects can also be sensitized to several other allergens such as Cor a 8 (lipid transfer protein) and Cor a 9 (11S globulin) and perhaps Cor a 11 (7S globulin) that are related to more severe symptoms as these allergens are homologues of allergens in other nuts and peanut[22]. Studies [23;24] have shown that early life food sensitisation/ allergy may be associated with concurrent or subsequent childhood airways disease (wheeze or asthma). Measurement of lung function could help quantify impact of such disease relationships. Findings obtained may also have long-term consequences since impairment of lung function in childhood asthma has been shown to track into adulthood [25-27]. It is therefore, important that we get a better understanding of the relevance of sensitisation to specific food proteins in the development of clinical allergy as well as the co-existing and cross-sensitisation to particular proteins in foods and aero-allergens.

In many patients seen in clinical practice, particularly those suffering from non-IgE mediated allergy or non-allergic FHS, diagnosis can only be made by means of a combination of

clinical history and dietary investigations (diagnostic exclusion diets). This is because it is often not obvious which foods may be causing the symptoms. The length of time needed to establish a diagnosis will depend on the frequency of symptoms, how strict the diet is, symptoms involved and the disease pattern. A successful elimination diet will improve or resolve the symptoms.

There are four types of diagnostic exclusion diets [28]:

- Single exclusion diet

This excludes all sources of a single food (eg milk) as identified from the patient's dietary history.

- Multiple food exclusion diet

A multiple exclusion diet excludes a number of foods at the same time. Foods most commonly associated with a particular FHS reaction are usually avoided such as milk and egg for eczema [29], and milk, egg and wheat for eosinophilic diseases [30]. The major food allergens (peanuts, tree nuts, sesame seed, mustard seed, cows' milk, eggs, fish, shellfish, soy, wheat, celery, lupin, molluscs and sulphites)[31] are usually the first foods to be avoided during a multiple food exclusion diet. The number of foods avoided and combination of foods will depend on the symptoms. This often reflects clinical practices rather than research data. In addition to these, pork, bacon, liver and offal, maize/corn, citrus fruits, berries, potatoes, tomatoes, onions, herbs and spices, chocolate, food colours and food preservatives may also be excluded.

- Few Foods diet also referred to as an oligoallergenic diet

A few foods diet includes only a few foods that 1) are known to rarely cause allergic symptoms in the population and 2) are not regularly eaten by the patient. It generally includes 2 meats (lamb and turkey), 2 starches (rice and corn), 2 fruits (pears and nectarines), 2 vegetables (sweet potato and butternut squash) and only water as a drink [32]. Sometimes a less restrictive few foods diet may be used, particularly if it will improve patient compliance.

- Elemental and protein hydrolysate formula diets

Amino-acid based formulae are used in infants and young children and elemental (sip) feeds in older children and adults in the diagnosis of a range of diseases [32].

It is important that patients should be well-educated before embarking on a diagnostic test diet [17]:

For all types of exclusion diets, patients need to be clearly educated regarding avoidance of

food(s), label reading, suitable alternatives and following a healthy balanced diet, despite the dietary restrictions. Dietetic expertise is of particular importance when dealing with children's diets. As well as foods and beverages, non-dietary sources of substances that can provoke reactions may also need to be excluded, but this is very individual and may not always be necessary.

Oral provocation tests/Food challenges

If symptoms improve, dietary exclusion needs to be followed by a food challenge in hospital or at home.

Generally speaking, all patients with either a history of immediate symptoms or a positive SPT/specific IgE tests, should be invited to a controlled setting (hospital) for a food challenge. All other patients could either undergo a food challenge at home depending on the facilities and staff available but only if there is no risk of the patient developing immediate severe symptoms [17;33].

Some clinicians argue that a food challenge is risky and perhaps should not be performed. However, Ziljstra et al.[34] showed that parents of children with suspected peanut or hazelnut allergy show high levels of anxiety about a food-allergic reaction. After DBPCFC, the anxiety was significantly lower, even in the group with a positive outcome.
We have obtained ethical permission in December 2009 from the Southampton and South West Hampshire Research Ethics Committee (B) for validating the recipes that will be used in the double blind placebo controlled food challenges (DBPCFC).

Management of FHS

Once diagnosed, children need to be instructed on a number of issues to avoid symptoms or even fatalities. Avoidance of the offending food or foods, whilst providing a nutritionally complete diet, is currently the only way to prevent reactions[35]. This can be difficult to achieve and has socioeconomic and quality-of-life consequences for families[36]. There are no clear guidance documents or protocols for the management of food hypersensitivity as a number of factors will determine the management strategy for each child such as the food(s) involved, mechanisms involved natural history of the particular food allergy and the characteristics of the food protein involved. Adrenaline auto-injectors may be prescribed to some patients suffering from IgE mediated food allergy. Healthcare professionals should demonstrate the correct administration of these and review the technique with families on an ongoing basis. However, there is no evidence at present to indicate what advice patients

would prefer, how well patients adhere to our advice and to what extent a dietary consultation affects health related quality of life. Most importantly, dietary advice given differs from centre to centre, with no standardised/validated dietary education tools available.

Health related quality of life (HRQoL)

Although some progress has been made on establishing prevalence figures for FHS, the effect of FHS (either diagnosed or perceived) in quality of life (QoL) has only recently been studied and there is still a need for more in depth knowledge. This will enable clinicians to better understand patients, leading to better support. QoL is a broad concept that pertains to an individual's overall satisfaction with their life[37] . The component of overall quality of life that pertains to an individual's health is called HRQoL and is defined as the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient [37].
The few studies measuring HRQL have found significantly reduced HRQL in patients with food allergy and their families [38;39]. They found that several areas of QoL are affected, such as family and social activities, emotional issues and family economy, basically all aspects of family life. Food-hypersensitive children are to a large extent also limited in performing social activities without adult supervision. There is currently only one validated HRQoL questionnaire specific for food allergy in children aged 0 -12 available[40]. However, no study has previously looked at the affect of perceived FHS vs. truly diagnosed and managed FHS on the HRQoL.

It is known that allergic conditions such as food allergies, eczema and asthma co exist[41;42]. However, there is no clear understanding if lung function per se (with or without a diagnosis of asthma) may play a role or is associated with food allergy.

There is compelling evidence that along with environmental factors genetics plays an important role in food allergy[42]. However, the specific genetic loci modulating risk for food allergy need to be identified. The causes of food allergy are still unknown, although there is a strong association between genetic susceptibility to food allergy and IgE mediated allergy, no particular gene has been identified. Currently we are following up a cohort of children at 9 years who have been followed up since infancy and this provides us with a unique opportunity to study genetics and gene-environment interactions involved in food allergy.

Recall bias

Many epidemiological studies are guilty of recall bias, the effect of this is however unclear, particularly in the field of food allergy. Despite suspecting that this recall bias may have an effect on the reliability of the data, it is still used to inform national policies in the UK. For example, Hourihane et al.[43] determined that peanut allergy reflects increased consumption of peanut by pregnant and nursing mothers - even though some of these mothers completed the questionnaires 16-18 years after the children were born. This paper was however, the main source of information on which the COT report of 1998[44] regarding peanut avoidance during pregnancy and lactation was based. Ten years later, the COT withdrew this advice based on the prospective data from the Isle of Wight [45]. Another such example is the work from St. Mary's Hospital, London[46], showing that environmental exposure coupled with low oral intake of peanut, could be the precursor for peanut allergy. As the Food Frequency Questionnaire (FFQ) used in this study was only validated for recall accuracy over a 2-year period, their questionnaire could only be used in a subgroup of children who were younger than two years at the start of the study[46] - even though some of the children were 4 years old at the time the FFQs were completed. This piece of work has led to the funding of the LEAP (www.leapstudy.co.uk) and the EAT study (www.eatstudy.co.uk), funded by the National Institute of Health in the USA and the Food Standards Agency in the UK. We have prospectively obtained information from the parents on the FAIR study during the child's first 3 years of life and we are now in the ideal position to test the effect of recall 10 years later, with minimum effort from the parents. This information can help to inform better research designs in future, preventing unnecessary changes in national policies.

In summary, it is important to have access to national data on the prevalence and incidence of FHS in order to plan the health care of the allergic community. Reliable data can only be obtained by using a diagnostic work-up which includes careful history taking, skin prick tests or specific IgE tests where indicated, dietary exclusion and finally and oral food challenge. Once diagnosed, patients should be advised regarding appropriate management strategies. In terms of management of those suffering from FHS or perceiving them to suffer from FHS, it is important to understand the impact on their quality of life.

Aims and objectives

Aim:

To determine the prevalence and natural history of FHS in children age 8-10 years referred to as the FAIR cohort and it's effect on quality of life.

Objectives

1. To determine health related quality of life in children with perceived and diagnosed FHS.
2. To determine sensitisation status to 7 major food allergens
3. To determine the sensitisation status to 3 aero-allergens
4. To determine the number of foods reported a cause adverse food reactions and which foods these included.
5. To determine the number of adverse food reactions reported and which symptoms these included.
6. To determine the number of children with diagnosed FHS by means of a food challenge.
7. To determine the number of children with diagnosed FHS on the basis of a good clinical history and skin prick test result.
8. Determine the incidence of sensitisation to foods and aero-allergens and diagnosed FHS by comparing the data from the FAIR children at the age of 3 years to the data obtained from this follow-up at 8-10 years.
9. To determine sensitisation to particular food and aero-allergen proteins and it's role in development and remission of allergies.
10. To determine patients needs regarding dietary consultations, how well patients adhere to dietary advice and if a dietary consultation affects health related quality of life.
11. To determine the spirometry/lung volumes to assess the co-relation of the symptoms, sensitisation and lung volumes with diagnosed food allergy.
12. To determine genetic associations with food allergy in future, depending on funding
13. To determine the effect of 9-10 year recall bias on information provided regarding feeding the infant (now 9-10 years old)

Methods

Study description

Study design

Whole population birth cohort study

Study site

The David Hide Asthma and Allergy Research Centre (DHAARC) on the Isle of Wight and 46 primary schools on the Isle of Wight.

Study population

All children (via their parents) who participated in the FAIR study will be asked to participate in this follow up.

Main exposures and/or confounders and/or outcomes to be measured

Sensitisation to a panel of food and aero-allergens as well as any other identified by history. Diagnosed FHS by means of food challenge to any food allergen, substance or additive.

Selection of study population

Inclusion criteria

All children recruited as part of the FAIR birth cohort.

Exclusion criteria

None

Sampling

All 969 children (via their parents) who participated in the FAIR study will be asked to participate in this follow up.

Study procedures

Procedures at enrolment

We are aiming to follow-up these children based on the methods used for recruitment of the school cohorts in the FAIR study [47;48].

Questionnaire at home

We have access to the details and addresses of the children as obtained during the FAIR study and their current addresses will be verified on the NHS care records service. In order to recruit the children for this follow-up, we will post the letter of invitation (appendix 1), study information for parents (appendix 2 and 3), study information for children with a weblink for a video (appendix 4), consent form (appendix 5 and 6), assent form (appendix 7 and 8), a self-administered questionnaire enquiring regarding possible adverse reactions following food ingestion and using a validated health related quality of life questionnaire (appendix 9) and a self addressed envelope to the parents/guardians of all eligible pupils. They will be asked to send their completed questionnaires and consent forms directly to the Allergy Centre. A letter with the date of the school visit will be sent to all of those indicating that they are happy to undergo the skin prick testing at the school or allergy centre (appendix 10).

After approximately two weeks reminders (appendix 11) will be sent, followed by a second reminder letter when necessary (appendix 31).

For parents and children who indicate (appendix 5 and appendix 7) that they would like to undergo SPT at the school, a letter with an appointment at the school (appendix 10) will be sent. In case of a positive SPT, a letter with an appointment for a blood test will be sent (appendix 13), only if the parents indicated that they are happy to receive an appointment. Consent and assent for the blood test will be taken on the day (appendix 35 and 36).

For parents and children who indicate (appendix 5 and appendix 7) that they would rather come to the Allergy Centre for skin prick tests and possible blood tests, a letter with an appointment at the Allergy Centre will be sent (appendix 37). A consent (appendix 38) and assent form (appendix 39) for weight, height, SPT and blood test will be signed on the day.

Following on from this, for those who indicated that they are happy for the child to undergo a blood test, a further information sheet with information regarding the blood test, lung function test, saliva sample and feeding questionnaire will be sent (appendix 40 (adult) and appendix 41 (child)), together with a reply slip indicating that they are happy to come for an appointment OR happy to be phoned to discuss the study further. On return of these, an appointment letter (appendix 42) will be sent or the parents will be contacted. A consent (appendix 43) and assent (appendix 44) form will be signed on the day. Parents who consent to completing the feeding questionnaire (appendix 45), will be asked to do so during their visit to the Allergy Centre.

A separate parent information sheet (appendix 3), consent form, letter with appointment (appendix 6 and 32) and assent form (appendix 8), but the same children's video (appendix 4) will be sent to participants living on the mainland. A separate consent (appendix 33) and assent form (appendix 34) will be signed on the day if they choose to come the Isle of Wight for weight, height, SPT and blood tests. Those that indicated they are happy to be contacted by the research staff about a possible blood test and further parts of the study, will be phoned by the research team, who will explain the amendment to the study and send appendix 40 and 41 (as above) in the post together with a reply slip indicating if they are happy to come for an appointment OR happy to be phoned to discuss this. On return of these an appointment letter (appendix 42) will be sent or the parents will be contacted. From our records so far, we know that this include only 11 study participants. A consent (appendix 43) and assent (appendix 44) form will be signed on the day. Parents who consent to

completing the feeding questionnaire (appendix 45), will be asked to do so during their visit to the Allergy Centre.

School visit

The Local Education Authority, as well as the head teacher and governors of all the primary schools on the Isle of Wight will be approached by Professor Dean regarding participation in this study. Upon agreement, Dr. Venter will visit each of the schools and discuss the logistics of the visits to the school with the head teacher. A letter from the head teacher will be included in the information sent to the parents (appendix 12). During each of the school visits, children will be weighed and height measured by the dietitian, undergo a skin prick test by the allergy nurse to the three aero-allergens tested for in the FAIR study (house dust mite *dermatophagoides pteronyssinus*, cat, grass) and seven food allergens (milk, egg, wheat, cod, peanut, lupin and sesame) using the standard NHS SPT forms. SPTs will be conducted with commercial extracts of standard food and aeroallergens (Soluprick SQ allergens-ALK Allergologisk Laboratorium A/S, Horsholm, Denmark). In the case of fruits and vegetables a prick-to-prick test will be offered to the fresh product (all prick-to-prick testing will be performed at the Allergy Centre). Histamine and physiological saline will be used as positive and negative controls respectively. An experienced allergy nurse will perform all the SPTs. The parents and children will be given the option of attending the Allergy Centre for the skin test sessions should they wish to do so.

In case of sensitisation to one of the aero-allergens the appropriate standard NHS advice will be provided to the children. The results will be communicated to the parents who will be given an opportunity to discuss concerns if they wish to do so.

Visit to the Allergy Centre for blood test, spirometry and saliva sample

The bloods will be taken from the children by an experienced research fellow. Prior to the bloods being taken a local anaesthetic cream will be applied on their skin. For the spirometry, the Koko test will be used and for the saliva sample, children will be asked to produce either a sample in a saliva pot or a buccal swab will be performed.

Dietetic Consultation

Two members of the research team will screen the questionnaires regarding reported current problems with food and those who reported an adverse reaction to a food will be contacted. Children with an appropriate history and their parents will be questioned in detail to ascertain which foods were implicated in producing the symptoms.

In case of sensitisation to one of the food allergens, any reported problems to foods, or known allergies to foods the, dietitian (Dr. Venter) will contact the family by phone to book a dietary consultation.

The consultation with the dietititan will include:

- Taking a diet history using the standard NHS diet record cards
- Dietary advice regarding avoidance and suitable food substitutes using the standard NHS dietary information sheets
- Children will be asked to avoid the food for a period of 2 – 6 weeks depending on individual circumstances. If the symptoms improve or clear up, the child will be invited for a food challenge. If the symptoms do not improve or clear up an alternative diet may be instructed or another cause for the symptoms may be sought.

Focus groups

There are no available data regarding patient's needs regarding the safe and effective management of food allergies and intolerances, their adherence to dietary avoidance advice and the effect of a dietary consultation on their quality of life. Focus group discussions will be conducted with parents following the dietary consultation to enquire about their information needs. The letter of invitation (appendix 14) and parental information sheet (appendix 15) will be handed to the parents at the end of the dietary consultation. Parents will be invited to take part in the focus group discussions (FGD) and the purpose and procedures will be explained. A separate consent form for this part of the study will be provided (appendix 16).

The number of focus groups conducted will depend on when data saturation is reached i.e. recruitment will cease when there is no novel data. Focus group discussion will be held at the Quay Arts centre on the Isle Wight, which is considered to a neutral environment for both the parents and the researchers.

A general discussion guide will be prepared prior to the FGDs.

Key point for discussion during the focus groups will include (appendix 17):

1. Knowledge of managing food allergy:
    - How do you manage your child's food allergy?
    - Are you clear about which foods should be avoided?
    - Are you clear about any emergency medicine that you may need to use?

- Which questions about foods do you child regularly ask you?
- Do you feel able to answer these?
- Where did you find out the information to answer these questions?
- Are you concerned about any reactions/symptoms that your child may develop?
- Why?
- What is your main concern?
- Are you concerned about your child not outgrowing the food allergy/intolerance
- Why? What information would you like about this?

2. Managing food avoidance:

a. Reading labels:

- What are you looking for when you read food labels?
- How easy do you find it to read food labels?
- If not easy, why not?
- If easy, why is it easy?
- What could be improved?
- Where did you find out about reading food labels?

b. Eating outside of home:

- What is your experience of eating away from home e.g. in restaurants or at children's' parties?
- Do you experience any problems when eating away from home e.g. in restaurants or children's parties? If so, what?
- Do you find sorting out the school dinners/lunch boxes very difficult? If so, why? What does your child think of their lunch box?

c. Going on holiday:

- Do you experience any problems when going on holiday?
- What kind of problems do you experience? What would make it easier?

3. Effect of managing food avoidance:

- What is the most difficult aspect of adhering to this food avoidance regime?
- What could be done to make this easier? Are there any benefits to managing food avoidance?
- Do you have any problems or difficulties at home? Can you describe these?

4. Impact of dietitian's advice:

- What advice did you receive on managing food avoidance?
- Did you find the advice from the dietitian helpful and if so, in which way?
- Is there anything else you would have liked to have known about?
- Did the advice from the dietitian affect your quality of life in any way? If so, how?
- Can you give me an example?

But the FGD will develop into a participant led discussion towards the end of the FGD. Dr. Heather MacKenzie, known in the area of health related quality of life paediatric food allergy research, will lead the FGD. Dr. MacKenzie is ideally suited for the role of facilitator as she in not a dietitian and does not have expert opinions on dietary food avoidance.

The focus group will start with an introduction of the facilitator and an invitation to the participants to introduce them. The purpose of the FGD will be explained, what information is needed and how this information will be used. The facilitator will steer the topics against the time allowed, although discussion time will be allowed for topics identified by the focus group participants. The focus groups will be audio-recorded and transcribed verbatim. In addition, the observer (Jane Grundy – allergy nurse) will keep a record of the content of the discussion as well as emotional reactions and group interaction.

Based on the information obtained from the focus group discussions, future dietary advice provided to allergic individuals and their parents will be tailored. Individuals who identify a particular need or gap in their knowledge will be invited for a further dietary consultation.

Food challenges:

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

- Those with a positive SPT that never knowingly had the food or large amounts of the food previously.
- Those who indicated a previous adverse reaction to foods (regardless of their SPT data) who improved on an exclusion diet
- Those children with a previously confirmed food allergies and intolerances who are in need of a follow-up challenge to determine if they have developed a tolerance

Children will be excluded from food challenges where there is a clear history of anaphylaxis to a specific food; when suffering from ongoing disease such as seasonal allergy during the season when they are affected; if they are taking medication that could influence the challenge result or patients who are considered unsuitable for the challenge on the day of the challenge e.g. children with a temperature, flare-up of eczema etc. A food challenge information sheet will be given and discussed with each participant prior to the food challenge when they see the dietitian for their follow-up dietary appointment (appendix 18 - 25). The dietian will discuss a suitable date for the challenge and an appointment will be sent

using the standard NHS appointment card. We will either perform open or double blind placebo controlled food challenges based on the symptoms of the child and the food involved. On the day of the challenge, consent and assent will be taken (appendix 26 and 27). Following consent a food challenge will be performed. When IgE mediated reactions were suspected either by SPT result or history, challenges will be performed in a hospital setting.

Challenges will be performed at home when the history clearly indicated delayed development of symptoms and the SPT was negative. Some of these home challenges may commence at hospital and continue at home. Reactions during home challenges will recorded by parents on food and symptom diaries (appendix 28) and verified by the research team. Food challenges will be performed based on the food challenge protocols (appendix 29 – *sample food challenge protocol*) previously used for the FAIR study[49] and the recipes validated during the validation study (part 1 of this fellowship).

Those with a negative response to the food challenges will be recommended to eat the food normally. Those with a positive challenge will be given dietary advice on continued avoidance of the food using standard NHS diet sheets. All information obtained during history taking and during the food challenges will be recorded on the FAIR study challenge forms for data entry and analysis (appendix 30). Parents will be phoned one month after the challenge by the author to enquire whether they have introduced the food into the child's diet in case of a negative challenge.

Newsletter

A newsletter will be send to the parents and children every year of the study to keep them up to date with the study developments.

Measurement of outcomes

Reported food related problems

The reported prevalence of adverse reactions to foods and rates of foods avoided will be established using a questionnaire completed by the parent and children. They will also be asked to describe the symptoms that they experienced.

Focus group discussions

Focus group discussions

- The focus group discussions will identify client specific needs in terms of barriers and enablers in order to successfully manage their FHS and a description including contextual information.

Skin prick test results

The wheal developing after the skin prick test will be measured after being transferred to paper from the skin with translucent tape. Measurement will be undertaken in a standard fashion, measuring the largest wheal diameter and the diameter orthogonal to it. The mean wheal diameter will then be calculated. Results will be expressed as positive if the mean diameter was 3 mm or more in presence of a negative control and a positive histamine reaction after 12-15 minutes.

Specific IgE results

Specific IgE to any of the food proteins studied will be considered positive if the levels are >0.35 kU_A/L.

Spirometry

We will follow the American Thoracic Society guidelines to ensure spirometry validity and reproducibility. As recommended, the highest of three FEV_1 measurements within 5% of each other will be used. The Koko system will be used. To perform this test the subject will be required to be free from respiratory infection for 14 days, not taken short acting β_2-agonist medication for 6 hours, long acting β_2-agonist medication for 12 hours and abstained from caffeine intake for at least 4 hours. We will record forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), mid expiratory flow (MEF), peak expiratory flow (PEF). Percent predicted for age, height, sex and ethnic origin will be calculated for the above data and forced expiratory ratio (FEV_1/FVC).

Saliva

Saliva samples will be taken and stored, in case the participants decline their bloods to be taken. Analysis looking for genetic associations with food allergy will be conducted in the future, pending on funding.

Food challenge outcome

Challenges are considered positive when the patient experiences symptoms in line with the history during the food challenge or when symptoms related to FHS is experienced during

the food challenge and verified by the supervising clinician. Challenges are considered negative when no symptoms are experienced during the food challenge; symptoms are experienced during the placebo phase of a DBPCFC, or when symptoms are reported during the food challenge that cannot be verified by the supervising clinician. When symptoms are experienced during both the active and placebo phase of a DBPCFC, the challenge needs to be repeated. The supervising clinician will make the final decision based on clinical discretion and the safety of the patient.

Sample size

All 969 children (via their parents) who participated in the FAIR study will be asked to participate in this follow up.

Data management

Data will be anonymised and, when not in use, secured in locked cabinets or password protected in the case of electronic records.

Proposed analysis

All data will be double entered by different operators on SPSS (SPSS Inc, Chicago, USA). Frequency tables will be produced from which prevalence rates will be computed for reported symptoms, foods involved, sensitisation status, and diagnosed FHS to each allergen together with 95% confidence intervals. Prevalence rates in this follow-up (8-10 years) will be compared to the same population at 3 years of age using McNemar's test.

Feeding questionnaires

Data obtained during the first year of life will be transferred on to appendix 45 for each study participant by the MSc student and checked by Dr. Carina Venter. This questionnaire (A) will be compared against the data in the questionnaire (B) completed by the parents during their visit to the Allergy Centre. The information provided by the two questionnaire will be compared by the MSc student with guidance from the statistical team at the university with paired T-tests.

Health related quality of life as measured by questionnaire

HRQoL will be compared between children with suspected FHS and those with confirmed FHS using the total aggregated score (30 items) from the validated questionnaire developed by DunnGalvin et al[40].

In view of the large anticipated sample, we plan to compare subgroups using analysis of variance, adjusting for gender (a potential confounder).

Analysis of focus groups

All focus groups will be audio-recorded using a digital voice recorder, and transcribed verbatim. The focus group facilitator will also take notes of any salient topics after the FGD, which will be used to aid analysis. Analysis will be facilitated using MaxQDA, a programme designed to aid qualitative data analysis. The data will be analysed using a thematic content analysis approach[50]. This approach involves fourteen steps; but generally speaking, the method involves a process of becoming immersed in the data, open coding, and identification and checking of themes.

Ethical considerations

Confidentiality

Data will be anonymised and the research will adhere to local and national guidelines and legislation and the articles within the Declaration of Helsinki. The project will satisfy the requirements of a Local Research Ethics Committee.

Informed consent

Informed consent will be taken from the parents regarding study participation and undergoing skin prick testing and specific IgE testing(appendix 5-8).Additional informed consent will be sought for food challenges (appendix 27, 26) and focus group participation (appendix 17). Consent will be obtained for each food challenge will be taken seperately. Consent will be taken only after ensuring that the research participant/parents are clear about the purpose and nature of the research, what the research involves, and that there are no risks involved, that they are free to decline participation and change their mind after consent was given. Participants will be allowed two weeks to make a decision about participation and undergoing SPT or food challenges.

Consent will be taken to store the samples collected for further tests related to allergy to be done in future.

Logistics

Distribution of responsibilities

The study co-ordinator (Mrs. Gill Glasbey) will oversee the running of the project and the administration.

The research nurse (Jane Grundy) will perform the skin prick tests and assist with the medical supervision of the food challenges.

The clinician (research fellow) will oversee and take the medical responsibility of the food challenges along side the primary investigator (allergy dietitian).

The clinical research fellow will be responsible for taking the bloods and performing the spirometry testing.

A Post Doctorate researcher who obtained her PhD into HRQoL (Dr. Heather Mackenzie) will carry out the focus group discussions. Mrs Jane Grundy will act as the observer during the focus group discussions.
Prof SH Arshad and Dr. Graham Roberts will take overall responsibility for added measures such as the spirometry and blood/saliva samples and analysis.

Resources

The study has been funded by the National Institute of Health Research.

Timetable

<table>
<tr><td colspan="12">2010</td><td colspan="12">2011</td></tr>
<tr><td>J</td><td>F</td><td>M</td><td>A</td><td>M</td><td>J</td><td>J</td><td>A</td><td>S</td><td>O</td><td>N</td><td>D</td><td>J</td><td>F</td><td>M</td><td>A</td><td>M</td><td>J</td><td>J</td><td>A</td><td>S</td><td>O</td><td>N</td><td>D</td></tr>
<tr><td colspan="3">Ethics</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td colspan="15">School visits and SPT</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td colspan="13">Food challenges, follow up clinics, dietetic consultations</td><td></td><td></td><td colspan="6"><u>Blood tests, saliva</u> samples and feeding questionnaires</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="8">Focus group discussions</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="14">Data analysis and dissemination, but this may continue till the end of the Fellowship. Which is 31 March 2014</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>

Dissemination and Outcome

Dissemination of this research will primarily target the participants and their parents. Additionally, abstracts for presentations will be prepared for submission at appropriate national and international meetings, and results will be submitted to most relevant peer-reviewed academic journals.

References

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Appendix 8H

The David Hide Asthma & Allergy Research Centre
St. Mary's Hospital
Newport
Isle of Wight
PO30 5TP

Direct Tel. No. (01983) 534178

Food Allergy and Intolerance Research (FAIR) Study
Information Sheet to Parents/Guardians of children for Blood test and Lung function test

Dear Parent(s)/Guardian(s)

We would like to thank you for your continued involvement and support in our study. The causes of food allergy and its relationship to asthma and other allergic conditions, have not been clearly understood and more research looking into the possible causes and also the factors to help in diagnosis and better management of these conditions are required.

Why are we contacting you?

Your child recently underwent a skin prick test at their school or at the Allergy Centre. As you might remember, we initially informed you that blood tests will be done only if your child's skin prick test is positive for food allergens and you and your child have indicated that you would consider your child undergoing a blood test. We now invite you and your child to have a blood test or collection of saliva irrespective of the skin prick test result together with a lung function test.

You may also remember when your child was a baby, we asked questions about how you fed them, when you started weaning and which solid foods you were giving your baby. We now would like to ask you the same questions to see how our memory of events is affected after 10 years.

.**What is the purpose of this part of the study?**

This study will help us to understand why children develop allergic problems and what we can do to prevent them. We are also continuing our work to understand how our genes are involved in the development of allergic conditions. Certain genes have been linked with the development of asthma and food allergies. We need to undertake further research work to understand this link. If we are to maximise our chance of discovering how our genes are involved in the development of asthma and other allergic conditions, we need to look at the genes of as many of the group as possible. We can do this by taking a small amount of blood or alternatively we could collect a small amount of saliva from your child or swab the inside of their mouth. Initially we did not think we could have the facility for the above tests to be done for all children, but we have recently appointed a new doctor at the Allergy Centre, who will help us with the study.

Many epidemiological studies are based on information obtained years after the event occurred such as how babies were fed and which foods were given to them. With the data we obtained from you when your child was a baby, we are now in an ideal position to compare data collected at two different time points and look at how reliable and accurate this information is after a long period of time.

Does my child have to have a blood test and lung function test done and provide a saliva sample?

Your child does not have to have any tests done or provide us with a saliva sample. It is entirely up to you to decide. If you decide to have any of the tests done, you will have to sign the consent form on the day and you are welcome to change your mind at any point. Please sign the reply slip and send back to us in the prepaid envelope.

Do I have to complete the questionnaire?

You do not have to complete the questionnaire, but we will give you time to complete the questionnaire during your visit to the centre.

What happens next?

Depending on your choice, once we have your reply slip we will send you an appointment at the David Hide Asthma & Allergy Centre (St Mary`s Hospital, Newport, PO30 5TG) or phone you

Blood test: This will be done by a trained, experienced nurse or medical doctor. Anaesthetic cream (EMLA) will be applied prior to taking blood to numb the skin and 10 to 20 mls of blood will be taken.

Lung function test: This is to measure your child's lung volumes and will take roughly 10 minutes. Your child will be asked to blow through a tube connected to the computer and guided by animated pictures on the screen (blowing down the piggy's houses). No medications will be given and no complications are expected for your child.

Saliva sample – If you are not happy to allow us to take some blood, we will ask for either a saliva sample (we will ask you to spit into a small cup) or buccal swab (the inside of your cheek is gently swabbed).

Questionnaire – We will ask you to complete this during your visit to the centre.

Any preparation needed?

For the lung function test: Your child will have to avoid drinking or eating any caffeine (eg coffee, tea, coke, chocolate) for 4 hours; (if you take asthma medication please do not use your reliever inhaler (eg ventolin, salbutamol, terbutaline, bricanyl) for 6 hours; long acting inhaler (eg salmeterol, serevent, seretide, eformoterol, oxis) for 12 hours; and antihistamines for 72 hours. If you have had a respiratory infection such as colds and flu in the previous 2 weeks or are taking oral steroids we will rebook your visit at a convenient time for you).

What are the benefits of taking part?
Most children participating in the study will be healthy volunteers. Some of the children may have asthma, eczema and other allergies. The study does not include any treatment for any condition. However, the information from this study will help us to better care for children with possible allergies and develop strategies for prevention.

What are the possible disadvantages and risks of taking part?
There are no disadvantages or risks in taking part in this study. The only issue is a possible temporary minor discomfort some children may experience with blood tests. The doctor and nurse present during the test will deal with any problems immediately. We will not be asking for any more of your time by completing the questionnaire as you can answer the questions while you are at the centre.

What if there is a problem?

If you have any questions or concerns, please contact Dr. Vereesh Patil, Dr Carina Venter, Mrs Jane Grundy or Mrs Gill Glasbey at The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight. Telephone: 01983 534178. Email: carina.venter@port.ac.uk. If you still have questions or concerns, you can contact Alexandra Punter (Lead for Research and Development, St Mary's Hospital, Newport, Isle of Wight, PO30 5TG; email alex.punter@iow.nhs.uk) or Prof. Tara Dean, Associate Dean Research, University of Portsmouth, 2 King Richard 1st Road, Portsmouth, PO2 1FR; email: tara.dean@port.ac.uk).

In the highly unlikely event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation against St Mary's Hospital but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my child get paid for his/her participation?

Your child will receive a gift voucher (£10) for his/her participation in the study, and we will reimburse any travel expenses incurred.

What is the duration of this part of the study?

We would expect the whole appointment including the blood test, lung function test and providing a saliva sample to take no longer than 1-2 hours. The questionnaire will take 5 minutes to complete.

Nothing else will be required of you.

Will my child's taking part in the study be kept confidential?

Yes. All the information about your child's participation in this study will be kept confidential. Only the study personnel will have access to your child's personal details. The data we collect from your child will not be labelled with their personal details and will be stored securely. Your child will not be individually identified in any reports or publications resulting from the study. We

will keep your child's data on file for use in future studies approved by the Research Ethics Committee. Data from the questionnaire will be anonymous and only used for publications related to the study.

What will happen to any samples I give?

The samples will not be labelled with your child's name or address so that the researchers analysing them will not know that the sample belongs to you. With your permission, we would like to store some blood for use in further studies into asthma and allergic disease. We will only use these stored samples for studies reviewed and approved by the Local Research Ethics Committee. If we collect saliva or a buccal swab from you, genetic material would be collected from these and stored for use in further studies into allergic disease.

We are looking at which of our genes are involved in the development of asthma and other allergic diseases. For this work we can use blood, saliva or buccal swab samples. The results we obtain will help us to understand why some people develop asthma and allergies. The results will not directly help you and will not have any individual significance to you so we will not be able to give you or your GP, your individual results.

Involvement of the General Practitioner-

We will send you a standard letter indicating your blood results. On your request, we will copy this letter to your GP and put in your NHS notes.

What will happen to the results of the research study?

We aim to publish the results of the study in medical journals so that other doctors and researchers can use our data. We will send you regular updates of the study results via a newsletter and website http://www.iow.nhs.uk/index.asp?record=1436

Who is organising and funding the research?

The researchers at The David Hide Asthma and Allergy Research Centre and the University of Portsmouth are organising and carrying out this study. The study is being supported by the National Institute of Health Research (NIHR), who has awarded Dr. Venter a five year post doctoral fellowship.

Who has reviewed the study?

The study has been reviewed by five international experts in the field of food allergy as well as the research panel of the NIHR. This study was given a favourable ethical opinion for conduct in the NHS by the Southampton and South West Hampshire Research Ethics Committee (B).

How long do I have to decide whether my child should take part?

Your decision to participate in this study is entirely voluntary. You should take as much time as you need.

Thank you for taking time to read this information sheet.

REPLY SLIP:

Food Allergy & Intolerance Research (FAIR) Study

Child's Name: …… Child's Date of Birth: ……

I am happy to have an appointment at the Allergy Centre sent to me for blood test/lung function test/saliva sample and questionnaire

OR

I would like to be contacted for further information

Tel no: …… Mobile No. ……

Please state what time you are available to be contacted and return this slip in the reply paid enveloped provided

	Hours between 9.00 am – 7.00 pm
Monday	
Tuesday	
Wednesday	
Thursday	
Friday	

Appendix 8I

The David Hide Asthma & Allergy Research Centre
St. Mary's Hospital
Newport
Isle of Wight
PO30 5TP

Direct Tel. No. (01983) 534178

Food Allergy and Intolerance Research (FAIR) Study
Child Information sheet

Thanks for your participation in the study so far and now we would like to invite you for a breathing test and blood test or saliva sample. The exact reason why someone develops asthma and food allergies is not clear and we need to understand more.

Do I have to have the tests?

No, it is entirely up to you and your parents if you want to have these done.

What will happen to me when I do the tests?

Breathing test: You will be asked to blow through a tube connected to a computer and try and blow down the piggy`s houses. You will be asked to take a big breath in and then to blow as hard as you would to blow birthday candles.

Blood sample: We will apply a "magic"* numbing cream to your arm, so that it is more comfortable, before we take the blood sample

Saliva/Buccal sample: If you are not happy to allow us to take some blood, we will ask for either a saliva sample (we will ask you to spit into a small cup) or buccal swab (the inside of your cheek is gently swabbed).

Questionnaire: We will be asking your parents to complete a questionnaire on how you were fed when you were a baby. This will be done during your visit to the centre. We have already asked your parents these questions, but would like to see how well parents remember 10 years after you were born.

Did anyone else check the study is OK to do?

Before any research is allowed to happen, it has to be checked by a group of people called a Research Ethics Committee. They make sure that the research is fair. This

project has been checked by the Southampton and South West Hampshire Research Ethics Committee (B).

Will doing tests help me?

No – but it may help us in future to find out why children become allergic to foods and how to find out if they are allergic or not.

What happens when the research stops?

The researchers, Carina and Jane, will be able to tell doctors, nurses and dietitians about how many children do have food allergies or intolerances, and how to find out which ones are allergic.

Will the test upset me or what if something goes wrong during the tests?

Our allergy nurse, Jane, and our doctor, have lots of experience in looking after children and will be able to help out in case of any problems.

Will anyone else know I'm doing this?

No – we will not tell anyone that you are involved, unless you want us to.

What if I don't want to do the tests anymore?

If at any time you don't want to do the tests any more, just tell your parents, the doctor, Carina or Jane. They will not be cross with you.

Thank you for reading this – please talk it through with your parents. You are welcome to phone us if you think of any questions when you get home - Carina or Jane on 01983 534178.

Please discuss with your parents and if interested let us know.

* For the ethics committee: We are using the word "magic" as this is what they call the local anaesthetic cream on children's ward.

Appendix 8J

Letter with appointment for blood/lung function test

NHS
Isle of Wight
The David Hide Asthma & Allergy Research Centre
St. Mary's Hospital
Newport
Isle of Wight
PO30 5TG

Direct Tel. No. (01983) 534178

TD/GG

Dear Parent(s)/Guardian(s)

Food Allergy and Intolerance Research (FAIR) Study

Thank you very much for your help with the FAIR study.

We have now booked an appointment for (CHILD'S NAME) to undergo a blood test or give a saliva sample and lung function test at (PLACE and TIME). **You will be asked to complete a short questionnaire during your visit at the Allergy Centre.**

Thank you once again for you participation in the study. Please feel free to let us know if you or your child has decided not to participate in this part of the trial.

Yours sincerely
On behalf of the FAIR Study Team

Prof. Taraneh Dean
Deputy Director of The David Hide Asthma & Allergy Research Centre
Associate Dean (Research) University of Portsmouth

Food Allergy & Intolerance Research
FAIR

Version 2 **3 October 2011** **REC Ref No. 10/H0504/11**

Appendix 8K

NHS
Isle of Wight
The David Hide Asthma & Allergy Research Centre
St. Mary's Hospital
Newport
Isle of Wight
PO30 5TG

Direct Tel: (01983) 534178
Direct Fax: (01983) 534907

Food Allergy and Intolerance Research (FAIR) Study
Researchers involved: Carina Venter, Jane Grundy and Gill Glasbey
Blood Test and Lung Function Test

Please initial box

I confirm that I have read and understand the information sheet dated **(3 October 2011) (version 2)** for the above study. ☐

I have now had the opportunity to consider the information, regarding the blood tests and questionnaire, ask questions and have had these answered satisfactorily. ☐

I understand that my child's participation is voluntary and that my child is free to withdraw at any time without giving any reason, without her/his medical care or legal rights being affected. ☐

I understand that relevant sections of my child's medical notes and data collected during the study, may be looked at by individuals from the Isle of Wight NHS Primary Care Trust or from regulatory authorities where it is relevant to my child's taking part in this research. ☐

I give permission for these individuals to have access to his/her records. ☐

I understand that my GP will only be informed of my child's participation in the study if my child requires a food challenge or any other treatment. ☐

I consent to my child undergoing a blood test ☐

I do not want a blood sample to be collected but am happy for saliva sample to be taken ☐

I consent to my child to undergo a lung function test ☐

I am happy to complete the questionnaire about feeding my child as a baby ☐

I give permission for the blood/ saliva sample to be used for investigations of medical conditions relating to allergic diseases (eg food allergy, asthma, eczema, hay fever). ☐

I give permission for the sample to be used for genetic research aimed at understanding the genetic basis of allergic diseases (eg food allergy, asthma, eczema, hay fever). ☐

Appendix 8K

PTO

The undersigned certify that the Information Sheet has been read and understood by the parent/carer

_____	_____	_____
Parent/Guardian Name (in block letters)	Signature	Date

_____
Child's Name

_____	_____	_____
Investigator Name	Signature	Date

Appendix 8L

NHS
Isle of Wight
The David Hide Asthma & Allergy Research Centre
St. Mary's Hospital
Newport
Isle of Wight
PO30 5TG

Direct Tel: (01983) 534178
Direct Fax: (01983) 534907

Food Allergy and Intolerance Research (FAIR) Study

Researchers involved: Carina Venter and Jane Grundy

Please circle the answers you agree with or ask your parents to help you.

Have you read the information sheet?	Yes / No
Do you understand what we would like you to do today?	Yes / No
Have you asked all the questions you want about blood tests?	Yes / No
Did you understand all the answers you got?	Yes / No
Do you understand it's OK to stop taking part at any time?	Yes / No
Are you happy to have a lung function test?	Yes / No
Are you happy to have a blood test?	Yes / No
If you don't want blood sample taken, are you happy for saliva/buccal sample?	Yes / No
I am happy for my parents to fill in a questionnaire about how I was fed as a baby	Yes / No

If you do want to take part, you can write your name below or ask your parents to help you to do so.

Your name _____ Date _____

Researcher Name _____ Sign _____ Date _____

Thank you for your help.

Appendix 8M (A&B) **Feeding questionnaire** **Study No.** _____

A= completed by researchers from data obtained when FAIR children were infants (2001-2002)
B = completed by parents

FAIR Study

9/10 Year Questionnaire

Child's Name & Address				Date of questionnaire	/ /	
				Sex	Male[1]	Female[2]
	Height	ins	cms	Date	D/K	
	Weight	lbs oz	kgs	Date	D/K	
Child's date of birth:						
Mother's Name						
Telephone No.	E-mail address:					

1 Who completed questionnaire?

Mother[1]		Father[2]		Grandparent[3]		Guardian[4]		Other[5]		Who

2

Did you breast feed at all?	Yes[1]		No[2]

3 If Yes, how long did you breast feed for before adding in drinks [other than water], formulas or food)

Up to 1 month[1]		Up to 2 months[2]		Up to 3 months[3]		Up to 4 months[4]	
Up to 5 months[5]		Up to 6 months[6]		More than 6 months[7]		D/K[8]	

4 If you did breast feed, how long did you breast feed for at all (i.e. might have given some formula as well or started weaning)

Up to 1 month[1]		Up to 2 months[2]		Up to 3 months[3]		Up to 4 months[4]		Up to 5 months[5]	
Up to 6 months[6]		Up to 9 months[7]		Up to 12 months[8]		12 months or more[9]		D/K[10]	

5 Why did you stop breast feeding?

Reason	Code

6 Did your baby have a bottle of formula whilst in hospital?

Yes[1]		No[2]		D/K[3]		N/A[4]	

7 Did you give your baby any formula at any point (i.e. either as a Top up drink or as the baby's main drink

Yes[1]		No[2]	

8 If Yes, when did you first introduce formula?

Up to 1 month[1]		Up to 2 months[2]		Up to 3 months[3]		Up to 4 months[4]		Up to 5 months[5]	
Up to 6 months[6]		Up to 9 months[7]		Up to 12 months[8]		12 months or more[9]		D/K[10]	

9 If you did give your baby formula, which ones did you use?

Formula	code	Formula	code	D/K

10 When did you first give your baby solid foods?

	weeks	D/K	

Study No. _____

11 If not sure please could you estimate

	weeks

12 Which were the first 3 baby foods used?

Food	code	Food	code	Food	code	D/K

13 Did you use commercial baby food?

Yes[1]		No[2]	

14 At what age did you introduce the following foods into your child's diet?

Wheat containing foods (e.g. baby rusk, baby cereals, cereals, pasta, bread, cakes, biscuits)	<3 mths[1]		<6 mths[2]		<9 mths[3]		>9 mths[4]		D/K[5]	
Dairy foods (e.g. yoghurt, fromage frais, custard, ice cream, butter, margarine, cow's milk in food, cheese)	<3 mths[1]		<6 mths[2]		<9 mths[3]		>9 mths[4]		D/K[5]	
Fish	<3 mths[1]		<6 mths[2]		<9 mths[3]		>9 mths[4]		D/K[5]	
Whole egg	<3 mths[1]		<6 mths[2]		<9 mths[3]		>9 mths[4]		D/K[5]	
Soya	<3 mths[1]		<6 mths[2]		<9 mths[3]		>9 mths[4]		D/K[5]	
Tree nuts – almonds, brazil nuts, pecan nuts, hazel nuts, walnuts etc. (e.g. in chocolate, crunchy nut cornflakes, choc chip cookies, pesto sauce, vegetarian meals)	<3 mths[1]		<6 mths[2]		<9 mths[3]		>9 mths[4]		D/K[5]	
Peanuts (e.g. Bombay mix, peanut butter, peanut brittle, peanut cookies, Snickers bar, some vegetarian meals)	<3 mths[1]		<6 mths[2]		<9 mths[3]		>9 mths[4]		D/K[5]	

15 When your baby was 6 months old, were you consciously avoiding any food items from their diet?

Yes[1]		No[2]		D/K[3]	

16 If yes, what?

Food	code	Food	code

17 Did you avoid peanuts during your pregnancy?

Yes[1]		No[2]		Never eat[3]	

18 If yes for what reason?

Thank you for taking the time to complete this questionnaire.

Appendix 8N

r.•l:b1
National Research Ethics Service
NRES Committee South Central - Southampton B
Bristol REG Centre
Level 3 Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

Tel: 0117 3421384
Fax: 0117 3420445

24 November 2011

Dr Carina Venter
NIHR Post-Doctorate Research Fellow, University of Portsmouth
University of Portsmouth
School of Health Sciences and SW
2 King Richard 1st Road
Portsmouth
P021FR

Dear Dr Venter

Study title:	An in depth investigation of Food Hypersensitivity in 8-10 year old children: Its natural history, incidence after infancy and its impact on health related quality of life.
REC reference:	1O/H0504/11
Protocol number:	see letter
Amendment number:	3
Amendment date:	03 October 2011

The above amendment was reviewed on 16 November 2011 by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation:

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Questionnaire: Feeding questionnaire	1	03 October 2011
Letter of invitation to participant	2	03 October 2011
Participant Consent Form: Child: Assent Form for blood, spirometry, saliva and feeding questionnaire	2	03 October 2011
Participant Consent Form: Parent: for blood, spirometry, saliva and feeding questionnaire	2	03 October 2011
Participant Information Sheet: Child informatio sheet for blood, spirometry, saliva and feeding questionnaire	2	03 October 2011

Appendix 8N

This Research Ethics Committee is an advisory committee to the South Central Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within
the National Patient Safety Agency and Research Ethics Committees in England

Participant Information Sheet: parent Information Sheet -for blood, spirometry, saliva and feeding questionnaire	2	03 October 2011
Protocol	5 (FAIR follow-up)	03 October 2011
Notice of Substantial Amendment (non-CTIMPs)	3	03 October 2011
Covering Letter	SA.3	04 October 2011
(None)	3	03 October 2011

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

1O/H0504/11: Please quote this number on all correspondence

Yours sincerely

Dr Helen McCarthy
Chair

E-mail: scsha.swhrecb@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Mrs. Alexandra Punter, /OW NHS Primary Care Trust*

NRES Committee South Central - Southampton B

Attendance at Sub-Committee of the REC meeting on 16 November 2011

Narne.	*Profeisioh*	*Capacity*
Mrs Janet Brember	Pharmacist	Expert
Dr Giles MY Tan	Consultant Psychiatrist	Expert

Appendix 8O

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Ethics Letter

02-Apr-2013

Ethics Reference #: S12/01/002
Title: The impact of recall on the accuracy of dietary information

Dear Mrs Zoe VAN ZYL,

At a meeting of the Health Research Ethics Committee that was held on 20 March 2013, the progress report for the abovementioned project has been approved and the study has been granted an extension for a period of one year from this date.

Please remember to submit progress reports in good time for annual renewal in the standard HREC format.

Approval Date: 20 March 2013 Expiry Date: 20 March 2014

If you have any queries or need further help, please contact the REC Office 0219389207.

Sincerely,

REC Coordinator
Mertrude Davids
Health Research Ethics Committee 2