EAT
Enquiring About Tolerance

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A randomized controlled trial of early introduction of allergenic foods to induce tolerance in infants

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This report is dedicated to the memory of Sarah Reading and the tireless work of her father, David Reading, co-founder of the Anaphylaxis campaign.

The EAT Study Team hope this research might make a difference for all those who have been affected by food allergies.

EXECUTIVE SUMMARY

INTRODUCTION AND RATIONALE

The point prevalence of self-reported food allergy (FA) in a recent systematic review was around 6%,[1] and for particular foods, specifically peanut[2] and egg,[3] appears to be rising. The role of allergen consumption in early infancy, and its effects on the development of allergy or tolerance to food proteins remains uncertain.

The World Health Organization Global Strategy for Infant and Young Child Feeding,[4] supported by the UK Government,[5] recommends exclusive breastfeeding for the first six months with nutritious complementary foods introduced thereafter and continued breastfeeding up to the age of two years or beyond.[6] The UK Government infant feeding information leaflet for parents, "Weaning – starting solid food", adopts a more pragmatic target of ***around*** six months exclusive breastfeeding.[7] It also states that if a mother decides to introduce complementary foods before six months, there are some foods that should be avoided as they may cause allergies including: "wheat-based foods…eggs, fish, shellfish, nuts (and) seeds." There is little evidence that this reduces allergic disease.[8] Interventions involving maternal diet during pregnancy alone,[9] or pregnancy and lactation[10], and alterations to the timing and type of solid food introduction in infants[11] have thus far failed to halt the rise in food allergy. Furthermore, there is now observational evidence that early introduction of cows' milk,[12] egg[3] or peanut[13] during infancy may prevent the development of food allergies.

In 2010, the UK government published the latest of its quinquennial reviews of infant feeding practice in the country.[14] Whilst the current UK Government guidelines advise avoiding introducing allergenic foods before six months of age, the current feeding regimen of UK mothers clearly delays introduction significantly later than six months; at 8-10 months of age only 8% of infants had been given peanuts or peanut products.[14]

The significant trend towards later introduction of solid foods and longer duration of exclusive breastfeeding in the UK has coincided with the prevalence of food allergy appearing to increase.[1] It is currently unclear whether there is any causative effect of later solid food introduction on food allergy development but whilst delayed introduction of allergenic foods prevents an allergic reaction occurring, there is no evidence to suggest it prevents the development/acquisition of sensitisation and may simply delay the manifestation of a pre-existing allergy.

Recent research suggests that induction of oral tolerance (immunological unresponsiveness) to food proteins is possible, and that this may help reduce the risk of food allergy in childhood.[15] The LEAP (Learning Early About Peanut allergy) study found that the early introduction of peanut into the diet of high risk atopic infants protects against the development of peanut allergy.[16,17]

The Enquiring About Tolerance (EAT) Study has a broader scope, namely to test the hypothesis that the early introduction of multiple allergenic foods from three months of age

in an unselected population of exclusively breastfed infants will as a primary outcome reduce the prevalence of food allergy and as a secondary outcome influence asthma, eczema, allergic rhinitis and the prevalence of combined allergic disease by three years of age.

METHODS

The EAT Study is a population-based randomized controlled trial which enrolled exclusively breastfed infants from England and Wales, regardless of atopic status or family history of allergy. Infants who had consumed anything other than breast milk or water since birth, were part of multiple births, were born prematurely, had any serious medical condition or who were participating in other medical research were not eligible for enrolment.

Between 13 and 17 weeks of age, enrolled infants were randomly assigned to one of two groups, the Standard Introduction Group (SIG) or the Early Introduction Group (EIG). Those randomized to the SIG were asked to comply completely with the UK government infant feeding guidelines of exclusive breastfeeding until around six months of age and no consumption of allergenic foods before six months of age. After six months of age, introduction of allergenic foods was left to parental discretion. Infants in the EIG were randomized to the sequential introduction of the six chosen allergenic foods, alongside continued breastfeeding. The six allergenic foods selected to form the trial's intervention, cows' milk, peanut, cooked (boiled) hen's egg, wheat, sesame and fish (cod), were chosen from the foods most commonly found to be responsible for IgE-mediated allergic food reactions in children globally.[18,19] For safety reasons, infants in this group were skin prick tested in duplicate to whole foods for raw egg white, fresh cows' milk and tahini; and to cod, wheat and peanut using commercial solutions (Stallergene, Didcot, UK). Those showing any sensitisation (SPT>0mm, no upper limit) received an open incremental food challenge. Children who were not sensitised, or who were sensitised but had a subsequent negative food challenge, were asked to follow the EIG introduction regimen. Those diagnosed as allergic on the basis of a food challenge were advised to avoid that food or foods and continue the introduction regimen for the other allergenic foods. Fundamental to the trial design was the intention that breast milk should remain the infant's predominant source of nutrition until at least six months of age, regardless of study group.

Online questionnaires were completed monthly by participating infants' parents until 12 months of age, and every three months between 12 and 36 months of age. These questionnaires monitored in detail consumption of allergenic foods, recorded data on adverse events, allergy symptoms and general health and behaviour.

All children in both groups were invited to return for a clinic visit at 12 months of age and at 36 months of age where they received skin prick testing to the six intervention foods and a panel of aero-allergens and tree nuts. Participants also received an eczema examination, anthropometric assessment, dietetic consultation and those sensitised to any of the six intervention foods received a food challenge to confirm tolerance or diagnose allergy.

RESULTS

The EAT Study recruited 1303 infants demographically and geographically representative of the general UK population. Of these, 1178 (90%) children's primary outcome status was

evaluable, 1162 (89%) within the *a priori* visit window for the final three year visit. The primary outcome was the prevalence of IgE-mediated food allergy after follow-up to three years of age. Although a general population study, the EAT cohort was enriched (compared with the general population) with 82% of parents reporting they had a history of eczema, asthma or hay fever in comparison to the 58% reporting history of atopy in another UK study.[20] Visible eczema was seen in 24% of three month olds at enrolment. 33 children (5.1%) in the EIG were sensitised to one or more of the six intervention foods at enrolment with seven children found to be allergic following open food challenge and therefore asked to exclude one or more of the study foods from the early introduction regimen.

Breastfeeding rates in the EAT Study were well above national figures with over 97% of mothers in both groups breastfeeding at six months of age, in comparison to one in three mothers in the Infant Feeding Survey 2010, and 29% of those in the SIG exclusively breastfeeding to six months of age.

The primary outcome of IgE-mediated food allergy to one or more of the six intervention foods was reduced in the EIG, compared with the SIG, by 20% from 7.1% to 5.6% but the difference was not statistically significant (p=0.32). Of the primary outcome diagnoses 95% were achieved with the highest level of diagnostic evidence - through a double blind placebo controlled food challenge (DBPCFC). The infants with visible eczema at enrolment represent those at highest risk of developing food allergy. In this group, there was a 14% reduction in the prevalence of food allergy in the EIG compared with the SIG but this difference was not statistically significant (p=0.56). The prevalence of both egg and peanut allergies was also lower in the EIG than SIG and by 51% for peanut but this difference did not reach statistical significance. Sensitisation to the six study foods was lower in the EIG than SIG participants at both 12 months and 36 months of age but not statistically significant with the exception for wheat at both time points.

Of the SIG participants whose primary outcome status was determinable, 93% adhered to the protocol, while 43% of EIG adherence evaluable participants complied with the protocol and consumed at least 3g of allergenic food protein for five or more of the study foods for five or more weeks before six months of age. Partial adherence among EIG participants was not associated with any significant increase in allergy prevalence when compared to the SIG adherent participants implying that attempts to follow the early introduction regimen were not detrimental if the per-protocol target was not achieved. Among those who adhered with the study protocol, the prevalence of the primary outcome at 3 years was 7.3% in the SIG and 2.4% in the EIG. This 67% reduction was statistically significant (p=0.01). In the subgroup of high risk infants with visible eczema at three months of age a significant reduction of 73% in the prevalence of food allergy was observed (p=0.04).

Food specific adherence with the EIG protocol showed some very significant effects. Egg per-protocol consumption resulted in a reduction in the prevalence of egg allergy from 5.5% to 1.4% (p=0.009) and amongst peanut per-protocol adherent EIG participants there was not a single case of peanut allergy, a reduction from 2.5% to 0% (p=0.003). Similarly for sesame, there were no sesame allergic children among those complying with the protocol for sesame consumption in comparison to three allergic children (0.6%) in the SIG (p=0.56).

Food sensitisation was also significantly reduced among per-protocol adherent participants at 12 months of age: 17.3% in SIG to 10.1% in EIG (p=0.01); and 36 months of age: 10.2% in SIG to 3.3% in EIG (p=0.002).

The effectiveness of the trial intervention was strongly dose dependent and increased with the number of weeks the food was eaten and the volume of allergenic food protein consumed. Most strikingly for peanut, 2g/week consumption or more commenced from 3 months of age almost completely prevented peanut allergy.

There was a marked influence of race on food allergy rates, being much higher in non-white participants with a stepwise increase from white (5.3%), to mixed ethnicity (9.4%), to Asian/black/Chinese participants (19.3%), p<0.0005. Conversely there was a statistically significant stepwise reduction in adherence most notable in the EIG with only one in seven Asian/black/Chinese participants adhering to the protocol (p=0.01).

No significant reductions in the prevalence of other allergic diseases (eczema, asthma or allergic rhinitis) were observed in either intention-to-treat or per-protocol analyses.

The early introduction of allergenic foods was safe with no cases of anaphylaxis in EIG participants during the initial introduction regimen. All of the 33 baseline sensitised EIG participants were invited to undergo food challenge: 7 were positive, 22 were negative and four did not return for their challenge. Reactions in the seven participants were mild, half requiring no treatment.

Monthly adverse event data from online questionnaires showed that the early introduction of allergenic foods occurred without significant sequelae. Reports of vomiting and constipation were significantly higher in the EIG in the first couple of months of the introduction regimen which could be associated with the introduction of allergenic foods or, more likely, with the introduction of complementary foods in general. There was no effect of the trial intervention on growth of participants throughout the study.

In summary, there was no significant difference between the prevalence of food allergy to any of the six intervention foods in EIG and SIG participants when an intention-to-treat analysis was carried out. However, a significant reduction in food allergy prevalence in EIG compared to SIG participants was seen when those adherent with the study protocol were considered.

IMPLICATIONS

- ***EIG adherence with early introduction regimen - overall versus food specific***

The EAT early introduction per-protocol definition had to be set *a priori*. Clearly with 43% of EIG adherence evaluable mothers achieving this goal this would suggest that the bar was set too high for the overall per-protocol consumption target. However, on an individual food level, there were a number of foods where the 57% of EIG participants who were non per-protocol overall, were adherent at a food specific per-protocol level.

The increased number of EIG participants contributing to the food specific per-protocol analyses increases statistical power. We did not anticipate being able to see food specific

effects but we were able to do so. The larger number of EIG participants in these analyses gives us greater confidence in the generalisability of the results to a wider population of UK children.

- ***Per-protocol role of ethnicity***

Non-white participants were much more likely to be allergic and much less likely to adhere to the early introduction regimen. When they did adhere it appeared to have the same beneficial effect. This has strong public health implications for how a message of early allergenic food introduction could be conveyed effectively to the non-white community.

FURTHER WORK

- ***Unique cohort***

The EAT cohort represents an extraordinarily closely studied group of breastfed children. A wealth of data has been collected of which this report only touches on a small part. There is scope for a large body of work going forward some of which would fall under the remit of the FSA's areas of interest.

- ***Cohort follow up***

The highly significant per-protocol effects at a food specific level warrant a follow on study of the cohort to determine whether the benefits of intervention are preserved over time. This has important safety and public health implications. The high retention rate of more than 91% of the original population will facilitate this.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

GLOSSARY

AE	Adverse Event
BMI	Body Mass Index
COMA	Committee on Medical Aspects *of Food Policy*
CTCAE	Common Terminology Criteria for Adverse Events
DBPCFC	Double-Blind, Placebo-Controlled Food Challenge
EIG	Early Introduction Group
ELISA	Enzyme-Linked Immunosorbent Assay
FA	Food Allergy
FFQ	Food Frequency Questionnaire
FLG	Filaggrin
FPIES	Food Protein Induced Enterocolitis
FSA	Food Standards Agency
GCP	Good Clinical Practice
IDMC	Independent Data Monitoring Committee
ISAAC	International Study of Asthma and Allergies in Childhood
LEAP	Learning Early About Peanut allergy
LRTI	Lower Respiratory Tract Infection
MUAC	Mid Upper Arm Circumference
NCI	National Cancer Institute
OCC	Open Cumulative Challenge
OIC	Open Incremental Challenge
POEM	Patient-Oriented Eczema Measure
SAE	Serious Adverse Event
SDS	Standard Deviation Score
SIG	Standard Introduction Group
sIgE	Specific Immunoglobulin E
SPT	Skin Prick Test
SCORAD	SCORing Atopic Dermatitis
TEWL	Trans-Epidermal Water Loss
TSC	Trial Steering Committee
UCV	Unscheduled Clinic Visit
UK	United Kingdom
URTI	Upper Respiratory Tract Infection
WHO	World Health Organization

CHAPTER 1 – AIMS AND OBJECTIVE OF THE INVESTIGATION

The point prevalence of self-reported food allergy (FA) in a recent systematic review was around 6%[1] and for particular foods, specifically peanut[2] and egg appears to be rising.[3] The role of allergen consumption in early infancy, and the effects of this on the development of allergy or tolerance to food proteins remains uncertain.

The World Health Organization (WHO) Global Strategy for Infant and Young Child Feeding,[4] endorsed by the UK Government,[5] recommends exclusive breastfeeding for the first six months with nutritious complementary foods introduced thereafter and continued breastfeeding up to the age of two years or beyond.[6] The UK Government infant feeding information leaflet for parents, "Weaning – starting solid food", adopts a more pragmatic target of around six months exclusive breastfeeding.[7] It also states that if a mother decides to introduce complementary foods before six months, there are some foods that should be avoided as they may cause allergies including: "wheat-based foods…eggs, fish, shellfish, nuts (and) seeds." When allergenic foods are introduced it recommends that this be done one food at a time to detect reactions.[21]

Between 1998[22] and 2009[23] the United Kingdom government had a more restrictive policy, recommending avoidance of peanut consumption in high-risk families during pregnancy, lactation and to the child until three years of age. The American Academy of Pediatrics from 2000[24] to 2008[25] also recommended high-risk infants avoid solids until six months of age, dairy products until one year of age, hen's egg to two years and peanuts, tree nuts and fish to three years of age.[24] However the evidence basis for both the instigation and the revocation of these guidelines was limited.[8]

Interventions involving maternal diet during pregnancy alone,[9] or pregnancy and lactation[10], and alterations to the timing and type of solid food introduction in infants[11], have thus far failed to halt the rise in food allergy. The significant trend towards later introduction of solid foods and longer duration of exclusive breastfeeding in the UK has coincided with the prevalence of food allergy appearing to increase.[1] Whilst delayed introduction of allergenic foods prevents an allergic reaction occurring, there is no evidence to suggest it prevents the acquisition of allergic sensitisation to food proteins, and may simply delay the manifestation of a pre-existing allergy.

However, there is observational evidence that the introduction of cow's milk,[12] egg[3] or peanut[13] during infancy may prevent the development of food allergies and emerging evidence from a growing number of randomized controlled trials that early introduction of hen's egg and peanut can prevent egg and peanut allergies respectively.[15,17] The Australian Society of Clinical Immunology and Allergy issued guidelines in 2010 recommending solid food introduction from around 4 to 6 months and that no particular allergenic foods need to be avoided.[26] The more recently published guidelines produced by the European Academy of Allergy and Clinical Immunology's Taskforce on Prevention are similar to the Australian guidelines and recommend that there is no need to avoid introducing complementary foods beyond 4 months and that current evidence does not justify recommendations about withholding or encouraging exposure to potentially allergenic foods after 4 months.[27]

Contemporaneous with the Australian publication, in 2010, the UK government published the latest of its quinquennial reviews of infant feeding practice in the country.[14] Although the UK Government guidelines no longer stipulate delaying the introduction of allergenic foods beyond six months of age, the current feeding regimen of UK mothers clearly does delay introduction. At 8-10 months of age only 8% of infants had been given any peanuts or peanut products and only 2% had been given them once a week or more. Frequencies of consumption of less than once weekly or never were reported for nuts 98%, eggs 73% and fish 44%.[14] Almost half (45%) of mothers of 8 to 10 month old infants avoid giving their infant a food: 48% avoided nuts, 14% eggs, 10% dairy and 6% fish.[14] Fears about allergies were reported as the predominant reason for avoidance of individual foods in an infant's diet.

Three observational studies have found that delayed introduction of solids was related to an increased risk of asthma and eczema.[28-30] Reverse causality has been proposed as a possible explanation. However, Zutavern found no evidence of feeding practices playing a different role in the development of asthma and eczema with respect to: mother's opinion of child's eczema status at year one; and parental allergy, asthma, and atopy status.[30] Similarly, a recent study found that the delayed introduction of cereal grains (after the age of six months) was associated with an increased risk of wheat allergy.[31] Data have also emerged with regard to fish consumption with a study finding that introducing fish before nine months of age was associated with a reduction in eczema prevalence.[32]

There are data from a variety of sources to suggest that delaying the introduction of allergenic foods might not be the correct approach. Clinical observations from the Philippines in Southeast Asia[33] and Ghana in Africa,[34] where high amounts of peanuts are consumed in different snack forms during infancy, suggest a low rate of peanut allergy. As these differences could be due to genetics, we have examined these geographical variations more carefully by comparing the prevalence of peanut allergy in Jewish children in the UK and Israel.[13] The prevalence of peanut allergy in the UK was 1.85%, and the prevalence in Israel was 0.17% ($p< 0.001$). Despite accounting for atopy, the adjusted risk ratio for peanut allergy between countries was 9.8 (95% CI, 3.1-30.5) in primary school children. Peanut is introduced earlier and is eaten more frequently and in larger quantities in Israel than in the UK. The median monthly consumption of peanut in Israeli infants aged 8 to 14 months is 7.1g of peanut protein, and it is 0g in the UK ($p<0.001$). The median number of times peanut is eaten per month was eight in Israel and zero in the UK ($p<0.0001$).

To complement this observational work, a number of randomized controlled trials (RCTs) have been set up to establish the role of the introduction of specific allergenic foods early in life on development of food allergies (Table 1). The EAT study is one of eight such studies, the others being: Learning Early About Peanut allergy (LEAP) (high risk population, peanut),[35] Solids Timing for Allergy Research (STAR) (high risk population, egg),[15] Hen's Egg Allergy Prevention (HEAP) (general population, egg),[36] Beating Egg Allergy (BEAT) (high risk population, egg), Preventing Peanut Allergy in Atopic Dermatitis (PEAAD) (high risk population, peanut), Starting Time for Egg Protein (STEP) (high risk population, egg) and Preventing Atopic Dermatitis and Allergies (PreventADALL) (general population, milk, egg, wheat and peanut).

In summary, four of the eight trials are looking at introduction of hen's egg only, two at peanut only and two at multiple allergenic foods. The age at introduction of allergenic food(s), and the form in which the food is introduced, varied between trials and makes comparisons more difficult.

Three studies have published their results and have suggested that early oral tolerance induction is possible and may help reduce the risk of food allergy in childhood.[15]

1. The LEAP Study published results in early 2015 and is the first RCT looking at the introduction of peanut protein in a population of 628 high risk children (based on diagnosed egg allergy and/or moderate to severe eczema) between four and 10 months of age.[17] The results show over 80% reduction in peanut allergy at five years of age among those regularly consuming peanut from infancy, in comparison with those avoiding peanut. This reduction in peanut allergy remained in children negative on skin prick test to peanut at enrolment (13.7% in the avoidance group in comparison to 1.9% in the consumption group, $p<0.001$) and those with a skin prick test of 1-4mm at enrolment (35.3% in the avoidance group and 10.6% in the consumption group, $p=0.004$).[17]

2. The STAR (Solids Timing for Allergy Research)[15] looked at early hen's egg introduction and gave less conclusive results than LEAP. STAR recruited high risk four month old infants with moderate to severe eczema, reflected in 36% (24/67) of infants having hen's egg specific IgE more than 0.35 kU/l at enrollment.[15] STAR concluded that the induction of immune tolerance pathways and reduction in egg allergy incidence can be achieved by early regular oral egg exposure in infants with eczema but reductions in egg allergy prevalence did not reach statistical significance. At 12 months, there was a non-significant reduction in the proportion of infants in the egg consumption group (33%) diagnosed with IgE-mediated egg allergy (based on a challenge to pasteurized raw egg) compared with the control group (51%). However, the authors cautioned that when high-risk infants are first exposed to egg they may suffer severe allergic reactions because many are already sensitised by four months of age; 31% (15/49) of the intervention group reacted to their pasteurized raw whole hen's egg powder, 10 on first exposure, 1 with anaphylaxis.[15]

3. The HEAP (Hen's egg Allergy Prevention)[36] trial was looking at early hen's egg introduction in the general population.[36] The study did not find any effect of early consumption of pasteurized hen's egg starting at 4-6 months in preventing egg allergy up to age 12 months (eight children receiving pasteurized egg white powder showed positive hen's egg-specific IgE compared with only four in the placebo group). 6% (23/406) were positive to egg at screening (hen's egg specific IgE more than 0.35 kU/l). Of the 17 who underwent double-blind, placebo-controlled, food challenges, a remarkable 94% (16/17) were positive, with 3 having anaphylactic reactions (respiratory or cardiovascular system impairment). Furthermore, in the active group, two further children reacted to the pasteurized egg white powder with first exposure at home, one with an anaphylactic reaction.[36]

The STEP (Starting Time for Egg Protein) and BEAT (Beating Egg Allergy) trials are expected to publish during 2016 and will provide further data on the early introduction of hen's egg. The PreventADALL study is considering a similar hypothesis to EAT, that the early introduction of multiple foods may prevent food allergy, and to date has recruited a cohort of approximately

700 women antenatally. In this intervention the mothers are being asked to offer tastes of peanut, egg, milk and wheat, rather than a recommended amount of allergen protein.

EAT STUDY AIMS AND OBJECTIVES

The LEAP study did not investigate the efficacy of introduction to other allergenic foods nor did it examine whether this approach could prevent peanut allergy in children from the general population. The EAT Study was set up to address these issues. Specifically, the aim was to test the hypothesis that the early introduction of multiple allergenic foods into the diet of infants from a general population cohort from three months of age results in a reduced prevalence of food allergies between one and three years of age.

The study was additionally designed to ascertain whether the early introduction of allergenic foods leads to a reduction in the prevalence of other allergic diseases by three years of age, specifically asthma (including atopic wheeze), eczema, allergic rhinitis (including aero-allergen sensitisation), combined food allergy prevalence (including food sensitisation) and the prevalence of combined allergic disease.

Finally, the trial aimed to establish whether the early introduction of allergenic foods had any deleterious or harmful effects.

Table 1 Summary of Current Studies Investigating the Hypothesis that the Early Introduction of Allergenic Foods Can Induce Oral Tolerance

Name of Trial	Country	Type	Size	Intervention group	Control group	Intervention period	Primary outcome	Current status (June 2015)
Enquiring About Tolerance (EAT)	UK	RCT, open label, general population	1303	Exclusive BF with introduction of CM, HE, W, S, F, P* (4g/week each food)	Exclusive BF with CM, HE, W, S, F, P avoidance until 6 months of age.	3-36 months (per-protocol compliance measured until 6m of age)	Allergy to any of 6 intervention foods between 1 and 3 years (challenge)	Completed March 2015
Learning Early About Peanut allergy (LEAP)	UK	RCT, open label, high risk (infants with moderate/ severe eczema and/or egg allergy)	640	P (6g/week)	P avoidance	4-11 months to 5 years	P allergy at 5 years (challenge)	Completed May 2014
Solids Timing for Allergy Research (STAR)	Australia	RCT, blinded high risk (infants with moderate/severe eczema)	86	Pasteurized raw whole HE powder (~6.3g/week)	Placebo powder (rice)	4 months to 8 months	Sensitisation + raw HE open challenge/expert decision at 12 months	Completed May 2012
Hen's egg Allergy Prevention (HEAP)	Germany	RCT, blinded, general population	406	Pasteurized raw HE white powder (~7g/week), HE free diet	Placebo powder (rice), HE free diet	4-6 months to 12 months	HE sIgE, HE allergy at 12 months (challenge)	Completed Spring 2015
Beating Egg Allergy (BEAT)	Australia	RCT, blinded, moderate risk (sibling/parent with allergy)	600	Pasteurized raw ?whole HE powder (0.5g/day - 3.5g/week)	Placebo powder (rice)		HE allergy at 12 months (challenge)	Completed 2015
Preventing Peanut Allergy in Atopic Dermatitis (PEAAD)	Germany	**Self-allocated**, high risk (infants with atopic dermatitis)		P flakes or butter (3 times/week)	P avoidance	5-30 months for 12 month period	P sIgE, P allergy 12 months after intervention start (challenge)	Recruitment and follow-up ongoing
Starting Time for Egg Protein (STEP)	Australia	RCT, blinded, moderate risk (atopic mothers)	1512	HE powder (~2g/week)	Placebo powder (rice)	4-6.5 months to 10 months of age	Sensitisation + raw HE open challenge/expert decision at 12 months	Recruitment completed Nov 2014. Follow-up ongoing
Preventing Atopic Dermatitis and Allergies (PreventADALL)	Sweden and Norway	RCT, open label, general population, factorial design (2x2)	2500	1. "Tastes" of P, M, E, W 4 times/week by 4m of age 2. Bath with bath-oil and Ceridal face cream for at least 5 times/ week from 2 weeks-9 months	Unknown	Until at least 26weeks and "best if continued"	Unknown	Recruitment ongoing (700 recruited at 18 week antenatal scan)

***CM (cows' milk), HE (hen's egg), W (wheat), S (sesame), F (fish), P (peanut)**

CHAPTER 2 – METHODS

The EAT Study is a population-based randomized controlled trial which enrolled exclusively breastfed infants from England and Wales, regardless of atopic status or family history of allergy. Infants who had consumed anything other than breast milk or water since birth, were part of multiple births, were born prematurely, had any serious medical condition or who were participating in other medical research were not eligible for enrolment. A current household member with a food allergy was not an exclusion criterion.

Ethical approval for the EAT Study was provided by St Thomas' Hospital REC (REC Reference 08/H0802/93) in October 2008 and the study was registered with the International Standard Randomized Controlled Trial Number Register (14254740). The trial adhered to the principles of Good Clinical Practice as produced by the International Conference on Harmonised Tripartite Guideline for Good Clinical Practice produced in June 1996[37] and adopted by the Medical Research Council in March 1998.[38]

RECRUITMENT

Initial recruitment to the EAT Study began in March 2009 via information given to women at 12 and 20 week antenatal ultrasound appointments at both St Thomas' and Kingston Hospitals in London. Antenatal recruitment generated insufficient interest and postnatal recruitment was initiated in October 2009. Postnatal recruitment was carried out using the Bounty Parenting Network, a UK-wide organisation offering information and resources to registered parents. Bounty also provided targeted mailing for its members and the EAT Study produced a customised leaflet (Appendix 1) which Bounty sent directly to all its families in England and Wales with infants aged five to eleven weeks of age. This happened every month and was complemented by an email providing information about the study which was also sent to the same families receiving a postal leaflet. Interested families could call the Study's dedicated free phone number or email a recruitment email address to check their eligibility and find out more about taking part. There was also a study website giving information on participation and how to find out more about what that would involve. Families who contacted the study team and were eligible for enrolment were sent a full information sheet and consent form (see Appendix 2) and an appointment to attend the initial clinic visit for randomisation and baseline measurements when their infants were between 13 and 17 weeks of age. Targeted advertising generated 6202 calls and emails to the study team.

After assessment of eligibility, 1319 families attended an initial clinic visit and were randomized and enrolled onto the study. Study enrollment took place from 2nd November 2009 to 30th July 2012. The main reason for infants not being eligible for enrolment was the cessation of exclusive breastfeeding before the initial clinic visit (Figure 1). Follow-up took place up until March 2015 (Figure 2).

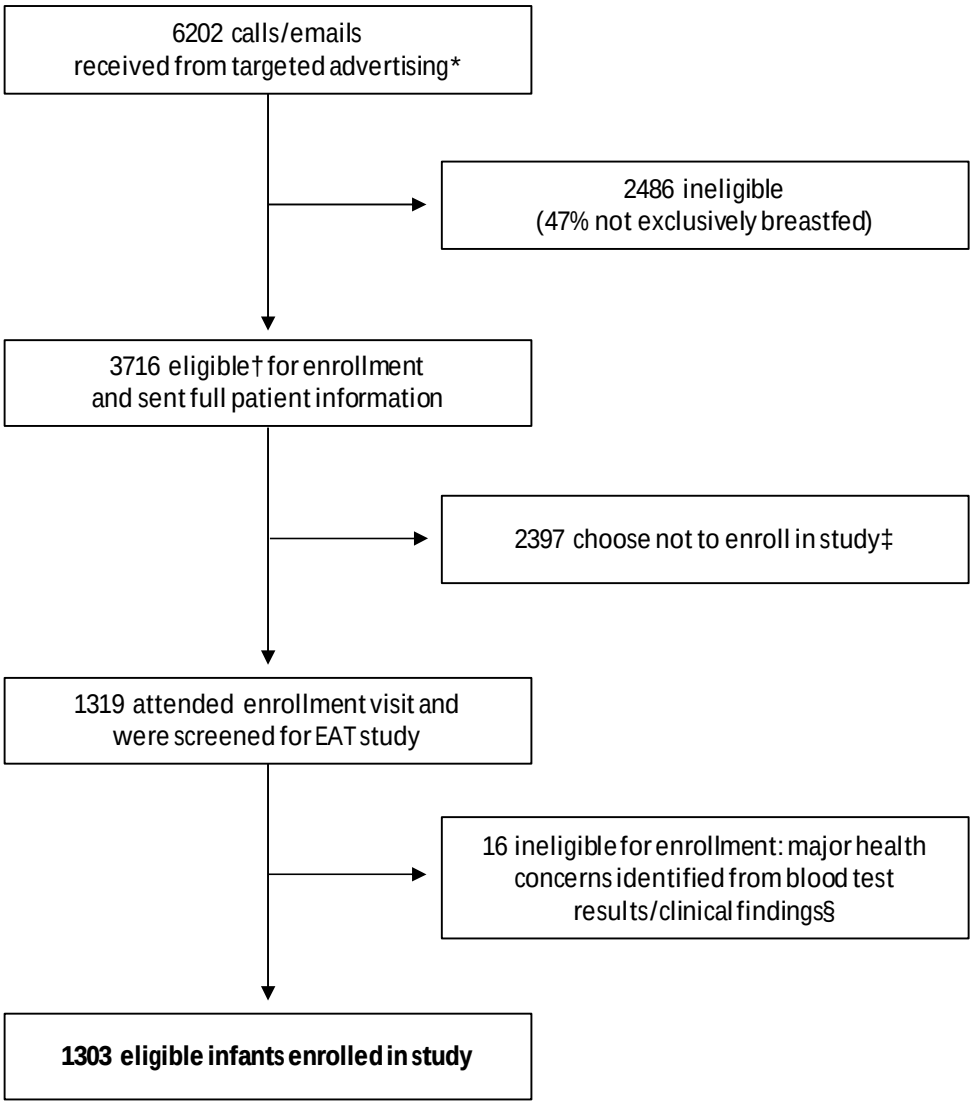


Figure 1 EAT Study Recruitment

*Direct mailing of families with infants aged 5-11 weeks of age in England and Wales

†Exclusively breastfed at enrollment, 37+ weeks gestation, singleton birth, no parental report of major health concerns, not taking part in other research, willing to attend 3 study visits over 3 year period, willing to be randomized to either study group, not planning to move from UK for study duration.

‡Reasons included concerns about participation requirements on reading of the full patient information sheet, wanting to have more flexibility with early feeding, concerns about travelling to London, child's father not happy with participation, unable to reach enrolment visit without introducing formula and/or solid food, too many other commitments.

§ Eight infants randomized to each group: conditions included severe vitamin D deficiency, severe iron deficiency, severe failure to thrive, familial hypercholesterolemia, congenital stridor, epidermolysis bullosa and cartilage hair hypoplasia syndrome

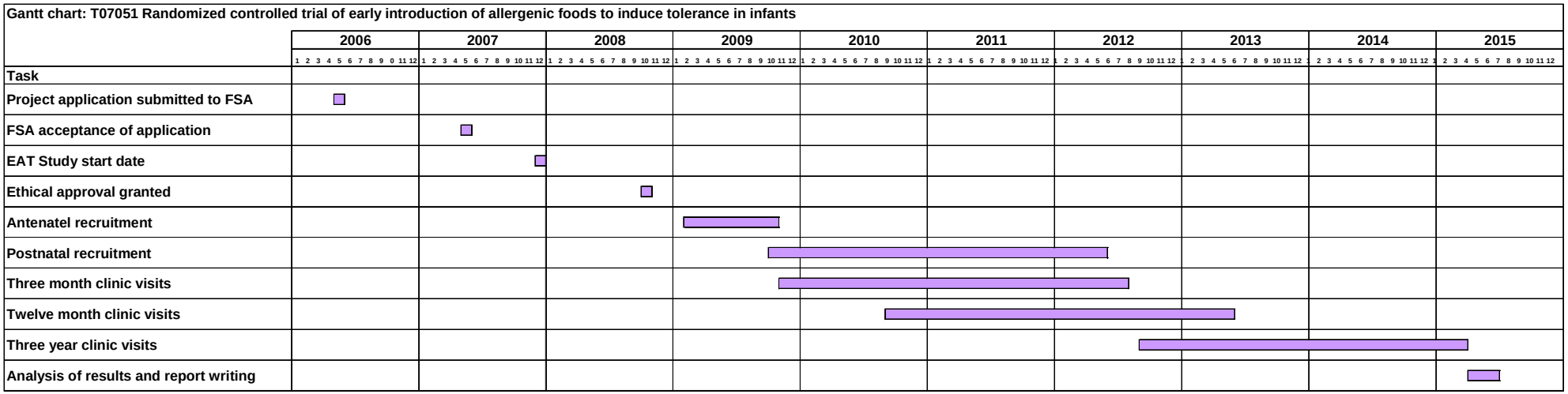


Figure 2 EAT Study Gantt Chart

Trial design

Between 13 and 17 weeks of age, enrolled infants were randomly assigned to one of two groups, the Standard Introduction Group or the Early Introduction Group (Figure 3).

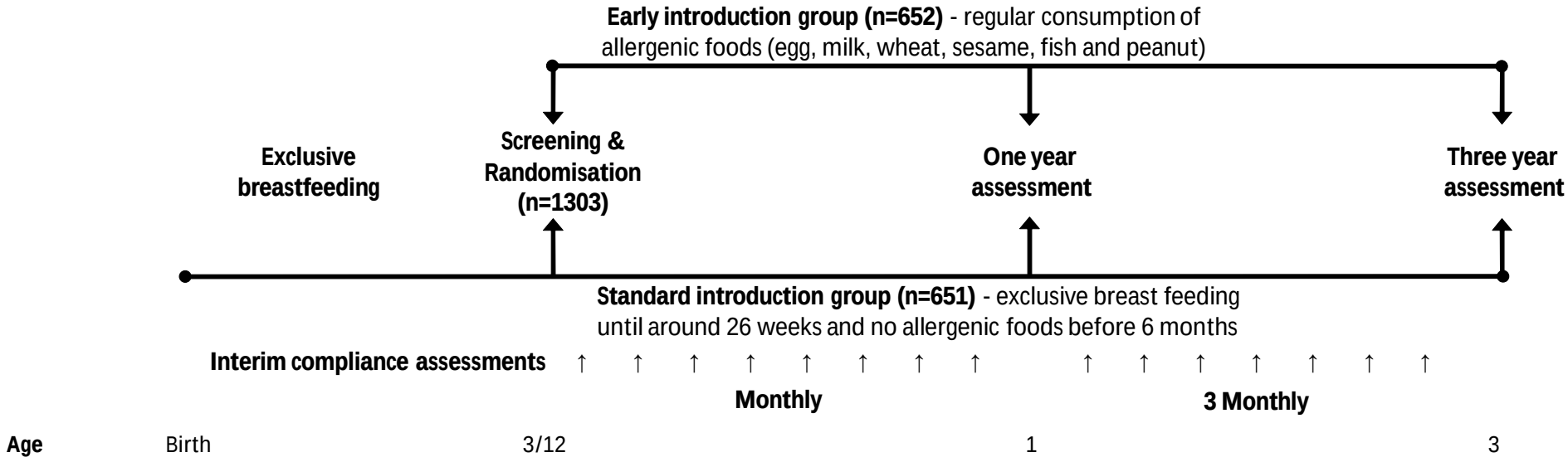


Figure 3 Overall EAT Study Design.

RANDOMIZATION

Participants were randomly assigned to treatment using a centrally administered independent randomisation service. The randomisation was not stratified given the number of participants. Given the nature of the intervention, to introduce real allergenic foods in comparison to continued exclusive breastfeeding, a placebo group was not appropriate and therefore the study participants could not be blinded to their allocation group. However, the study outcomes are based on food challenges that include blinded assessment and objective measures of sensitisation (skin prick test results) and specific IgE measurements. The latter were measured by laboratory staff blinded to the child's allocation status.

STANDARD INTRODUCTION GROUP (SIG)

Those randomized to the SIG were asked to comply completely with the UK government infant feeding guidelines of exclusive breastfeeding until around six months of age and no consumption of allergenic foods before six months of age. After six months of age, introduction of allergenic foods was left to parental discretion. Support and advice was provided by our clinical and dietetic team to encourage and help families meet this exclusive breastfeeding target. The per-protocol criteria for the SIG are listed in Table 2. These reflect a pragmatic interpretation of the current UK status quo – i.e. an incomplete following of the infant feeding recommendations. Thus allergenic food introduction from five months (criterion C) by which point 75% of mothers in the Infant Feeding Survey 2010 (IFS2010) have introduced solids to their baby including rusks (hard, dry infant biscuits) and yogurts) and up to 300 mls per day of cow's milk formula consumption after enrollment (criterion D) were considered acceptable. The volume was chosen such that the majority of milk consumed by the infant was still breastmilk. The amount of breastmilk consumed by exclusively breastfed infants was reviewed in a recent systematic review.[39] At 3-4 months of age the mean transfer volume of breastmilk was 779 (standard deviation (SD) 40) grams/day, at 5 months 827 (SD 39) grams/day, and at 6 months 894 (SD 87) grams/day.

Table 2 Per-Protocol Criteria in the Standard Introduction Group

Per-Protocol definitions for the Standard Introduction Group
Criterion A: Exclusive breastfeeding for at least three months duration (water and/or oral rehydration solution allowed)
Criterion B: Continued breastfeeding up to five months of age
Criterion C: No consumption of peanut, egg, sesame, wheat or fish before five months
Criterion D: No introduction of cows' milk formula (or goat's milk formula) (or consumption of less than 300 mls/day) between three months and six months of age

EARLY INTRODUCTION GROUP (EIG)

Infants in the EIG were randomized to the sequential introduction of the six chosen allergenic foods, alongside continued breastfeeding. The six allergenic foods selected to form the trial's intervention, cows' milk, peanut, cooked (boiled) hen's egg, wheat, sesame and fish (cod), were chosen from the foods most commonly found to be responsible for IgE-mediated food reactions in children.[18, 19] Infants in this group were skin prick tested in duplicate to whole foods for raw egg white, fresh cows' milk and tahini; and to cod, wheat

and peanut using commercial solutions (Stallergene, Didcot, UK). Real food versions of egg white, cows' milk and tahini were chosen to maximise the allergenicity of the skin prick test and give fewer false negatives than may have occurred using the commercial solutions for these foods at this age.

Skin-prick test wheal size was the mean wheal size of the duplicate tests. A positive skin-prick test was defined as the presence of positive skin-prick test responses greater than zero. Skin-prick test responses are smaller in infants and lower responses have been interpreted as being of clinical signficance.[35,40-42]

Those showing positive skin-prick tests (any size - no upper limit) received an open incremental food challenge. Children who were not sensitised, or who were sensitised but had a subsequent negative food challenge, were asked to follow the EIG introduction regimen described below. Those diagnosed as allergic on the basis of a food challenge were advised to avoid that food(s) and continue the introduction regimen for the other allergenic foods.

Fundamental to the trial design was the intention that breast milk should remain the infant's predominant source of nutrition until at least six months of age, regardless of study group.

EIG INTRODUCTION REGIMEN

Following normal blood test results at enrolment (full blood count, bone, liver, renal and lipid profile tests), the EIG infants proceeded to introduce baby rice and/or pureed fruits or vegetables in the week following confirmation of normal blood tests until they were established on solid food. They then continued with these solids and additionally introduced cows' milk yoghurt on two days of the first week of the early introduction regimen. During weeks two and three, hard-boiled egg, cod, sesame and peanut were introduced sequentially in a random order with two new foods introduced per week. Finally, wheat was introduced in week four, reflecting the guidance on optimal timing of wheat introduction after four months of age[43] and by week five, infants were ideally consuming the required amount of all six allergenic foods each week (Figure 4). The introduction of non-allergenic foods was not restricted during this process, and the allergenic foods could be given in combination with other foods or each other once the allergenic foods had been successfully introduced and well tolerated. Dietetic and clinical support was provided throughout this process and the participant families could contact the study team via telephone or email with any questions or concerns.

The exact volume of allergen protein necessary to induce oral tolerance is unknown, but participants in the EIG were asked to consume the equivalent of 2g of each allergenic food protein twice each week (4g of allergen protein per food per week). The rationale for the choice of the 2g target was based on our earlier research investigating peanut consumption amongst Israeli and UK Jewish children.[13] In that study the median frequency of consumption of peanut was 8 times per month (i.e. twice per week) and the median monthly consumption amount was 7.1g (i.e. about 1g per dose). Whilst the Jewish infants were older than those in our study (8-14 months), the research also showed that significant numbers were eating much larger doses than the 1g average.

We therefore elected to adopt a twice weekly consumption regimen per food in accordance with this earlier research. We set our dose target at 2g. This allowed for infants falling short of this target to still be achieving a level of consumption that our earlier research had shown appeared to be tolerance inducing. The full weekly amount of allergenic foods therefore consisted of 25g of white fish, two small 40-60g portions of cows' milk yoghurt, two wheat-based cereal biscuits (e.g. Weetabix), one small (less than 53g) hard-boiled egg, three rounded teaspoons of peanut butter and three teaspoons of sesame paste (tahini).

The per-protocol criteria for the EIG group are listed in Table 3. Criterion C aimed for consumption of at least five of the six allergenic foods in at least 75% of the 4g recommended amount (3g of allergen protein per food per week) during at least five individual weeks between enrolment and six months of age.

Early introduction families completed consumption target diaries for the last four complete weeks preceding the child's monthly birthday, hence completion of the four, five and six month online questionnaires yielded 12 weeks of consumption target data.
The 12 week figure is a theoretical maximum as participants enrolled in the study up until they turned four months old; there was a temporal delay before any allergenic solids were started whilst safety blood results were reviewed and early introduction infants commenced on either baby rice cereal, a puréed fruit or a puréed vegetable for the first 5-7 days to establish them on solids.

Table 3 Per-Protocol Criteria in the Early Introduction Group

Per-Protocol definitions for the Early Introduction Group
Criterion A: Exclusive breastfeeding for three months duration (water and/or oral rehydration solution allowed)
Criterion B: Continued breastfeeding up to five months of age
Criterion C: Consumption of at least five of the allergenic foods in at least 75% of the recommended amount (3g allergen protein/week), for at least five weeks between three months and six months of age

CONSUMPTION MONITORING

Interim questionnaires were completed online monthly (SNAP Survey Ltd, snapsurveys.com) by participating infants' parents until 12 months of age, and every three months between 12 and 36 months of age. Within each interim questionnaire, both groups completed a food frequency questionnaire (FFQ) section assessing how frequently foods containing the six study allergens were being consumed (See appendix). EIG families additionally kept a weekly diary up until one year of age and monthly thereafter to assess the degree to which they were meeting the consumption target of 4g of each allergenic food protein per week. For each of the four complete weeks preceding the child's monthly birthday parents recorded their child's consumption of each of the allergenic foods. Guidance was provided to allow consumption to be recorded as a percentage of the recommended amount of each food (100%, 75%, 50%, 25% or less, not tried yet). These consumption percentages were then entered into the interim questionnaires.

YOUR BABY'S EARLY INTRODUCTION FOODS SCHEDULE

(After 5-7 days on just baby rice cereal, puréed fruits or vegetables)

EAT
Enquiring About Tolerance

WEEK 1

MON	TUES	WED	THURS	FRI	SAT	SUN
Baby Rice	**Cows' Milk Yoghurt**	Baby Rice	**Cows' Milk Yoghurt**	Baby Rice		

WEEK 2

MON	TES	WED	THURS	FRI	SAT	SUN
1	**Cows' Milk Yoghurt**	1	**Cows' Milk Yoghurt**	2		2

WEEK 3

MON	TUES	WED	THURS	FRI	SAT	SUN
1	**Cows' Milk Yoghurt** 3	1	**Cows' Milk Yoghurt** 3	2	4	2

WEEK 4

MON	TUES	WED	THURS	FRI	SAT	SUN
1 4	**Cows' Milk Yoghurt** 3	1 **Wheat***	**Cows' Milk Yoghurt** 3	2 **Wheat***	4	2

*Wait till your baby is at least 4 months of age before you introduce wheat!

Food 1: PEANUT **Food 2: SESAME** **Food 3: EGG** **Food 4: FISH**

WEEK 5 and Onwards

MON	TUES	WED	THURS	FRI	SAT	SUN
	**Cows' Milk Yoghurt** 	 **Wheat**	**Cows' Milk Yoghurt** 	 **Wheat**		

Guideline Amounts Per Week (or equivalents):

- 2 fish fingers or ¼ fish fillet (25 grams)
- 2 small pots cows' milk yoghurt (40-60 grams per pot)
- 2 wheat based biscuit cereal (e.g. Weetabix)
- 1 small hard-boiled egg
- 3 rounded teaspoons peanut butter
- 3 teaspoons tahini (sesame paste)

Additional Tips:

* Each 'serving' can be further split into 2-3 portions and given over the course of that day (e.g. ½ a teaspoon, ½ a Weetabix or equivalent, or ½ a pot of yoghurt at one time).
* Introduce wheat (and other cereals containing gluten such as rye, barley and oats) after your baby turns 4 months of age.
* After your baby is comfortably established on these key foods, you may give more of any one of these foods if your baby desires it.
* Remember your baby still needs frequent breastfeeding at this stage and breast milk should remain an important part of a baby's diet for the first year of life!
* If you are having trouble introducing these foods, or if your baby is regularly taking in half or less of the weekly guideline amounts of these foods, please contact us for advice.

QUESTIONS? NEED ADVICE?
Please Contact the EAT Study Team

Figure 4 Example of an EIG allergenic Food Introduction Regimen

COHORT ASSESSMENT

Participants in the study underwent a comprehensive series of investigations throughout the study aimed at understanding what causes sensitisation and food allergy to emerge (Table 5 overleaf). Scheduled assessments took place at one and three years of age and unscheduled clinic visits for investigation of parent-reported symptoms suggestive of food allergy.

INTERIM QUESTIONNAIRES

In addition to recording allergen consumption data, the interim questionnaires collected information on any adverse events (serious and non-serious), allergy symptoms and general health and behaviour. The questionnaires were the main portal through which parents communicated information about their child to the study team.

Maternal Quality of Life

The three month, one year and three year interim questionnaires used the World Health Organization's WHOQOL-BREF instrument to produce a quality of life profile.[44] This is a 26 item version of the WHOQOL-100 and assesses four broad domains of quality of life: physical health, psychological health, social relationships, and environment (Table 4). Four domain scores are derived which range from four to twenty. Domain scores are scaled in a positive direction (i.e. higher scores denote higher quality of life).

Table 4 WHOQOL-BREF Domains

Domain	Facets incorporated within domains
1. Physical health	Activities of daily living
	Dependence on medicinal substances and medical aids
	Energy and fatigue
	Mobility
	Pain and discomfort
	Sleep and rest
	Work Capacity
2. Psychological	Bodily image and appearance
	Negative feelings
	Positive feelings
	Self-esteem
	Spirituality/Religion/Personal beliefs
	Thinking, learning, memory and concentration
3. Social relationships	Personal relationships
	Social support
	Sexual activity
4. Environment	Financial resources
	Freedom, physical safety and security
	Health and social care: accessibility and quality
	Home environment
	Opportunities for acquiring new information and skills
	Participation in and opportunities for recreation/leisure activities
	Physical environnent (pollution/noise/traffic/climate)
	Transport

Table 5 Schedule of Events

Age	3/12 Initial Assessment	4-11/12 Monthly	One Year Assessment	15-33/12 3 Monthly	Three Year Final Assessment	Unscheduled Visit Assessment
Invitation & information	X					
Informed consent	Infant & Mother				Mother & Father	
General Assessments						
Physical examination	X		X		X	X
Medical history	X	X	X	X	X	X
Adverse events		X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Eczema evaluation	X	X	X	X	X	
Rhinitis evaluation			X		X	
Asthma evaluation	X		X		X	
Anthropometry	X	Child Health Record	X	Child Health Record	X	
Laboratory assessments						
Haematology	X		X		X	
Serum chemistries	X		X		X	
Serum lipids	X				X	
HbA1c					X	
Coeliac screen					X	
Allergy assessments						
Skin-prick testing (parental)					Parental	
Specific IgE (parental)					Paternal	
Skin-prick testing (child)	Intervention foods*		Extended panel		Extended panel	X
Specific IgE (child)	Intervention foods		Intervention foods		Intervention foods	
Diet						
Dietary education	X	X	X	X		X
FFQ (antenatal)	X					
FFQ (lactation - pre enrollment)	X					
5 day food diary		6/12	X		X	
Food reaction history		X	X	X	X	X
Adherence assessment		X	X	X	X	X

Microbiome						
Skin swabs	X		X			
Stool samples	X	5/12	X			
Domestic environment						
Dust collection	X		X			
Immunologic assessments						
Frozen PBMC T-cell assay	X		X		X	

*Early introduction group only

Key: PBMC peripheral blood mononuclear cells

SKIN PRICK TESTING

At one year of age skin prick testing was undertaken for the whole cohort with commercial solutions only to a panel of foods (the six intervention foods, soya and kiwi) and aero-allergens (house dust mite, cat, dog, six grass pollen mix and three tree pollen mix). At three years of age the one year investigations were repeated with additional skin prick tests with commercial solutions to Brazil nut, hazel nut, cashew, almond and walnut and also to salmonella free raw egg white. Attending parents underwent skin prick testing and blood testing.

SKIN

All children were examined for eczema at all three clinic visits, using the UK diagnostic criteria-based photographic protocol of the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Two.[38] Disease severity was determined by the Scoring Atopic Dermatitis (SCORAD) index.[39] SCORAD was categorized as mild (<15), moderate (15-40), and severe (>40).[45] Transepidermal water loss (TEWL) was measured using the Biox Aquaflux® AF200 closed condenser chamber device on the unaffected skin of the volar aspect of the forearm 2009.[46]

GROWTH

At each assessment visit, participants had the following measurements determined: weight, length or height, body mass index, head circumference, mid-upper-arm circumference, sub-scapular and triceps skin fold thickness.
Measurements were transformed into Z scores using the UK-WHO Child Growth Standards released in May 2009[47] and designed for all term births (gestation 37-42 weeks). Between 2 weeks and up to 4 years of age these use the World Health Organisation (WHO) Child Growth Standards published in 2006, which describe the optimal growth for healthy, breastfed children.[48]

BLOOD SAMPLING

Venous blood was obtained at each of the three visits. The enrolment sample was screened for the six most common filaggrin (FLG) mutations (R501X, 2282del4, R2447X, S3247X, 3673delC, and 3702delG).[31] Following safety blood measurement (full blood count, renal and liver function, bone metabolism), spare serum was stored (-70°) for determination of specific IgE antibody to the allergic foods and component resolved diagnostics to peanut. Peripheral blood mononuclear cells were stored in liquid nitrogen for subsequent lymphocyte studies.

FOOD DIARY

At 6, 12 and 36 months of age parents completed a five day food diary recording in detail their child's diet including portion sizes, ingredients and commercial food brands to allow a full nutritional breakdown of macro nutrients during the trial.

ANCILLARY PROJECTS

Several ancillary projects, detailed briefly below, were carried out in parallel to the main EAT Study.

MICROBIOME

The infant microbiome was assessed through the collection of skin swabs at 3 and 12 months and stool samples at 3, 5, and 12 months. Participants attending for their 3 and 12 month visits were swabbed on two surfaces (elbow crease and outer forearm) commencing from December 2011. Skin samples were immediately frozen and stored at -80°C, prior to DNA extractions. The stool samples were supplied at enrolment from October 2011, before any solids had been ingested by participants, with further samples being requested at five and 12 months of age. DNA from stool samples were extracted at our laboratories and extracts stored at -80°C prior to being sequenced.

DUST

To corroborate reported consumption of egg and peanut, dust samples were collected from the infants' beds at enrolment and at 1 year of age in order to measure egg and peanut protein levels in the dust by enzyme-linked immunosorbent assay (ELISA).[49] The measurement of peanut in household dust has been used to assess the infants' consumption of peanut as the level of this protein in dust has been shown to correlate well with a FFQ for consumption of peanut,[49] and was also used to corroborate peanut consumption in the LEAP study.[17]

ALLERGY DIAGNOSIS

IgE MEDIATED ALLERGY

PRIMARY OUTCOME - LEVELS OF EVIDENCE FOR FOOD ALLERGY

A diagnosis of food allergy was determined according to the levels of evidence given in Table 6.

Table 6 Definition of IgE Mediated Food Allergy for Primary Endpoint

Primary endpoint definition: **The period prevalence of IgE mediated food allergy to the six intervention foods between one and three years of age in both arms.**
Category 1A: A positive DBPCFC at one year or three years of age in a child sensitized to one of the six intervention foods **Category 1B**: A positive DBPCFC between one year and three years in a child attending an unscheduled clinic visit in a child sensitized to one of the six intervention foods *Whilst the first two categories related to events between one and three years of age, we included children potentially outside of this range in two exceptional circumstances:* **Category 2:** A positive challenge (open or DBPCFC) at between six months and one year of age that occurred in a child who was sensitized to one of the six intervention foods who subsequently refused a DBPCFC at one year and three years of age *Rationale: Below six months only intervention children had challenges so this category was restricted to those infants who are six months old or more.* **Category 3**: A food allergic history in a child with a SPT ≥5 mm *Rationale: There were likely to be a small number of children who had an immediate type allergic reaction and were significantly sensitized whose parents refused to allow them to undergo any further challenge.* The relative contributions of children to the final outcome in each of these four categories is presented separately as well as the overall cumulative figure.

The category system was hierarchical in that a participant meeting the criteria for Category 3 having had a history of a food reaction between six months and one year of life and having a skin-prick test response of 5 mm or more, would change to a higher level category if they subsequently had a positive double-blind, placebo-controlled challenge at the 1 or 3 year assessment (to Category 1A) or at an unscheduled visit after one year of age (to Category 1B).

PRIMARY OUTCOME DETERMINATION

Primary outcome negative: Participants with negative skin-prick tests at every time point were deemed primary outcome negative, regardless of whether they had previously eaten the study foods. If a participant required one or more food challenges (for suspected symptoms, food aversion or refusal, or positive skin-prick tests at the one or three year assessments) and the challenge outcomes were negative the child was deemed primary outcome negative.

Primary outcome positive: A participant was positive for the overall study outcome of allergy to one or more of the six foods if they were primary outcome positive to at least one of the six study intervention foods.
The study design meant that participants attending the one year assessment and having a positive double-blind, placebo-controlled food challenge to a food to which they were skin-prick positive, fulfilled the primary outcome definition even if they then failed to attend the three year assessment visit.
Primary outcome indeterminate: A participant who did not fulfil any of the categories described below and who failed to attend the final three year assessment visit within the visit window had an indeterminate primary outcome and could not be included in the intention-to-treat analysis.

NON-IgE MEDIATED ALLERGY

Each interim questionnaire also included a more generic question "Does your child have adverse reactions to any foods, such as eczema, breathing problems or gastrointestinal problems?" If they answered yes, they were asked to describe the problems and identify the suspected food/foods. The answers to these questions were coded by food and symptom type with clinical judgement used to identify those likely to indicate a non-IgE-mediated (eczema flare, reflux, diarrhoea, gastrointestinal discomfort), rather than IgE-mediated (hives, swelling, immediate vomiting), food allergy. These data were then used to give an indication of the prevalence of parent reported non-IgE type food symptoms.
Data were also collected about symptoms and signs suggestive of food protein induced enterocolitis syndrome and proctitis and investigated by food challenge where possible.

CHALLENGE REGIMEN

Families could report suspected allergy symptoms at any time during the study to the study team via telephone, email or at study visits and unscheduled clinic visits were then arranged accordingly. However the main portal of communication was the online questionnaires in which families were asked if their child had had any swelling of the skin and/or hives and if yes, whether this was related to consumption of a specific food. Questions were included to screen for both IgE and non-IgE mediated problems.

FOOD CHALLENGES - SCHEDULED ASSESSMENTS

All children who had a positive skin-prick test to one or more of the six intervention foods at the one year and/or three year assessments, or a history of a positive challenge less than one year of age were considered for a food challenge. The decision to challenge, the timing and the type of challenge undertaken were based on the participant's study group and frequency of consumption status.

Frequent consumption criteria (Figures 5 & 6) were as follows: (1) Consuming at least one EAT portion (2 grams or more of food protein) of the food within the last month; and (2) History of ever having consumed more than three EAT portions (2 grams or more of food protein at a time) of the food. All other participants were designated as infrequent or never consumers as appropriate. Further details are in Table 7 (scheduled challenges) and Figure 5 (one year assessment) & Figure 6 (three year assessment).

Participants who were found to be skin-prick test positive to peanut or sesame at the one year assessment underwent assessment in accordance with Table 7. Skin-prick test positive frequent consumers of peanut or sesame were told to maintain their consumption at the same rate. Early introduction group participants were encouraged to consume peanut and sesame in the recommended quantities. Infrequent or never consumers of peanut or sesame were told to avoid the food until the three year assessment when their skin-prick test status was determined and challenges undertaken as designated in Table 7. The reason for deferring the peanut or sesame challenges was that there was a theoretical risk that undertaking a sesame or peanut challenge in a standard introduction infant who had been exposed to little or no sesame or peanut could induce tolerance.

FOOD CHALLENGES - UNSCHEDULED CLINIC VISITS

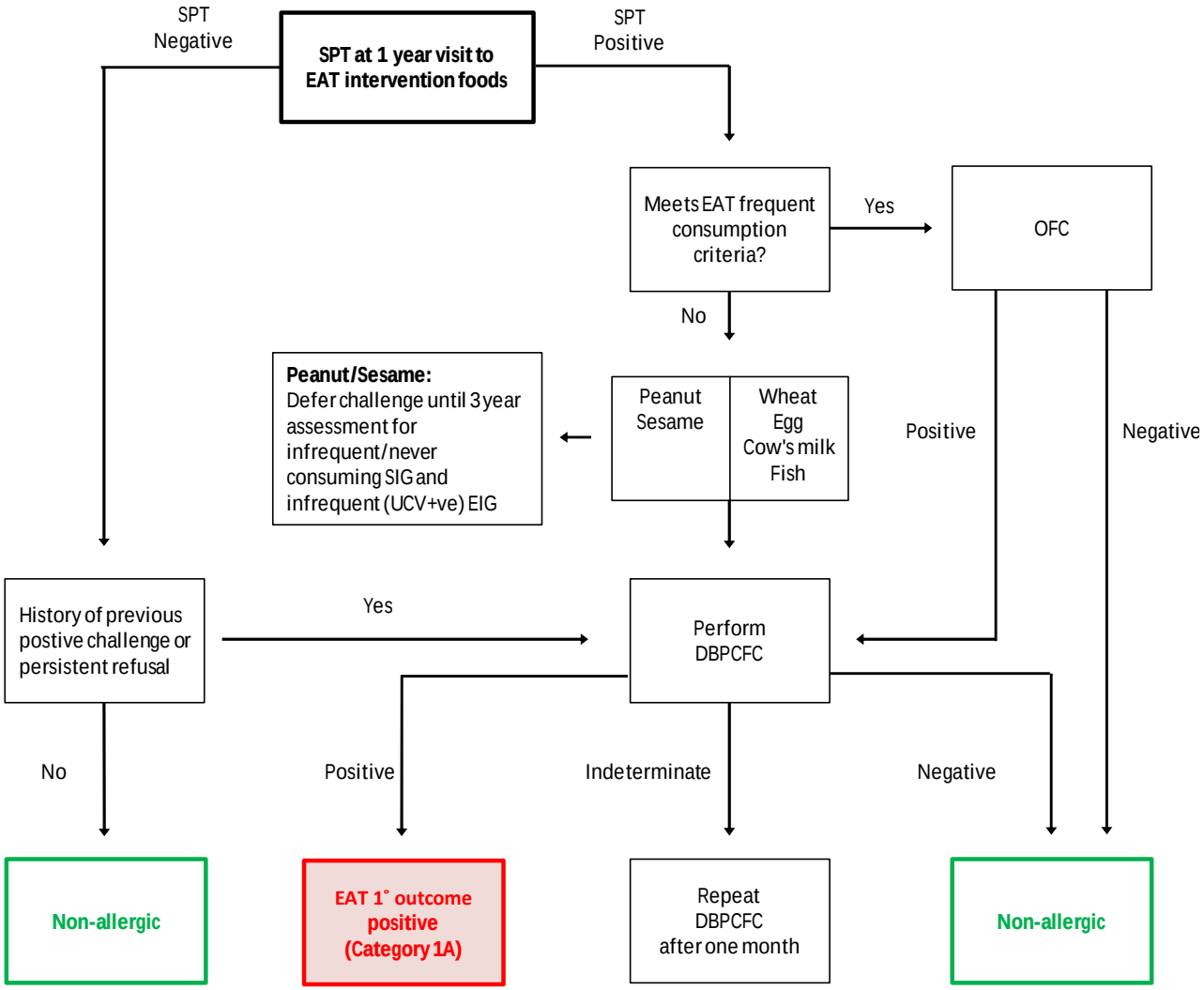
Families of participants reporting food aversion or refusal or a suspected food allergy were invited to attend an unscheduled clinic visit where the participant was assessed with skin-prick testing. Unscheduled food challenges were performed as indicated in Figure 7 and Table 8. Participants with a response of 5 mm or more were deemed allergic and told to avoid the food until a formal food challenge was undertaken six months after the initial reaction for cow's milk and 12 months for the other early introduction foods. Food challenges were open-label under one year of age and double-blind, placebo-controlled challenges after one year of age. The rationale for the time interval between food reaction and subsequent challenge was that families were felt to be unlikely to consent to a food challenge in the immediate aftermath of a definite food reaction. A suitable time period was chosen to ensure that the likelihood of outgrowing the allergy was minimal but that an acceptable amount of time since the allergic reaction had ensued that would ensure parents were likely to consent to the challenge.

FOOD CHALLENGES - DOSE REGIMEN

Double blind challenges were undertaken in incremental doses with a total dose of food allergen protein of 4.3 g for challenges undertaken at under three years of age and 5.3 g for those at three years of age. Open challenges in frequent consumers defined above consumed the same quantities of food allergen protein in a single dose (Tables 7 and 8).

DIETARY ASPECTS OF CHALLENGES

Extensive work went into devising the challenge regimens for each food taking into account the vast difference between a 4 month old baby and a three year old child (Table 9). Four month old infants were not able to consume large quantities of food and this influenced the design of the challenges in terms of total number of doses in the double blind challenges as well as the total amount of food that was offered. The food challenge proformas used in the EAT study are included in the Appendices.



* If has eaten standard EAT portion (≥2 grams in a single portion) in the past.

Figure 5 Determination of Food Allergy – One Year Assessment

Participants who were skin-prick positive (greater than 0 mm) to peanut or sesame at the one year assessment had their challenge to this food deferred until the three year assessment depending on their study group and consumption frequency (Table 7). Participants with a double-blind, placebo-controlled positive food challenge fulfilled the primary outcome definition (Category 1A - Table 6), regardless of whether they subsequently returned for the three year assessment. Participants who had negative challenges were non-allergic but not deemed primary outcome negative as an allergy could still develop between the one and three year assessments.

Key: SPT skin-prick test, UCV unscheduled clinic visit, OFC open food challenge, DBPCFC double-blind, placebo-controlled food challenge

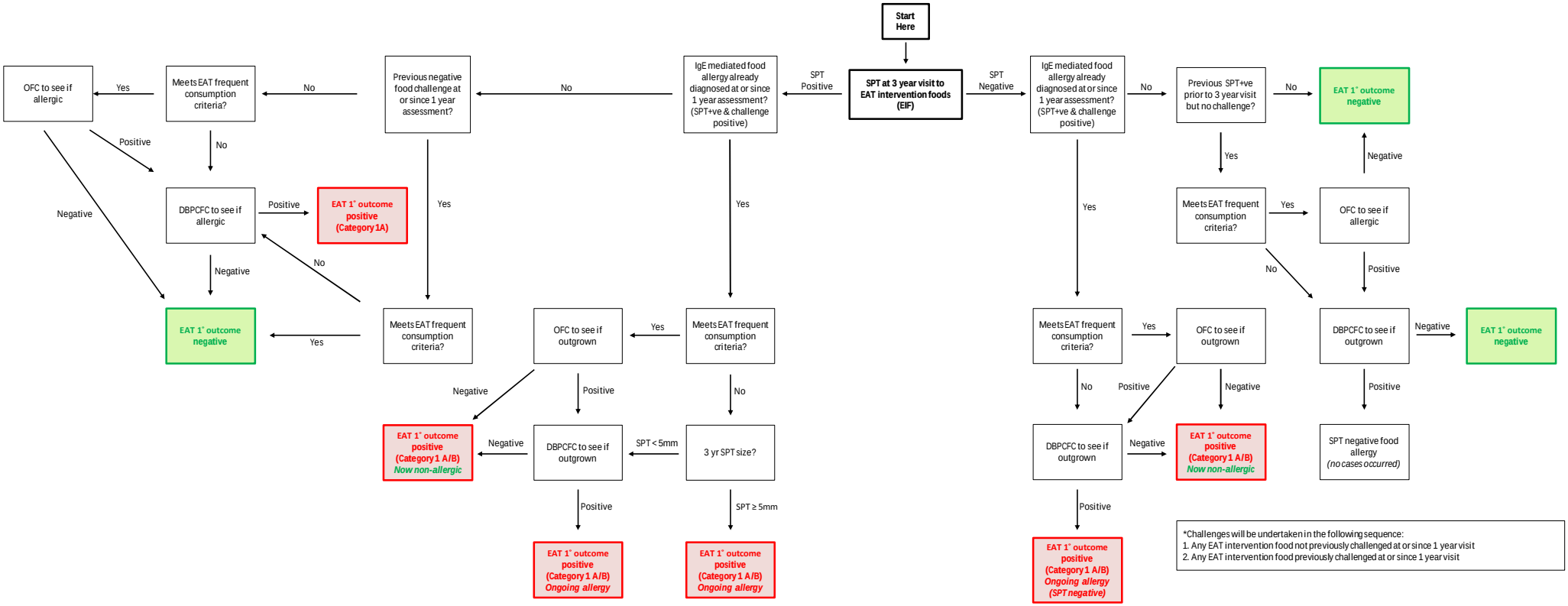


Figure 6 Three Year Assessment Visits - IgE Mediated food allergy

For each of the six early introduction foods, this algorithm was followed and a decision reached as to whether the participant was primary outcome positive or negative for that specific food. Participants who were primary outcome positive based on a positive double-blind, placebo controlled challenge at the three year assessment had a Category 1A level of evidence for primary outcome. Participants who had had a positive double-blind, placebo controlled challenge at the one year assessment were already Category 1A primary outcome positive. Participants who had had a positive double-blind, placebo controlled challenge at an unscheduled clinic visit since the one year assessment were Category 1B primary outcome positive (Categories defined in Table 6). The *frequent consumption criteria* are described previously.

Key: SPT skin-prick test, OFC open food challenge, DBPCFC double-blind, placebo-controlled food challenge

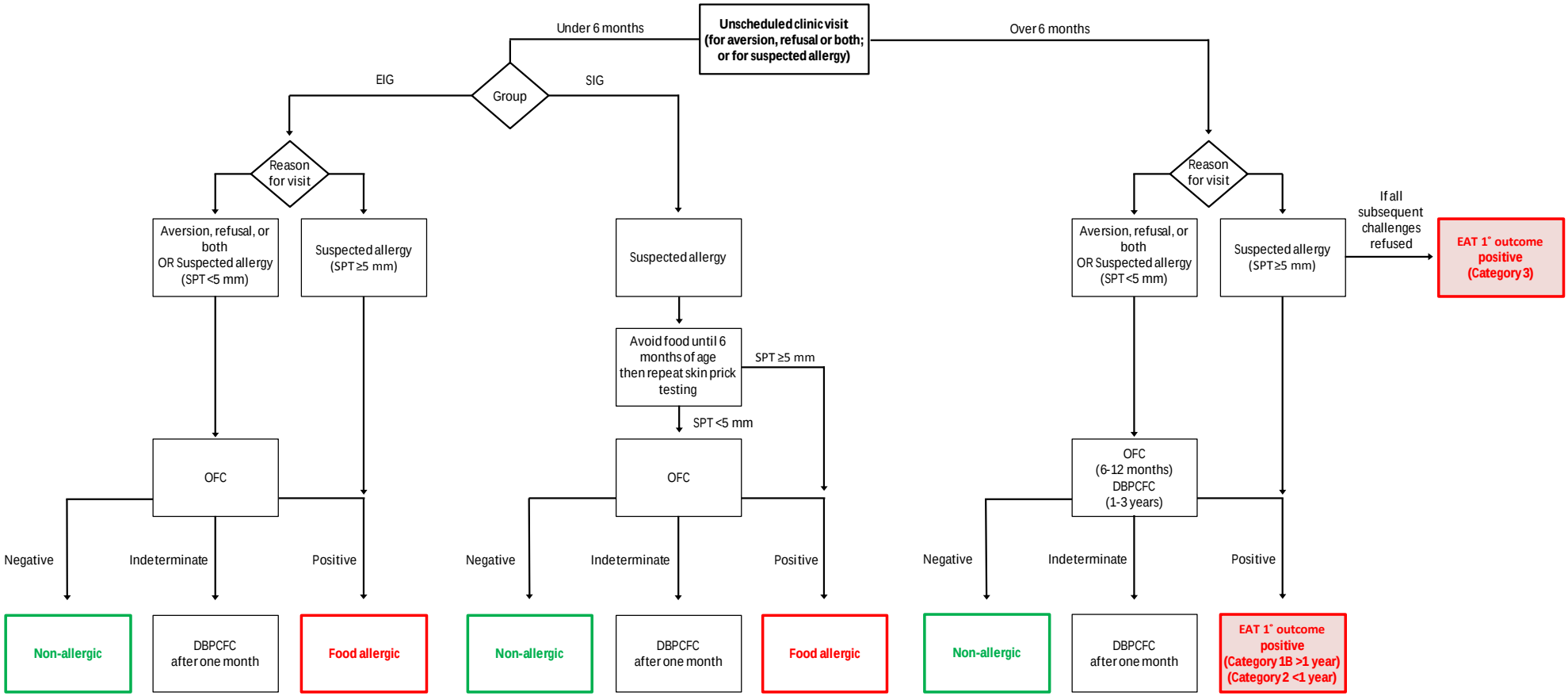


Figure 7 Food Challenge Algorithm - Unscheduled Clinic Visit

Participants attending an unscheduled clinic visit for food aversion, refusal or suspected allergy followed this algorithm. Early introduction group participants with positive open food challenges under six months of age were designated food allergic but this did not constitute EAT primary outcome positive status as this would have introduced a bias because only EIG participants were challenged under six months of age. Participants with a history of food allergy between 6 months and one year of age and with a skin-prick test result of 5 mm or greater fulfilled the EAT primary outcome at a Category 3 level of evidence. These participants were invited to undergo double-blind, placebo-controlled food challenges when they reached one year of age. Participants between six months and one year of age who had a positive open food challenge at an unscheduled clinic visit were designated primary outcome positive with a Category 2 level of evidence. Participants over one year of age who had a positive double-blind, placebo-controlled food challenge at an unscheduled clinic visit were designated primary outcome positive with a Category 1B level of evidence (Table 6). Participants who had negative challenges were non-allergic but not deemed primary outcome negative as an allergy could still develop before the three year assessment.

Key: SPT skin-prick test, OFC open food challenge, DBPCFC double-blind, placebo-controlled food challenge

Table 7 Challenge Programme – Scheduled Challenge Visits

Event	Allergy status	Food	Arm	Consumption frequency	Type of challenge	Dose regime(g protein)
3 month visit	SPT+ve	All	EIG	Not applicable	Open incremental challenge	2.0 g (0.1, 0.2, 0.5, 1.2)
1 year visit	SPT-ve	All	Both	Infrequent/Never (UCV+ve)	DBPCFC*	4.3 g (0.1, 0.4, 1.3, 2.5)
	SPT+ve	All	Both	Frequent	Open cumulative challenge	4.3 g
		E M F W	EIG	Infrequent (Enrollment challenge +ve)	DBPCFC*	4.3 g (0.1, 0.4, 1.3, 2.5)
		E M F W	Both	Infrequent/Never (UCV+ve)	DBPCFC*	4.3 g (0.1, 0.4, 1.3, 2.5)
		E M F W	Both	Infrequent (No reaction) Infrequent (UCV-ve) Never	DBPCFC	4.3 g (0.1, 0.4, 1.3, 2.5)
		S P	SIG	Infrequent Never	Deferred until 3 year visit – avoidance advised	-
		S P	EIG	Infrequent (UCV+ve) (Enrollment challenge +ve)	Deferred until 3 year visit – avoidance advised	
		S P	EIG	Infrequent (No reaction) Infrequent (UCV-ve) Never	DBPCFC	4.3 g (0.1, 0.4, 1.3, 2.5)
3 year visit	Any SPT	All	Both	Infrequent/Never (UCV+ve ≥1 yr)	DBPCFC*	5.3 g (0.1, 0.4, 1.3, 3.5)
	SPT+ve	All	Both	Frequent	Open cumulative challenge	5.3 g
		All	Both	Infrequent (No reaction) Infrequent (UCV-ve) Never	DBPCFC	5.3 g (0.1, 0.4, 1.3, 3.5)

*NB Observe minimum interval since positive unscheduled clinic visit or enrollment challenges (M 6 months, E W F S P 1 year). Active dose were interspersed with placebo doses.

SPT+ve defined as greater than 0 mm.

Key: SPT skin-prick test, E Egg M Milk F Fish W Wheat S Sesame P Peanut, DBPCFC double-blind, placebo-controlled food challenge, UCV unscheduled clinic visit

Table 8 Challenge Programme – Unscheduled Challenge Visits

Event	Allergy status	Food	Arm	Consumption frequency	Type of challenge	Dose regime (g protein)
UCV (<1yr)	SPT+ve ≥5mm	All	Both	All	Challenge not done Deemed allergic	-
	SPT+ve <5mm	All	Both	All	Open incremental challenge	2.0 g (0.1, 0.2, 0.5, 1.2)
	SPT-ve	All	Both	All	Open cumulative challenge	2.0 g
	Any SPT	All	Both	Previous indeterminate challenge to food	Open incremental challenge	2.0 g (0.1, 0.2, 0.5, 1.2)
UCV (1yr+)	SPT+ve ≥5mm	All	Both	All	Challenge not done Deemed allergic	-
	SPT+ve <5mm	All	Both	All	DBPCFC	4.3 g (0.1, 0.4, 1.3, 2.5)
	SPT-ve	All	Both	All	Open cumulative challenge	4.3 g
	Any SPT	All	Both	Previous indeterminate challenge to food	DBPCFC	4.3 g (0.1, 0.4, 1.3, 2.5)

Key: SPT skin-prick test, DBPCFC double-blind, placebo-controlled food challenge, UCV unscheduled clinic visit
SPT+ve defined as greater than 0 mm.
Active dose were interspersed with placebo doses.

Table 9 Dietary challenge regimen – doses and vehicles

Challenge type	Total dose (g allergen protein)	Number of DB doses (A active, P placebo)	DB dose regimen (g allergen protein)	Number of open doses	Open dose regimen (g allergen protein)	Allergen form for blind doses	Allergen form for open doses
Under 1 year							
Open	2g	n/a	n/a	4 incremental or 1 cumulative	0.1,0.2,0.5,1.2 or 2g	n/a	M= yoghurt, E= hard boiled egg (pureed), C= cod fillet (microwaved & pureed), P= peanut butter, S= Tahini, W-Weetabix
Under 3 years							
DBPCFC* ***Frequent Consumer***	5.85g	3A 2P	0.5, 1.35, 2.0	1	2	M= milk powder (mixed into carrier food from parents), E= whole hen's egg powder (mixed into carrier food from parents), C= cod fillet (made into potato cakes), P= defatted peanut flour (baked into chocolate muffins), S= Tahini (baked into biscuits), W= wheat flour (made into pancakes)	M= yoghurt/milk/cheese, E= hard boiled egg/well-cooked omelette/fried egg, C= Fish fingers/cod fillet, P= Peanut butter/Peanut flour/Salted peanuts/Bamba/M&Ms, S= tahini/chocolate tahini/Hummus/Sesame snaps/sesame seeds, W= wholemeal bread/Pasta/Weetabix/Shredded/couscous
DBPCFC* ***Infrequent Never Consumer***	5.85g	4A 3P	0.1, 0.25, 0.5, 2.0	1	3		
DBPCFC**	4.3g	3A 2P	0.1, 0.4, 1.3	1	2.5		
FCC**	4.3g	n/a	n/a	1	4.3		

Challenge type	Total dose (g allergen protein)	Number of DB doses (A active, P placebo)	DB dose regimen (g allergen protein)	Number of open doses	Open dose regimen (g allergen protein)	Allergen form for blind doses	Allergen form for open doses
3 years							
DBPCFC*	7.85g	3A 2P	0.5, 1.35, 2.0	1	4	As above except:	
Frequent Consumer						E= whole hen's egg powder (mixed into choc filling within	
DBPCFC*	7.85g	4A 3P	0.1, 0.25, 0.5, 2.0	1	5	eggless cake or directly mixed into carrier food from	
Infrequent Never Consumer						parents), P= defatted peanut flour (baked into chocolate	
DBPCFC**	5.3g	3A 2P	0.1, 0.4, 1.3	1	3.5	muffins/fruit biscuits)	
DBPCFC†	5.325g	4A 3P	0.025, 0.1, 0.4, 1.3	1	3.5	P= defatted peanut flour, S= tahini	
High risk (P/S)							
FCC**	5.3g	n/a	n/a	1	5.3		
Above 1 year							
FPIES	Based on	n/a	n/a	3-4 doses	0.3g/kg + 2g	n/a	M= fromage frais/yoghurt, E= hard boiled egg, F= Fish fingers
Non-Severe	child's weight						
FPIES					0.06g/kg +2g	n/a	
Severe							

* Pre change date 27/07/11 ** Post change date 27/07/11 † From Protocol V4 (01.08.12)

ADVERSE EVENTS

Parents reported potential reactions to foods principally through the online questionnaire but could also contact the study team by a dedicated study telephone number or email. Parents were asked about the frequency of gastrointestinal symptoms including posseting, vomiting, colic, diarrhoea and constipation; infectious symptoms including upper and lower respiratory tract infections and bronchiolitis; and wheeze and eczema symptoms throughout the duration of the study.
All hospital accident and emergency department attendances were recorded and families were contacted if a participant was admitted to hospital so a full report could be documented.

ADVERSE EVENT

An adverse event is any occurrence or worsening of an undesirable or unintended sign, symptom, laboratory finding, or disease that occurs during participation in the trial.
An adverse event will be followed until it resolves or until 30 days after a participant terminates from the study, whichever comes first.

SERIOUS ADVERSE EVENT

A Serious Adverse Event (SAE) is any untoward and unexpected medical occurrence or effect that:

- Results in death. A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up after the completion of therapy must be reported whether it is considered treatment related or not.
- Is life-threatening – refers to an event in which, in the view of the investigator, the subject was at risk of death at the time of the event
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity
- An event that requires intervention to prevent permanent impairment or damage. An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Regardless of the relation of the adverse event to study participation, the event must be reported as a serious adverse event if it meets any of the above definitions.

GRADING AND ATTRIBUTION OF ADVERSE EVENTS

Grading Criteria

The study site graded the severity of adverse events experienced by study participants according to the criteria set forth in the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 3.0. This document provided a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events.

Adverse events were graded on a scale from one to five according to the following standards in the NCI-CTCAE manual:
Grade 1 = mild adverse event.
Grade 2 = moderate adverse event.
Grade 3 = severe and undesirable adverse event.
Grade 4 = life-threatening or disabling adverse event.
Grade 5 = death.
All adverse events were reported and graded whether they were or were not related to disease progression or treatment.

Attribution Definitions
The relation, or attribution, of an adverse event to study participation was determined by the site investigator. The site investigator also recorded the determination of attribution on the appropriate case report form and/or SAE reporting form. The relation of an adverse event to the study treatment was determined using the descriptors and definitions provided in Table 10.

Table 10 NCI-CTCAE Attribution of Adverse Events

Code	Descriptor	Definition
Unrelated Category		
1	Unrelated	The adverse event is clearly not related to study participation
Related Categories		
2	Unlikely	The adverse event is doubtfully related to study participation
3	Possible	The adverse event may be related to study participation
4	Probable	The adverse event is likely related to study participation
5	Definite	The adverse event is clearly related to study participation

IDMC

All safety data were reviewed periodically by the independent data monitoring committee (IDMC). In addition, SAEs were reported locally. The IDMC had the authority to withdraw any participants and/or terminate the study because of safety findings.

Membership of the EAT Study IDMC has been organized by the Food Standards Agency (FSA). As per Medical Research Council recommendations the membership consists of four individuals with expertise in the areas of paediatric allergy, paediatric research and trial management. One member is an experienced trial statistician.

STUDY MANAGEMENT

TRIAL STEERING COMMITTEE

The role of the EAT Study Trial Steering Committee (TSC) was to be the main decision making body. It had overall responsibility for scientific strategy and direction and had ultimate responsibility for ensuring the project's aims were delivered on time and within budget.

The TSC included external representatives with expertise in paediatric nutrition and the design of robust methodologies for collecting dietary data. The members of the TSC at completion of the project were:

Independent members
Professor Graham Roberts, Professor in Paediatric Allergy, Southampton University (Chair)
Professor David Strachan, St George's University of London (Vice Chair)
Professor Christine Edwards, University of Glasgow
Mr David Reading, Honorary Vice-President, Anaphylaxis Campaign (Lay Member)
Dr Mary Fewtrell, Reader in Childhood Nutrition, UCL Institute of Child Health

Dependent Members
Dr Michael Perkin, King's College London
Dr Kirsty Logan, EAT Study Coordinator (non-voting)
Dr Carsten Flohr, King's College London (non -voting)
Professor Gideon Lack, King's College London
Professor Janet Peacock, King's College London (principal Study Statistician)
Dr Salma Ayis, King's College London (assistant Study Statistician) (non-voting)
Professor Ian Kimber, Professor of Toxicology, University of Manchester (on behalf of FSA)

Observers (non-voting)
Ms Elizabeth Kendall, Food Standards Agency
Ms Shuhana Begum, Food Standards Agency

Former TSC members
Dr Joelle Buck, Food Standards Agency
Ms Sarah Hardy, Food Standards Agency
Professor Andy Grieve, King's College London (study statistician)
Professor Anne Greenough, King's College London

STATISTICAL ANALYSES

At study commencement the expected food allergy prevalence in the SIG was 6%. An analysis undertaken after three months of recruitment indicated that the EAT parental atopy rate was higher than a contemporary UK population based study.[20] Data from the Early Prevention of Asthma in Atopic Children (EPAAC) study was used to extrapolate the expected SIG food allergy rate based on the observed prevalence of 30% visible eczema amongst these initial participants.[50] Taken together the revised estimate of expected food allergy prevalence in the SIG group was 8%.

The trial has 80% power to detect a 50% relative reduction in the absolute prevalence of food allergy by three years of age (from 8% in the SIG to 4% in the EIG) assuming a 15% drop out rate. These numbers were used to calculate the final cohort size of 1302 infants (651 infants in each arm) yielding a final cohort size of 1106 infants (553 infants in each arm) after drop out.

The primary outcome and other comparisons of proportions were analysed using a chi-square test. Fisher's exact test was used if more than 80% of expected values were less than five and exact binomial confidence intervals were used except for analyses with small *n* where Jeffreys binomial confidence intervals were used as recommended by Brown et al.[51] Continuous outcomes were analysed using methods based on the Normal distribution where possible either if data were Normal or could be suitably transformed. All analyses were 2-sided with 5% significance level.

AD HOC ANALYSES

Statistical analysis followed an a priori analysis plan. Post hoc analyses that were undertaken to further explain the data but were not in the original statistical analysis plan are listed below:

1. Logistic modelling and dominance analysis of factors influencing being positive for the primary outcome (see Table 36)
2. Logistic modelling of factors influencing being evaluable for the primary outcome (see Table 72)
3. Logistic modelling and dominance analysis of factors influencing SIG non-adherence and EIG non-adherence (see Tables 69 and 70 respectively)
4. Adjusted per-protocol analysis (see Figures 24 and 25)
5. Does response analysis (Figure 33). Although a dose-response analysis was pre-planned, we divided consumption data into quartiles rather than the pre-specified quintiles because of the relatively low event rate of food allergy.

The adjusted per-protocol analysis was a conservative per-protocol analysis that adjusted the SIG food allergy prevalence by subtracting the number of baseline EIG participants who were challenge positive at enrollment and completed the study with a confirmed food allergy from both the numerator (the number of allergic SIG participants) and the denominator (the number of SIG per-protocol adherent participants). This conservative analysis is presented as EIG children who were already allergic at baseline clearly could not follow the protocol for that food and hence subtracting an equal number of allergic children from the SIG redresses this balance.

Logistic analysis was undertaken to establish: factors related to the primary outcome; factors that predicted non-adherence in the standard and EIGs. We also undertook a dominance analysis of factors contributing to being primary outcome positive and to being non-adherent in the two study groups. Dominance analysis discerns the relative importance of independent variables in an estimation model based on each variable's contribution to overall model fit statistics.

A number of the adverse events reported by parents in the online questionnaires had categorical responses based on frequency of symptoms. For the statistical comparison between groups, responses over particular periods were pooled, e.g. the number of participants reporting no episodes of wheezing was added for each interim questionnaire over the time period and this was repeated for each categorical response. These total counts for each category were then compared between study groups with a chi square test for trend.

HIGH RISK SUBGROUP

The high risk subgroup within EAT were defined as those infants with visible eczema at the enrolment visit.

CHAPTER 3 – RESULTS

The EAT Study recruited a cohort of 1303 three month old infants which was geographically representative of the population of England & Wales (Figure 8).

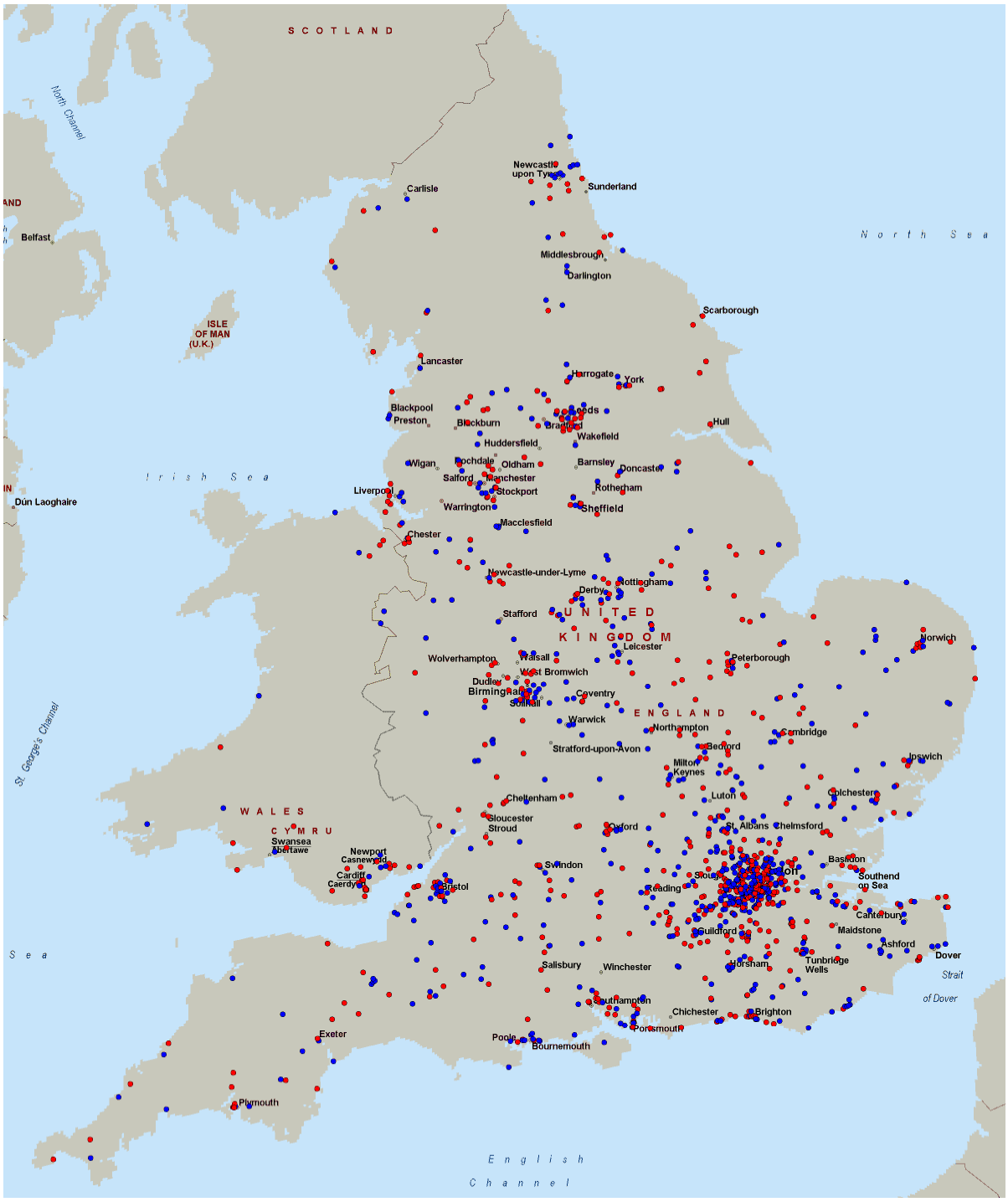


Figure 8 Location of EAT Study Participants

Key: SIG red circle, EIG blue circle

Table 11 Demographics and Clinical Assessment at Trial Enrolment

		SIG % (n/N)	EIG % (n/N)	UK Data %
Number in group		651	652	
Demography				
Median age at enrolment (weeks):		14.7 (n=651) (range 13.0 - 18.0)	14.7 (n=652) (range 12.9 - 18.0)	
Sex:	Male	52.1 (339/651)	48.2 (314/652)	51.3 [52]
	Female	47.9 (312/651)	51.8 (338/652)	48.7
Ethnicity:	White	84.0 (547/651)	85.4 (557/652)	87.1 [14]
	Black	2.9 (19/651)	3.4 (22/652)	3.6
	Asian	1.7 (11/651)	2.6 (17/652)	6.5
	Chinese	0.5 (3/651)	1.2 (8/652)	1.2
	Mixed	10.9 (71/651)	7.4 (48/652)	1.6
Home location:	Urban	77.4 (503/650)	77.3 (503/651)	81.5 [52]
	Rural (non-farm)	20.3 (132/650)	19.5 (127/651)	17.6
	Rural (farm)	2.3 (15/650)	3.2 (21/651)	0.9
Pet ownership		44.6 (290/650)	40.6 (264/651)	77.9* [53]
Maternal education:	≤16	6.2 (40/650)	5.2 (34/652)	18.8 [14]
(age at completion)	17-18	13.7 (89/650)	12.7 (83/652)	28.9
	>18	80.2 (521/650)	82.1 (535/652)	52.3
Smoking				
Maternal (in pregnancy)		3.9 (25/650)	3.2 (21/651)	11.5 [14]
Maternal (post partum)		3.1 (20/650)	3.4 (22/651)	13.3 [14]
Paternal		10.9 (71/650)	10.8 (70/651)	20.0 [14]
Family history				
Median maternal age (years):		33 (n=650) (range 19 – 46)	33.5 (n=652) (range 19 – 45)	49% 30 or over [14]

		SIG % (n/N)	EIG % (n/N)	UK Data %
Siblings	0	38.3 (249/651)	37.3 (243/652)	49.9 [14]
	1	36.9 (240/651)	39.3 (256/652)	33.5
	2	16.4 (107/651)	14.9 (97/652)	10.9
	3+	8.5 (55/651)	8.6 (56/652)	5.0
Birth history				
Mean birth weight grams (SD)		3560 (n=651) (487)	3570 (n=651) (489)	3489 (Ireland) [54] (512)
Mode of delivery:	Vaginal	77.3 (503/651)	72.4 (472/652)	76.2 [14]
	Caesarean	22.7 (148/651)	27.6 (180/652)	24.8
Mean gestational age (weeks)		39.7 (n=651)	39.9 (n=652)	
Participant enrolment atopy status				
Sensitisation (SPT>0):		Not applicable	5.1 (33/652)	1.2† (Denmark) [55]
Filaggrin mutation		11.5 (69/598)	12.2 (74/608)	10.5‡ (Ireland) [54]
Visible eczema		24.2 (157/650)	24.5 (160/652)	18.7 (Ireland)§ [54]
Median SCORAD (infants with eczema)		7.5 (n=157) (range 3.5 – 49.2)	7.5 (n=160) (range 3.5 - 75.0)	21.5¶ (Ireland)§ [54] (range 0-88)
EIG median age of allergenic food first consumption (weeks)				
Dairy		-	17.3	
Egg		-	19.6	
Fish		-	19.6	
Sesame		-	19.6	
Peanut		-	19.6	
Wheat		-	20.6	

	SIG % (n/N)	EIG % (n/N)	UK Data %
Family atopy status (self reported)			
Maternal			
Eczema	34.2 (222/650)	34.9 (227/651)	19.9 [20]
Asthma	26.8 (174/650)	25.8 (168/651)	13.0 [20]
Hay fever	46.9 (305/650)	43.8 (285/651)	25.2 [20]
Food allergy	16.9 (110/650)	21.8 (142/651)	27.5 [56]
Maternal atopy (E, A or HF)	63.2 (411/650)	61.9 (403/651)	40.8 [20]
Maternal atopy (E, A, HF or FA)	66.2 (430/650)	65.8 (428/651)	
Paternal			
Eczema	21.1 (137/650)	18.9 (123/651)	8.4 [20]
Asthma	23.5 (153/650)	21.8 (142/651)	12.0 [20]
Hay fever	41.1 (267/650)	40.3 (262/651)	20.7 [20]
Food allergy	10.0 (65/650)	11.2 (73/651)	14.0 [56]
Paternal atopy (E, A or HF)	55.7 (362/650)	50.5 (329/651)	30.4 [20]
Paternal atopy (E, A, HF or FA)	57.1 (371/650)	52.8 (344/651)	
Parental			
Parental atopy (E, A or HF)	83.9 (545/650)	80.0 (521/651)	57.7 [20]
Parental atopy (E, A, HF or FA)	85.4 (555/650)	82.5 (537/651)	51.0 [14]
Maternal allergenic food consumption			
During pregnancy	100.0 (639/639)	100.0 (631/631)	
During breastfeeding	100.0 (639/639)	100.0 (631/631)	

UK data used for comparison unless suitable equivalent study not available

* Pet ownership under 3 years of age

† Denmark. 3 months of age – cows' milk (0.6%) and hen's egg (0.6%) (commercial skin prick solutions) and fresh cows' milk (0.6%). Positive SPT defined as a mean-wheal size ≥2 mm larger than the negative control.

‡ Four filaggrin mutations assessed: R501X , 2282Del4, S3247X & R2447X

§ Ireland: 6 months of age.

¶ Mean SCORAD

** Parental and/or sibling (E, A, HF or FA)

BASELINE COMPARISON OF THE STUDY GROUPS

The median age at enrollment was 3.4 months (Table 11). The two groups were balanced in all respects at baseline with the exception of their having been more EIG participants born by Caesarean section (27.6% in the EIG versus 22.7% in the SIG, p=0.04). Caesarean section has been associated with an increased likelihood of food allergy[57] and therefore this imbalance would render the EIG at increased risk of food allergy thus not introducing a bias in favour of the EIG participants.

PARTICIPANT ATOPIC STATUS

The EAT cohort's atopy status, as one would anticipate from the nature of the study, was enriched in comparison to other unselected general population cohorts. Our filaggrin mutation inheritance rate (11.9%) was slightly higher than that observed in two general population studies in the Isle of Wight cohort study (10.3%)[58] and a recent Irish birth cohort study (10.5%).[54] Studies assessing unselected cohorts of 3 month old infants are rare. The EAT visible eczema rate at 3 months (24.4%) was higher than in the 6 month old infants examined in the Irish cohort study (18.7%), using the same diagnostic criteria, although the mean SCORAD amongst those with eczema was significantly higher in the Irish study than our study. The sensitisation rate in the EIG in EAT was higher than the 1.2% observation in the DARC cohort,[55] but the latter only tested for two foods, milk and egg, and used only a commercial skin prick test solution for the latter.

The EAT cohort was also enriched by the 82% of parents reporting they themselves had a history of eczema, asthma or hay fever, higher than the 51% rate of allergy (these conditions and self-reported food allergy in either parent or a sibling) reported in the IFS2010. In the latter, the rate in mothers with a managerial/professional occupation (more similar to EAT mothers) was 56%, still significantly less than EAT.

Table 11 also shows that at randomisation there was a higher prevalence of self-reported maternal food allergy in the EIG compared to the SIG group. However, for both groups, this reported figure is likely to substantially exceed the true prevalence of maternal food allergy. In a population-based study of 20,000 people in the UK, 20% of adults thought that they had a food allergy or intolerance, but only 1·8% of a subset of these patients had a positive challenge using a restricted range of eight selected foods.[59] Furthermore, the prevalence of asthma and hay fever was higher in the SIG as was combined maternal atopy both excluding and including food allergy.

At the three year visit, EAT parents underwent skin prick testing to a panel of airborne allergens as well as to any food that the parent suspects they are allergic to. This will allow an objective measure of the degree of atopy in EAT parents and the extent to which this corresponds with the high parent reported atopy rate.

This information was collected prior to randomisation and commencement of the study intervention and these differences have occurred by chance alone. If there were a higher rate of objective food allergy in the EIG mothers, then it is possible that it is influencing the study results as this may mean this group are more likely to develop atopic disease (although evidence has shown this would not predispose children to food allergy specifically).

However, if this was occurring, it would lessen the effect of the intervention and potentially underestimate any effect of the early introduction of allergenic foods. We are therefore confident that this is not inflating any intervention effect we do see.

RETENTION RATES

Retention rates in the study were extremely high with 91.3% of participants returning for the final clinical visit. Using the *a priori* agreed visit window for the final visit of up to 4 years of age, 90.0% of participants were eligible to be analysed for the primary outcome analysis.

The CONSORT flow diagram is presented in Figure 9. A higher number of EIG than SIG participants withdrew in the early stages of the trial due to problems or concerns with the early introduction regimen. While non-compliance itself was not a criterion triggering exclusion from ongoing participation in the study, some parents did not want to continue to try the early introduction process and opted to withdraw. The differential withdrawal rate is to be expected when what is being asked of one group is more difficult to achieve or more controversial than the other group.

Questionnaire response rates were high, particularly for the key questionnaires, with 94.0% of participants completing the final 36 month questionnaire (Table 12).

INFLUENCE OF STUDY GROUP ON RETENTION AND QUESTIONNAIRE COMPLETION

EIG retention and participation rates were significantly lower than the SIG (Table 12). Questionnaire completion rates were significantly lower in general in the EIG but not statistically different for three out of the four "key" questionnaires.

Table 12 Participation Rates at Different Points of Study

	Total % (n)	SIG % (n)	EIG % (n)	p value comparing SIG and EIG participants
Clinical visits				
Enrolment visit	100.0 (1303)	100.0 (651)	100.0 (652)	-
1 year visit	88.3 (1151)	92.3 (601)	84.4 (550)	<0.0005
3 year visit	91.3 (1189)	93.4 (608)	89.1 (581)	0.006
3 year visit *(at <4 years of age)*	90.0 (1173)	92.3 (601)	87.7 (572)	0.006
Key questionnaires				
3 month general	100.0 (1303)	100.0 (651)	100.0 (652)	-
3 month food frequency	97.5 (1270)	98.2 (639)	96.8 (631)	0.11
12 month interim questionnaire	88.3 (1151)	92.2 (600)	84.5 (551)	<0.0005
36 month interim questionnaire	94.0 (1225)	94.9 (618)	93.1 (607)	0.16
Total number of questionnaires completed - median (IQR)	16 (12-17)	17 (14-17)	15 (9-17)	<0.0005

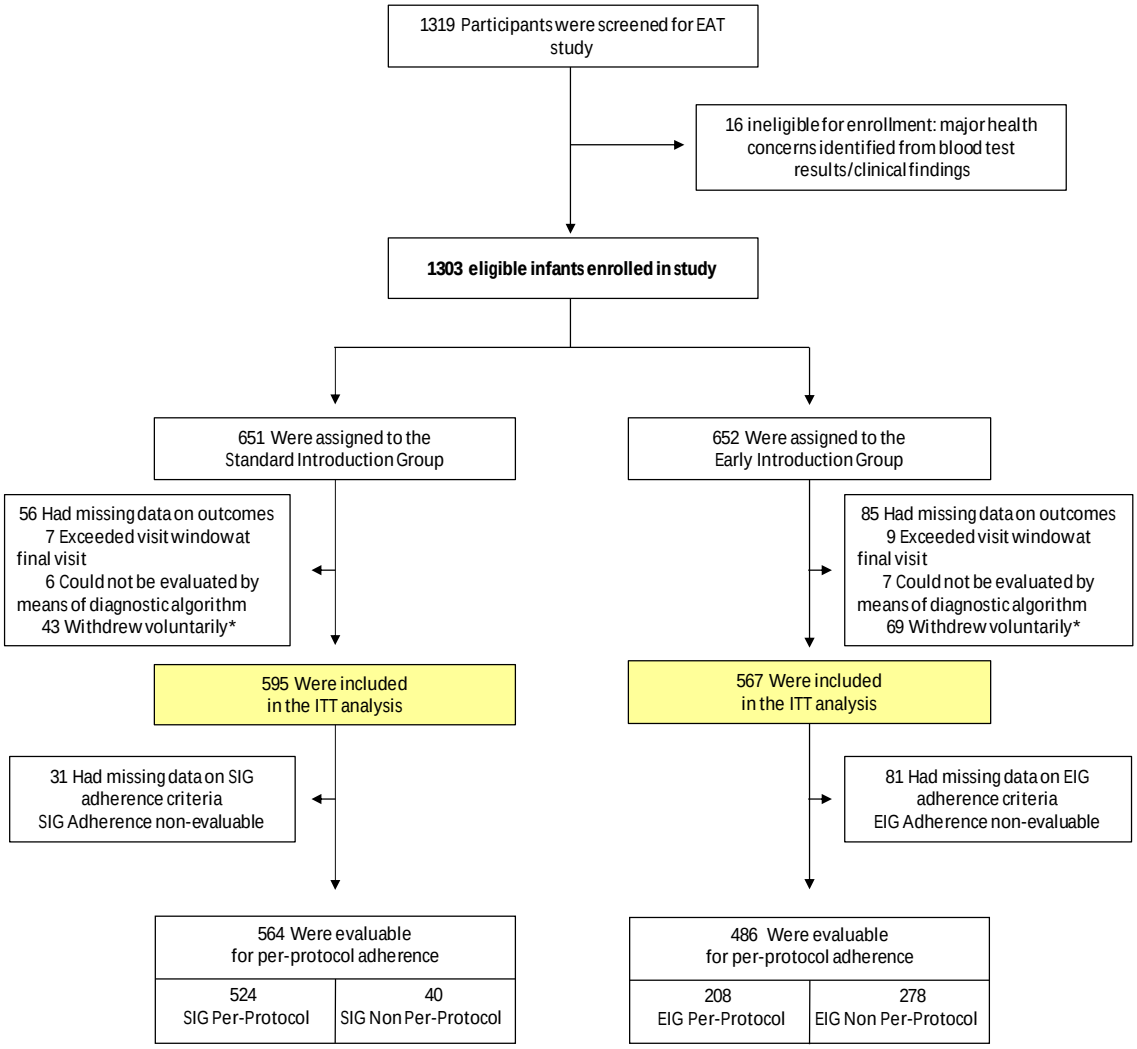


Figure 9 Enrollment and Randomization in the EAT Trial

*Reasons for withdrawal: 43 participants in the SIG and 69 participants in the EIG withdrew voluntarily from the study. Reasons given were as follows: concerns about the blood tests (SIG 0, EIG 2), emigration (SIG 10, EIG 12), expenses (SIG 1, EIG 1), family health issues (SIG 3, EIG 0), family issues (SIG 2, EIG 4), no reason given (SIG 11, EIG 16), lost contact with family (SIG 15, EIG 28), too far to travel for study assessments (SIG 0, EIG 1) and unhappy participating in the study (SIG 1, EIG 5).

The per-protocol included participants who adhered adequately to the assigned regimen which was defined as follows: Both groups: continued breastfeeding to at least five months of age; Standard introduction group: no consumption of peanut, egg, sesame, fish or wheat before five months of age and consumption of less than 300 mls per day of formula milk between three and six months of age; Early introduction group: consumption of at least five of the early introduction foods, for at least 5 weeks between three and six months of age, of at least 75% of the recommended dose (i.e. 3 g per week of allergenic protein).

BASELINE SPT DETAILS

At enrollment, 5.1% (33/652) of the EIG had a positive skin-prick test to an early introduction food (Table 13). Histamine, like the food allergens, was tested in duplicate. There were no children with double negative histamine responses.

All 33 were invited for food challenges to the relevant foods: seven were positive (to one or more foods), 22 were negative (to one or more foods) and four failed to return (Table 13).

If the enrollment challenge was negative, families were encouraged to feed their infant the recommended quantity of the specific food. Table 14 indicates that the experience of undertaking the challenge did not adversely affect a family's willingness to introduce the food into their infant's diet.

Of the seven baseline challenge positive participants, five were primary outcome positive, one primary outcome negative and one dropped out of the study (Table 13). Of the 22 challenge negative participants, one was primary outcome positive, three were non-evaluable and 18 remained non-reactive.

Reactions of the seven participants who had 10 baseline positive challenges between them were all mild (Table 15). Six challenges required no treatment and four were treated with antihistamines. There were no cases of anaphylaxis during the challenges and no intramuscular epinephrine was administered.

Both baseline allergic and skin-prick test positive early introduction participants were more likely to have visible eczema and be black, Asian or Chinese (Table 16).

Table 13 Skin-Prick Test and Challenge Results of Baseline Food Allergic and Skin-prick Test Positive Participants

ID	Enrollment visit		12 month visit			36 month visit			Study primary outcome status
	Skin-prick test (mm) at 3m	Enrollment challenge outcome	Skin-prick test (mm) at 12m	12m challenge outcome	12m primary outcome status	Skin-prick test (mm) at 36m	36m challenge outcome	36m primary outcome status	
Baseline food allergic (n=7)									
1	RE5	E+	Drop out	Drop out	Drop out	Drop out	Drop out	Drop out	Indeterminate
2	M5	M+	E6	M+* E+	Positive (E)	E2	M- E-	Negative	Positive (E)
3	M6 P2	M+ P+	M4 E1 P5	M- E- Pts	Indeterminate	P5	P-	Negative	Negative
4	M5 RE16	M+ Eind	P2	M+* Pne†	Indeterminate	M2 E3 C5 P6	Mdna E+ C- P+	Positive (PE)	Positive (PE)
5	RE7	E+	E6	E+	Positive (E)	Drop out	Drop out	Drop out	Positive (E)
6	M7 P4	M+ P+	M1 P1	M+ Pdna	Positive (M)	M1 E1 P5	Mdna(fc) E- P-	Indeterminate	Positive (M)
7	RE3 P3 W2	E- P- W+	M4 E6 P7 W6	Mdna(fc) E+ Pdna	Positive(EW)	E3 P7	MEWdna(fc) P+	Positive(P)	Positive(EPW)
Base line food skin-prick test positive - enrollment challenge: negative (n=22)									
8	RE5	E-	All negative	Not required	Negative	All negative	Not required	Negative	Negative
9	RE7	E-	E4	E-	Negative	All negative	Not required	Negative	Negative
10	M4 RE5	M- E-	All negative	Not required	Negative	All negative	Not required	Negative	Negative
11	RE4	E-	E5 P3	E- P-	Negative	All negative	Not required	Negative	Negative
12	P2	P-	All negative	Not required	Negative	All negative	Not required	Negative	Negative
13	P1	P-	All negative	Not required	Negative	All negative	Not required	Negative	Negative
14	RE2	E-	M5 E4	Mdna Eic	Indeterminate	All negative	E-	Indeterminate	Indeterminate
15	RE5	E-	E2	E-	Negative	0	Not required	Negative	Negative
16	M3	M-	All negative	Not required	Negative	All negative	Not required	Negative	Negative
17	P3	P-	All negative	Not required	Negative	All negative	Not required	Negative	Negative
18	RE7	E-	E7	Einc	Indeterminate	E2 W2	E- W-	Negative	Negative
19	RE16	E-	All negative	Not required	Negative	All negative	Not required	Negative	Negative
20	RE6	E-	M2 E7 C3	M+ E- C-	Positive (M)	M2 E5	M-	Negative	Positive(M)
21	RE3	E-	E7	Not required	Negative	E1	Not required	Negative	Negative
22	RE4	E-	All negative	Not required	Negative	C1 P1 W1	C- P- W-	Negative	Negative
23	RE2	E-	E1	E-	Negative	All negative	Not required	Negative	Negative
24	M5 RE6 P4	M- E- P-	E7 C4	C- Eic	Indeterminate	E4 C2 P4	E- P-	Negative	Negative
25	M4 RE5	M- Edna(fc)	All negative	Not required	Indeterminate	Drop out	Drop out	Drop out	Indeterminate
26	RE3	E-	E2	E-	Negative	E2 S3	Sdna(fc)	Indeterminate	Indeterminate
27	RE6	E-	All negative	Not required	Negative	All negative	Not required	Negative	Negative
28	RE7	E-	All negative	Not required	Negative	All negative	Not required	Negative	Negative
29	RE2	E-	Did not attend	Did not attend	Did not attend	All negative	Not required	Negative	Negative

Base line food skin-prick test positive - enrollment challenge: did not attend (n=4)									
30	M3 RE6	Mdna Edna	E3	M- E+	Positive (E)	E1	E+	Positive (E)	Positive (E)
31	M3	Drop out	Drop out	Drop out	Drop out	Drop out	Drop out	Drop out	Indeterminate
32	P2	Pdna	Did not attend	Did not attend	Did not attend	P13	P+	Positive (P)	Positive (P)
33	RE7	Edna	Did not attend	Did not attend	Did not attend	E2	E-	Negative	Negative

Table 14. Allergen Consumption Status by Six Months of the Baseline Food Allergic and Skin-prick Test Positive Participants

ID	Skin-prick test (mm) at 3m	Enrollment challenge outcome	EIG per-protocol status	Peanut consumption at 6 months	Egg consumption at 6 months	Milk consumption at 6 months	Sesame consumption at 6 months	Fish consumption at 6 months	Wheat consumption at 6 months	Study primary outcome status
Baseline food allergic (n=7)										
1	RE5	E+	Non-evaluable	Not tried yet[5]	Not tried yet[5]	50%[5]	Not tried yet[5]	Not tried yet[5]	Not tried yet[5]	Indeterminate
2	M5	M+	Non-evaluable	100%[7]	100%[7]	Not tried yet[7]	100%[7]	100%[7]	100%[7]	Positive (E)
3	M6 P2	M+ P+	No	Not tried yet	100%	Not tried yet	100%	100%	100%	Negative
4	M5 RE16	M+ Eind	No	50%	Not tried yet	Not tried yet	50%	50%	75%	Positive (PE)
5	RE7	E+		100%[7]	Not tried yet[7]	100%[7]	100%[7]	75%[7]	75%[7]	Positive (E)
6	M7 P4	M+ P+	No	Not tried yet	50%	Not tried yet	25% or less	100%	100%	Positive (M)
7	RE3 P3 W2	E- P- W+	No	50%[7]	100%[7]	100%[7]	50%[7]	100%[7]	Not tried yet[7]	Positive(EPW)
Base line food skin-prick test positive - enrollment challenge: negative (n=22)										
8	RE5	E-	Yes	100%	100%	100%	100%	100%	100%	Negative
9	RE7	E-	Yes	100%	100%	100%	100%	100%	75%	Negative
10	M4 RE5	M- E-	No	100%	100%	100%	75%	100%	100%	Negative
11	RE4	E-	No	Not tried yet[8]	100%[8]	100%[8]	Not tried yet[8]	Not tried yet[8]	Not tried yet[8]	Negative
12	P2	P-	Yes	100%	50%	100%	75%	100%	100%	Negative
13	P1	P-	Yes	100%	100%	100%	100%	100%	100%	Negative
14	RE2	E-	Yes	75%	25% or less	100%	75%	75%	75%	Indeterminate
15	RE5	E-	Non-evaluable	75%[5]	25% or less[5]	75%[5]	25% or less[5]	75%[5]	Not tried yet[5]	Negative
16	M3	M-	No	25% or less	25% or less	100%	25% or less	25% or less	25% or less	Negative
17	P3	P-	Non-evaluable	Not tried yet[5]	50%[5]	100%[5]	25% or less[5]	50%[5]	25% or less[5]	Negative
18	RE7	E-	Yes	100%	75%	100%	100%	100%	100%	Negative
19	RE16	E-	No	25% or less	25% or less	75%	25% or less	Not tried yet	Not tried yet	Negative
20	RE6	E-	No	100%	100%	Not tried yet	100%	100%	100%	Positive(M)
21	RE3	E-	No	100%	100%	100%	75%	100%	25% or less	Negative
22	RE4	E-	No	100%	50%	100%	75%	100%	100%	Negative
23	RE2	E-	Yes	50%	Not tried yet	75%	50%	50%	75%	Negative
24	M5 RE6 P4	M- E- P-	No	50%	50%	25% or less	50%	50%	50%	Negative
25	M4 RE5	M- Edna(fc)	No	100%[7]	Not tried yet[7]	Not tried yet[7]	100%[7]	100%[7]	100%[7]	Indeterminate
26	RE3	E-	Non-evaluable	50%[7]	75%[7]	100%[7]	25% or less[7]	50%[7]	100%[7]	Indeterminate
27	RE6	E-	No	100%[7]	100%[7]	100%[7]	100%[7]	100%[7]	100%[7]	Negative
28	RE7	E-	Yes	100%	100%	100%	100%	100%	100%	Negative
29	RE2	E-	Yes	75%	75%	100%	75%	75%	75%	Negative

Base line food skin-prick test positive - enrollment challenge: did not attend (n=4)										
30	M3 RE6	Mdna Edna	No	Not tried yet[5]	Not tried yet[5]	100%[5]	Not tried yet[5]	Not tried yet[5]	Not tried yet[5]	Positive (E)
31	M3	Drop out	No	50%	75%	100%	50%	100%	100%	Indeterminate
32	P2	Pdna	Non-evaluable	Not tried yet	No data	No data	No data	No data	No data	Positive (P)
33	RE7	Edna	Non-evaluable	No data	No data	No data	No data	No data	No data	Negative

[5] Six month questionnaire consumption data not available so data presented are from last week of the four weeks consumption data recorded in the five month questionnaire

[7] Six month questionnaire consumption data not available so data presented are from first week of the four weeks consumption data recorded in the seven month questionnaire

[8] Six month questionnaire consumption data not available so data presented are from first week of the four weeks consumption data recorded in the eight month questionnaire

In Table 14, the degree to which the 33 baseline skin prick test positive early-introduction group participants were consuming the early introduction foods by six months of age is shown. The percentage of the weekly recommended dose (4 g) is shown for each of the six foods for the last week before the participant turned six months of age. Where six month questionnaire consumption data was not available, data were obtained from the nearest chronological questionnaire that had been completed (see key above). The participants' per-protocol status is given. For the seven participants who were enrollment challenge positive, their per-protocol status was more likely to be non-adherent because of their being less of the six foods that were eligible to consume in the key introduction period (see Discussion and Implications)

Table 15 Details of 7 Children with Positive Food Challenges at Enrolment

ID	Food	FC symptoms	FC treatment	Reaction dose
1	Egg	Itchy rash	Antihistamines	Egg - dose 1 (0.1g)
2	Milk	≥3 hives	No treatment	Milk - dose 1 (0.1g)
3	Peanut	Rash, ≥3 hives and scratching	Antihistamines	Peanut - dose 1 (0.1g)
3	Milk	≥3 hives	No treatment	Milk - dose 1 (0.1g)
4	Egg	Mild abdominal pain*	No treatment	Egg - safety dose 1 (0.01g)
4	Milk	≥3 hives	No treatment	Milk - dose 1 (0.1g)
5	Egg	≥3 hives	No treatment	Egg - dose 1 (0.1g)
6	Peanut	Vomiting and scratching	No treatment	Peanut - dose 4 (1.2g)
6	Milk	≥3 hives	Antihistamines	Milk - dose 3 (0.5g)
7	Wheat	≥3 hives	Antihistamines	Wheat - dose 1 (0.1g)

Table 16 Demographics of Baseline Food Allergic and Skin-prick Test Positive EIG Participants

ID	Maternal History of Eczema	Filaggrin mutation	Sex	Ethnicity	Mode of delivery	TEWL (g/m^2h) at 3m	Visible eczema at 3m	Scorad
Baseline food allergic (n=7)								
1	No	No	Female	Black/Asian/Chinese	Caesarean	59.9	Yes	75
2	No	No	Female	White	Vaginal	12.2	No	0
3	No	No	Female	White	Vaginal	29.6	Yes	3.7
4	No	No	Male	White	Caesarean	10.7	Yes	25.7
5	No	No	Male	Black/Asian/Chinese	Vaginal	15.9	Yes	15.2
6	No	No	Male	Black/Asian/Chinese	Vaginal	17.4	Yes	53
7	No	No	Female	Black/Asian/Chinese	Vaginal	15.0	Yes	44.6
Base line food skin-prick test positive - enrollment challenge: negative (n=22)								
8	Yes	No	Female	White	Vaginal	11.5	No	0
9	No	Yes	Female	White	Vaginal	12.7	Yes	17.6
10	No	No	Female	White	Vaginal	13.8	Yes	11
11	No	No	Female	White	Vaginal	46.7	Yes	48.6
12	Yes	No	Female	White	Vaginal	10.4	No	0
13	No	No	Male	White	Vaginal	8.4	No	0
14	Yes	No	Male	White	Caesarean	18.2	Yes	14.6
15	No	No	Female	White	Caesarean	16.1	Yes	21.1
16	Yes	Yes	Female	White	Vaginal	29.2	Yes	18.1
17	Yes	No	Female	Mixed	Vaginal	12.1	No	0
18	Yes	Yes	Female	White	Caesarean	29.6	Yes	13.9
19	No	No	Male	Black/Asian/Chinese	Vaginal	10.3	Yes	21.8
20	No	No	Male	White	Vaginal	25.9	Yes	19.8
21	Yes	No	Male	White	Vaginal	13.9	Yes	7.2
22	No	No	Male	White	Caesarean	18.8	Yes	4.7
23	Yes	Yes	Female	White	Vaginal	27.8	Yes	11.1
24	No	No	Female	Black/Asian/Chinese	Vaginal	51.3	Yes	11.6
25	No	No	Female	Black/Asian/Chinese	Vaginal	7.8	No	0
26	Yes	No	Female	Black/Asian/Chinese	Vaginal	14.3	No	0
27	Yes	No	Male	White	Caesarean	13.3	No	0
28	No	No	Female	White	Vaginal	29.8	Yes	30.9
29	No	No	Female	White	Caesarean	10.0	No	0
Base line food skin-prick test positive - enrollment challenge: did not attend (n=4)								
30	No	No	Female	Black/Asian/Chinese	Vaginal	28.4	Yes	23.1
31	Yes	No	Female	Black/Asian/Chinese	Vaginal	15.5	No	0
32	Yes	No	Female	Mixed	Caesarean	27.8	No	0
33	No	No	Female	Black/Asian/Chinese	Vaginal	17.1	No	0

Key: TEWL Trans-epidermal water loss SCORAD SCORing Atopic Dermatitis index

BREASTFEEDING

The EAT Study aimed to maintain high breastfeeding rates in both groups and for there to be no detrimental impact of early allergenic food introduction on breastfeeding performance. This proved to be the case with breastfeeding duration being identical in both groups (Figure 10 - right hand panel) and significantly above equivalent UK infant feeding data from the IFS 2010. Virtually all mothers in both groups were still breastfeeding at six months of age (Table 17) and the median total duration of breastfeeding was one year's duration in both groups (Table 18).

Table 17 Percentage of mothers' breastfeeding at 6 months

	SIG % (n/N)	EIG % (n/N)	
Any breastfeeding at 6 months	97.8 (619/633)	97.2 (593/610)	p=0.52

Table 18 Total duration of breastfeeding

	SIG median (IQR)	EIG median (IQR)	
Duration of breastfeeding (weeks)	53 (38-68)	52 (36-66)	p=0.11

SIG BREASTFEEDING

The SIG were asked to aim for the UK target of around six month's exclusive breastfeeding. In the SIG, over 90% of infants at 4 months and 67% at 5 months of age were still being exclusively breastfed (Table 19). This significantly exceeds the IFS 2010 figure using as a baseline mothers in the IFS 2010 survey from England and Wales who had exclusively breastfed to three months of age (Figure 10).[14] At six months of age exclusive breastfeeding at 28.6% very significantly exceeded these equivalent mothers.

Table 19 Percentage of SIG mothers exclusively breastfeeding to around six months

	SIG % (n/N)	IFS 2010* %	Total UK %
Exclusive breastfeeding at 4 months	90.3 (574/636)	71.0%†	12%
Exclusive breastfeeding at 5 months	66.8 (425/636)	26.9%†	5%
Exclusive breastfeeding at 6 months	28.6 (182/636)	3.6%‡	1%

*Using as a baseline comparison IFS 2010 mothers in England and Wales who had exclusively breastfed their infants to three months of age
†p<0.0005 ‡p<0.01

EIG BREASTFEEDING

For the EIG, the intention was that exclusive breastfeeding ceased with the introduction of baby rice (or something similar) shortly after enrolment. This was achieved with EIG infants losing their exclusive breastfeeding status significantly faster than equivalent infants in the IFS2010 (Figure 10 - left panel, p<0.001).

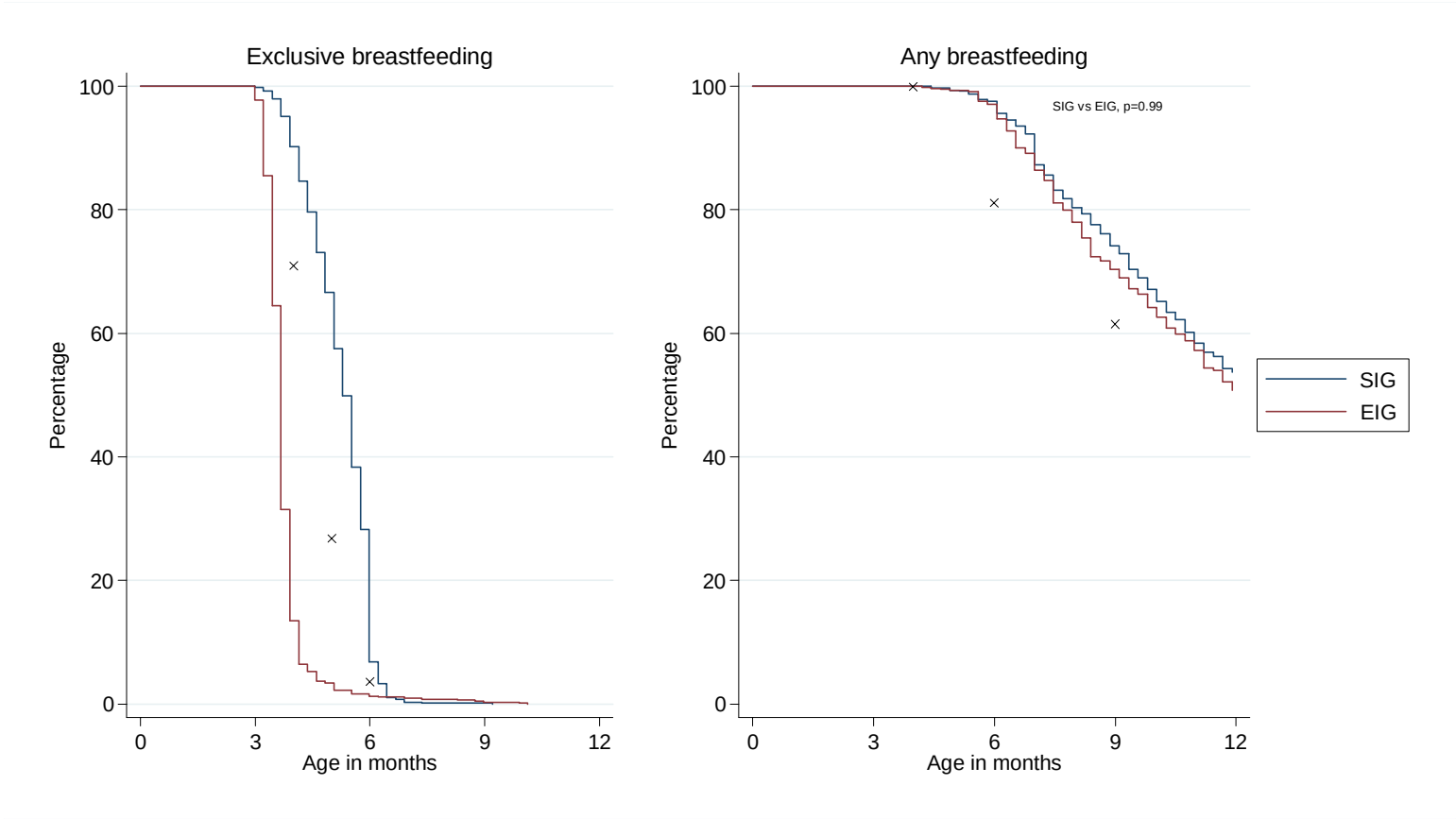


Figure 10 Breastfeeding in the EAT Cohort

Kaplan Meier survival curves for the age at which exclusive breastfeeding (left panel) and any breastfeeding (right panel) stopped. The resulting percentage is a measure of the proportion of children still being breastfed at any given age. Blue and red lines indicate the EIG and SIG participants respectively and the black crosses show the comparable data from the Infant Feeding Survey 2010, providing a UK population level comparison group. All comparisons between EIG or SIG and Infant Feeding Survey data at varying ages were significantly different, $p<0.001$. Exclusive breastfeeding stopped at an earlier age in the EIG than SIG reflecting adherence to the study protocol. Overall duration of breastfeeding in the EIG and SIG groups was identical indicating that there was no detrimental impact of early allergenic food introduction on breastfeeding performance. Data available for exclusive breastfeeding: SIG 633 (97.2%), EIG 622 (95.4%) and any breastfeeding: SIG 620 (95.2%), EIG 583 (89.4%)

COW'S MILK FORMULA CONSUMPTION IN THE SIG

Infant formula introduction in the SIG was minimal under six months: 2% in the SIG ever having had cow's milk formula by 4 months and 7% by 5 months. By six months of age 14.4% in the SIG had ever had cow's milk formula which was broken down further into 5.6% of evaluable SIG participants having been given cow's milk formula in a volume exceeding 300mls for one day or more (rendering them non per-protocol – see Table 2) and 8.8% had been given less than 300mls per day. Thus 85.6% of the SIG had never had any cow's milk formula by six months of age. Of the 8.8% introducing less than 300mls per day, the median age of introduction was 22 weeks.

The EIG recommended dose of cow's milk protein was 4g per week. By 4 months of age 1.6% (10/621) SIG participants had consumed 4g cow's milk protein per week or more of infant formula, by five months 6.5% (40/612) and by six months 10.5% (63/602). Cumulatively 11.5% (68/589) SIG participants consumed this amount or more before six months of age.

ALLERGENIC FOOD CONSUMPTION IN THE EIG

Figure 11 shows the level of allergenic food consumption in the EIG from enrolment to six months of age. The data are taken from the four, five and six month online interim questionnaires and refer to the four weeks previous to the participant's monthly birthday.

In the EIG, consumption was low for all allergenic foods except milk at four months of age but increased to a mean of at least twice weekly consumption for all allergenic foods at five and six months. However, whilst the median frequency of consumption of the six allergenic foods was at least twice weekly at five and six months of age, four of the six foods (peanut, egg, sesame and white fish) at 5 months and two (egg and white fish) at six months were being consumed by 25% of EIG participants only once a week.

By six months, consumption of each allergenic food had occurred in over 95% of EIG infants. The quantity of allergenic food consumed, and the ease of introduction, varied for each food. The protocol introduced cows' milk as the first allergenic food, and this also being a familiar infant food was reflected in the consumption results. By six months, the proportion of EIG infants consuming 100% of the recommended amount was: cows' milk 90%, peanut, wheat and fish 65%, and sesame and egg 50%. Adherence to the instruction to not introduce wheat before 4 months was 100%.

ALLERGENIC FOOD CONSUMPTION IN THE SIG

It was unknown whether mothers would adhere to the SIG regimen and avoid early introduction of the allergenic foods. Figure 12 shows the differences between frequency of consumption of allergenic foods in the SIG and EIG at four, five and six months of age. For every allergenic food at each age group, there was significantly higher consumption in the EIG than the SIG ($p<0.001$ for each food). Only 2.6% of evaluable SIG participants had introduced any peanut, egg, sesame, fish or wheat before five months of age (Criterion C, Table 2).

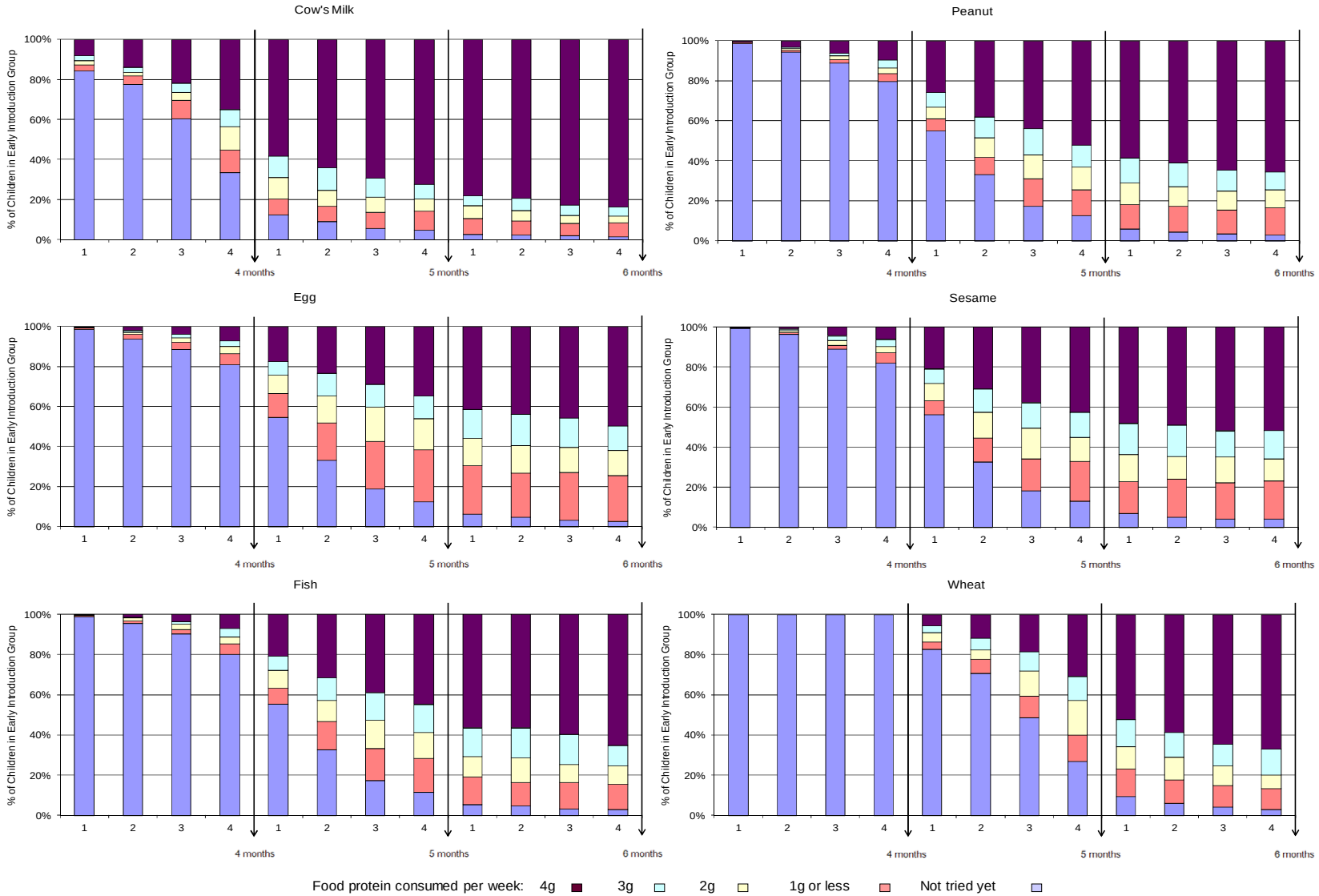


Figure 11 Consumption of Allergenic Foods by the EIG in the Four Weeks Prior to their Fourth, Fifth and Sixth Monthly Birthdays

Figure 11 shows the level of allergenic food consumption in the EIG from enrolment to six months of age. The EIG food schedule began with cows' milk as the first allergenic food introduced then sequentially peanut, egg, sesame and fish (cod) in a randomized order. All EIG participants introduced wheat last and always after 4 months of age. Each bar represents one week of consumption data per food and varying colours within each bar show the volume of food consumed in grams as reported by parents at monthly questionnaires (answered at the monthly birthday in reference to the preceding 4 weeks of consumption). Data available for 4 months 581 (89.1%), 5 months 548 (84.0%), 6 months 537 (82.4%)

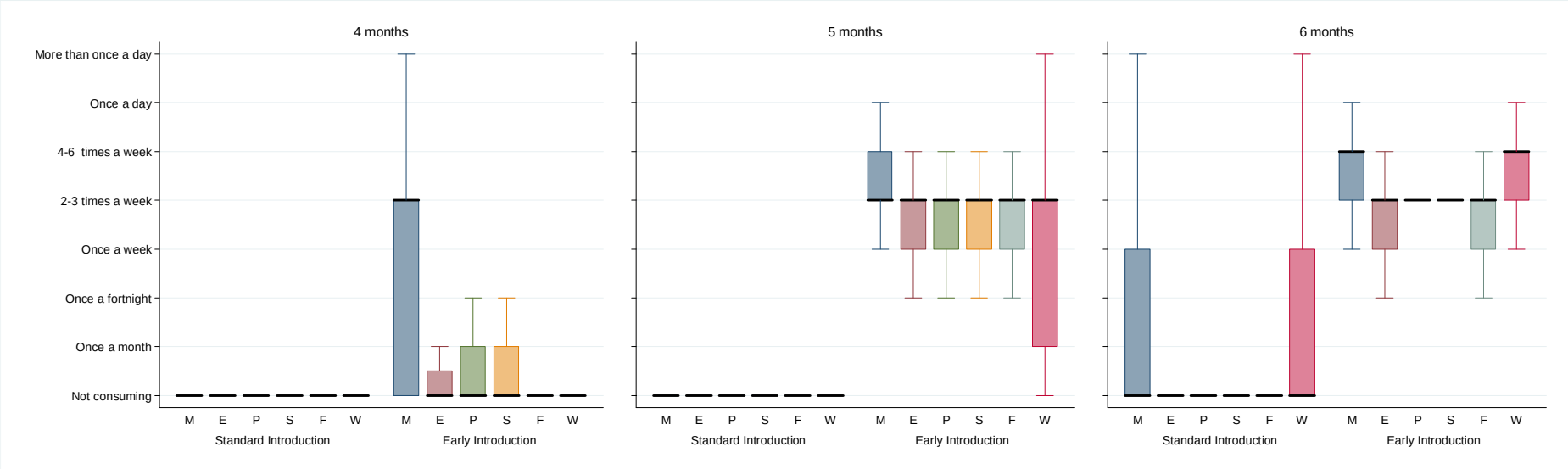


Figure 12 Differences in Frequency of Allergenic Food Consumption in SIG and EIG groups by Four, Five and Six Months of Age

Figure 12 shows the differences between frequency of consumption of allergenic foods in the SIG and EIG at four, five and six months of age. These data are taken from the four, five and six month questionnaires respectively where parents were asked to complete a food frequency questionnaire detailing how frequently their infant was consuming the six different allergenic foods (M cows' milk, E hens' egg, P peanut, S sesame F fish W wheat). The thick black bar indicates the median frequency of consumption for each food and the box upper and lower hinges show the 75th and 25th centiles respectively. For every allergenic food, at each age group, there was significantly more frequent consumption in the EIG than the SIG ($p<0.001$ for each food). Data available for 4 months: SIG 621 (95.4%) EIG 588 (90.2%), 5 months: SIG 612 (94.0%) EIG 550 (84.4%), 6 months SIG 605 (92.9%) EIG 542 (83.1%)

ADVERSE EVENTS

Each of the 17 online questionnaires collected data on the following conditions:

- Constipation
- Diarrhoea
- Posseting
- Vomiting
- Colic
- Wheeze
- Eczema
- Upper respiratory tract infections (URTI)
- Lower respiratory tract infections (LRTI)
- Bronchiolitis
- Other infections (with a free text box to describe symptoms/diagnosis)

It is important to note that the questionnaires were completed monthly from 4 months to 12 months of age. Hence questions during this time period ask about the frequency of symptoms in a preceding one month period. Between 12 months and 36 months, questionnaires were completed three monthly and hence questions record symptoms over a three month period.

DIARRHOEA

The number of days participants had diarrhoea is indicated in Figure 13. Up until one year of age there was a steady increase in both groups but the peak only being 1.5 days out of a one month period. In the right hand graph in Figure 13, the family is recording number of days with diarrhoea over a three month period. It seems apparent that families adjust the number of days of diarrhoea they report downwards as the 15 month figure is significantly less than three times the 12 month figure that one might have anticipated. Regardless there is then a steady decline in days affected. Whilst none of the differences between groups in the time periods indicated in Table 20 were statistically significant, from one year of age participants in the EIG had consistently less diarrhoea than participants in the SIG and this difference approached statistical significance (p=0.06).

This finding is noteworthy as one of the central reasons for the WHO advocating six months exclusive breastfeeding has been the reported protective effect on gastrointestinal infection. The WHO systematic review of the optimal duration of exclusive breastfeeding stated that: "Based primarily on an observational analysis of a large randomized trial in Belarus, infants who continue exclusive breastfeeding for six months or more appear to have a significantly reduced risk of one or more episodes of gastrointestinal infection".[60] However this finding was not replicated in the Millennium cohort, a UK based longitudinal study of 15,980 infants which reported that the age of introduction of solids had no effect on risk of hospitalization for diarrhoea.[61]

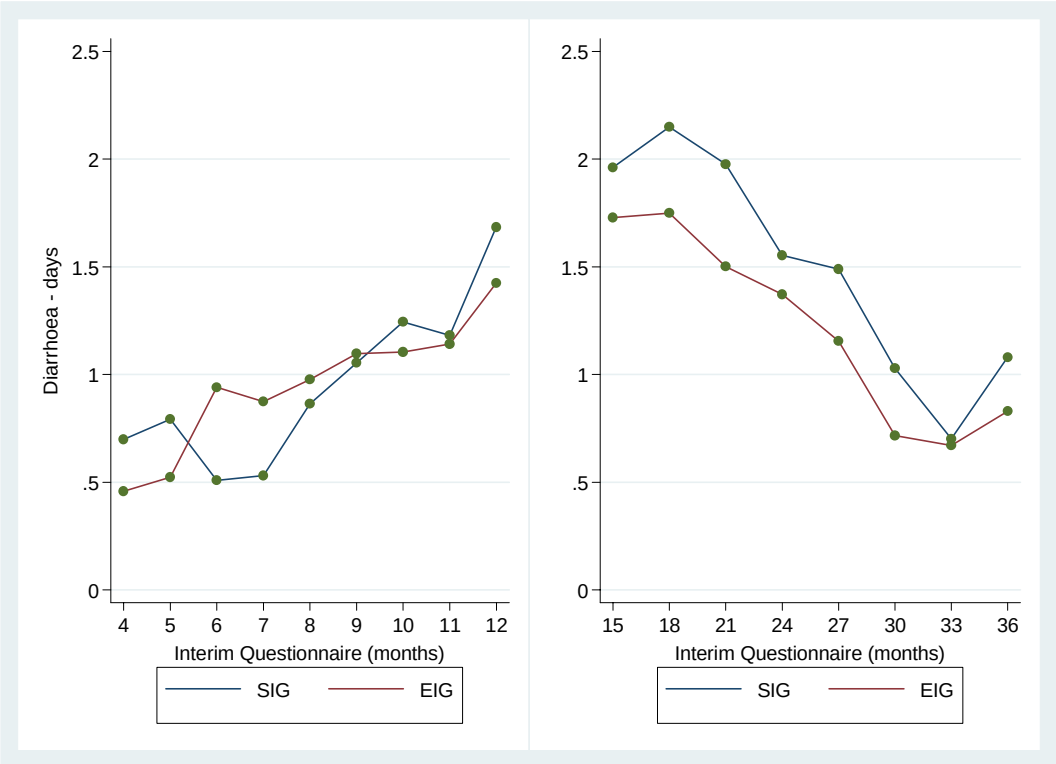


Figure 13 Number of Days that Participants Were Affected by Diarrhoea at Each Interim Questionnaire Time Point

Table 20 Adverse Event: Parent Reported Diarrhoea

	SIG Days affected Mean (SE)	EIG Days affected Mean (SE)	t test
4-6 months	0.66 (0.08)	0.62 (0.06)	0.68
7-12 months	1.14 (0.08)	1.19 (0.08)	0.68
15-36 months	1.75 (0.21)	1.32 (0.10)	0.06
4-36 months	1.22 (0.08)	1.09 (0.06)	0.20

CONSTIPATION

The number of days that participants had constipation is indicated in Figure 14. Again the absolute number of days that participants were affected by constipation was small (approximately one day or less per month under one year). However, for constipation the EIG group mean number of days affected was significantly higher between 4 and 6 months of age (Table 21, p<0.001) than in the SIG. This would appear to be an earlier manifestation and accentuation of the same peak seen in the SIG when solids were being introduced into their diet (with their peak constipation months being 6 and 7). The absolute difference remains small from a clinical perspective (one day difference in a month recorded in the five month interim questionnaire). Interestingly, from 27 months onwards a non-significant gap appears to open up in the reverse direction with more constipation in the SIG.

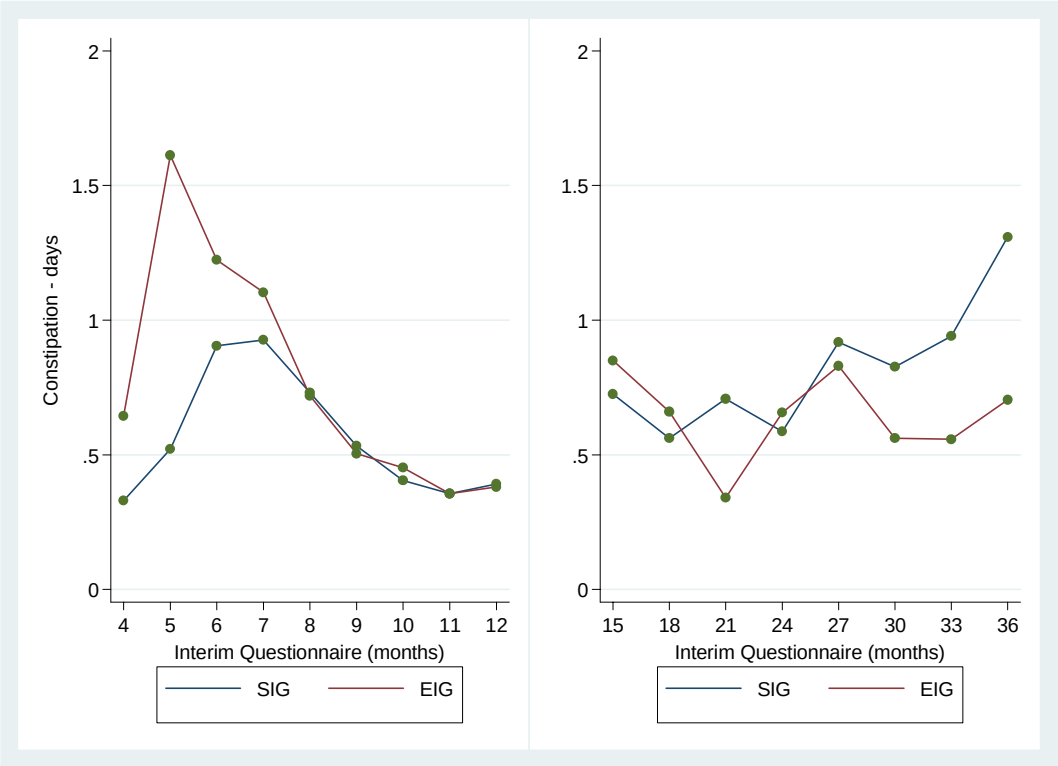


Figure 14 Number of Days that Participants Were Affected by Constipation at Each Interim Questionnaire Time Point

Table 21 Adverse Event: Parent Reported Constipation

	SIG Days affected Mean (SE)	EIG Days affected Mean (SE)	t test
4-6 months	0.57 (0.06)	1.14 (0.10)	<0.001
7-12 months	0.57 (0.06)	0.60 (0.08)	0.79
15-36 months	0.93 (0.16)	0.81 (0.12)	0.56
4-36 months	0.72 (0.08)	0.81 (0.07)	0.37

POSSETING

Families recorded a categorical response for the frequency with which their child had experienced posseting (Figure 15).

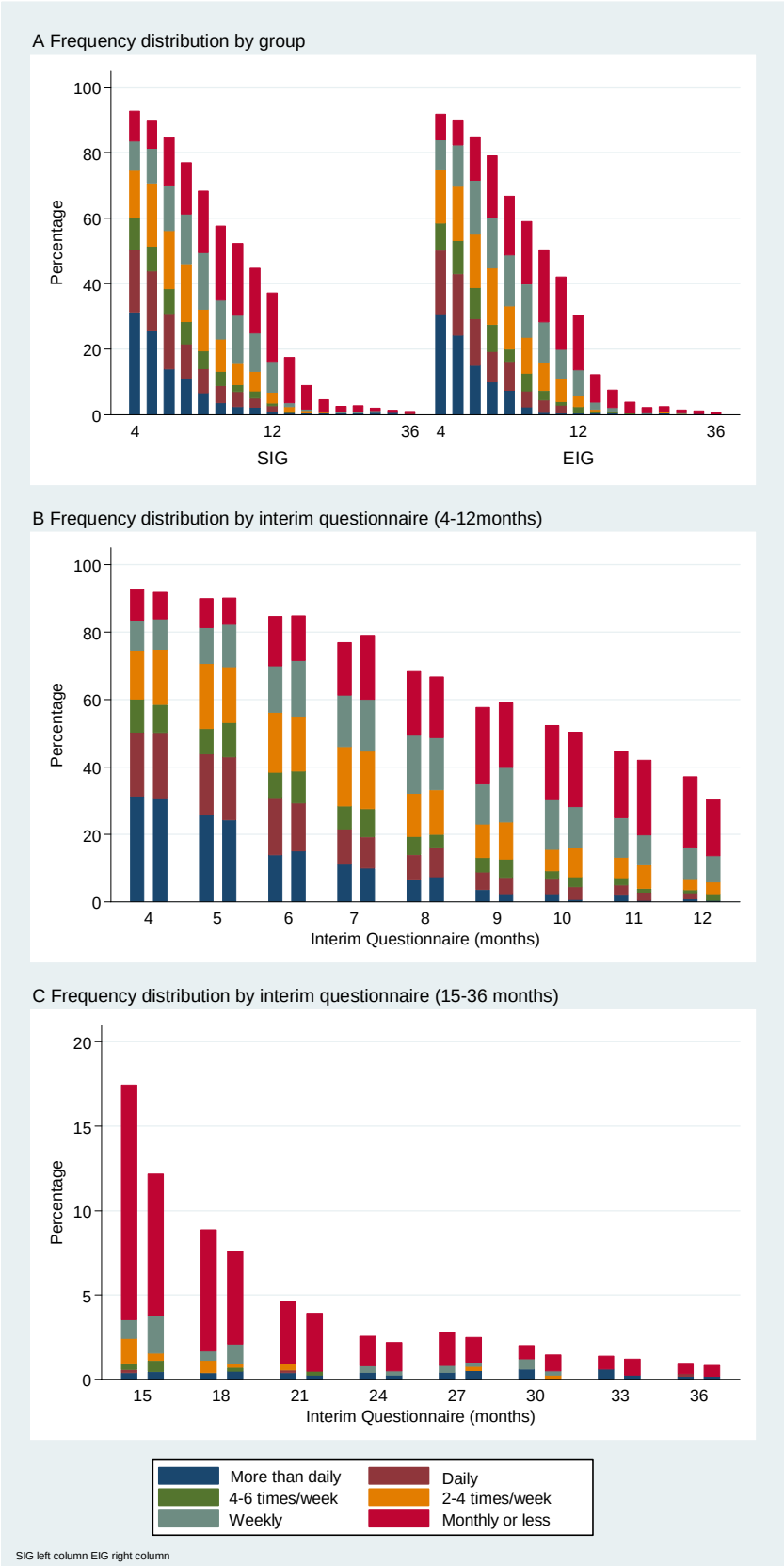


Figure 15 Adverse event: Parent Reported Posseting

The distributions by group (Panel A) appear remarkably similar and this is explored further with the distribution of posseting frequency shown by individual month for the two groups between 4 and 12 months of age in Panel B and between 12 and 36 months of age in Panel C. Note that the y axis scale changes in Panel C.

When grouped into time periods (Table 22), posseting occurred more frequently between 15 and 36 months in the SIG (p=0.01) although the absolute differences between the two groups were small. There was no difference between the two groups overall (p=0.90).

Table 22 Adverse Event: Parent Reported Posseting

	4-6 months		7-12 months		15-36 months		4-36 months	
Frequency	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**
Never	10.9 (200)	11.1 (185)	43.9 (1493)	45.8 (1332)	94.9 (4043)	96.1 (3431)	60.4 (5736)	60.7 (4948)
Monthly or less	10.8 (198)	9.7 (161)	20.0 (681)	19.4 (565)	3.9 (165)	2.9 (102)	11.0 (1044)	10.2 (828)
Weekly	11.0 (202)	12.6 (210)	13.4 (454)	12.6 (366)	0.4 (16)	0.5 (18)	7.1 (672)	7.3 (594)
2-4 times a week	17.2 (314)	16.4 (274)	9.3 (317)	10.0 (290)	0.3 (14)	0.1 (5)	6.8 (645)	7.0 (569)
5-6 times a week	8.3 (152)	9.3 (155)	3.6 (123)	3.9 (114)	0.1 (2)	0.1 (5)	2.9 (277)	3.4 (274)
Daily	18.0 (330)	17.5 (292)	5.4 (182)	4.8 (139)	0.1 (3)	0.0 (0)	5.4 (515)	5.3 (431)
More than daily	23.7 (434)	23.5 (392)	4.5 (152)	3.5 (102)	0.4 (17)	0.3 (10)	6.4 (603)	6.2 (504)
χ^2 for trend	0.92		0.11		0.01		0.90	

Responses for individual online questionnaires have been pooled across time periods to yield the total number of counts of the different categories

VOMITING

The same categories were used to record the frequency of vomiting (Figure 16).

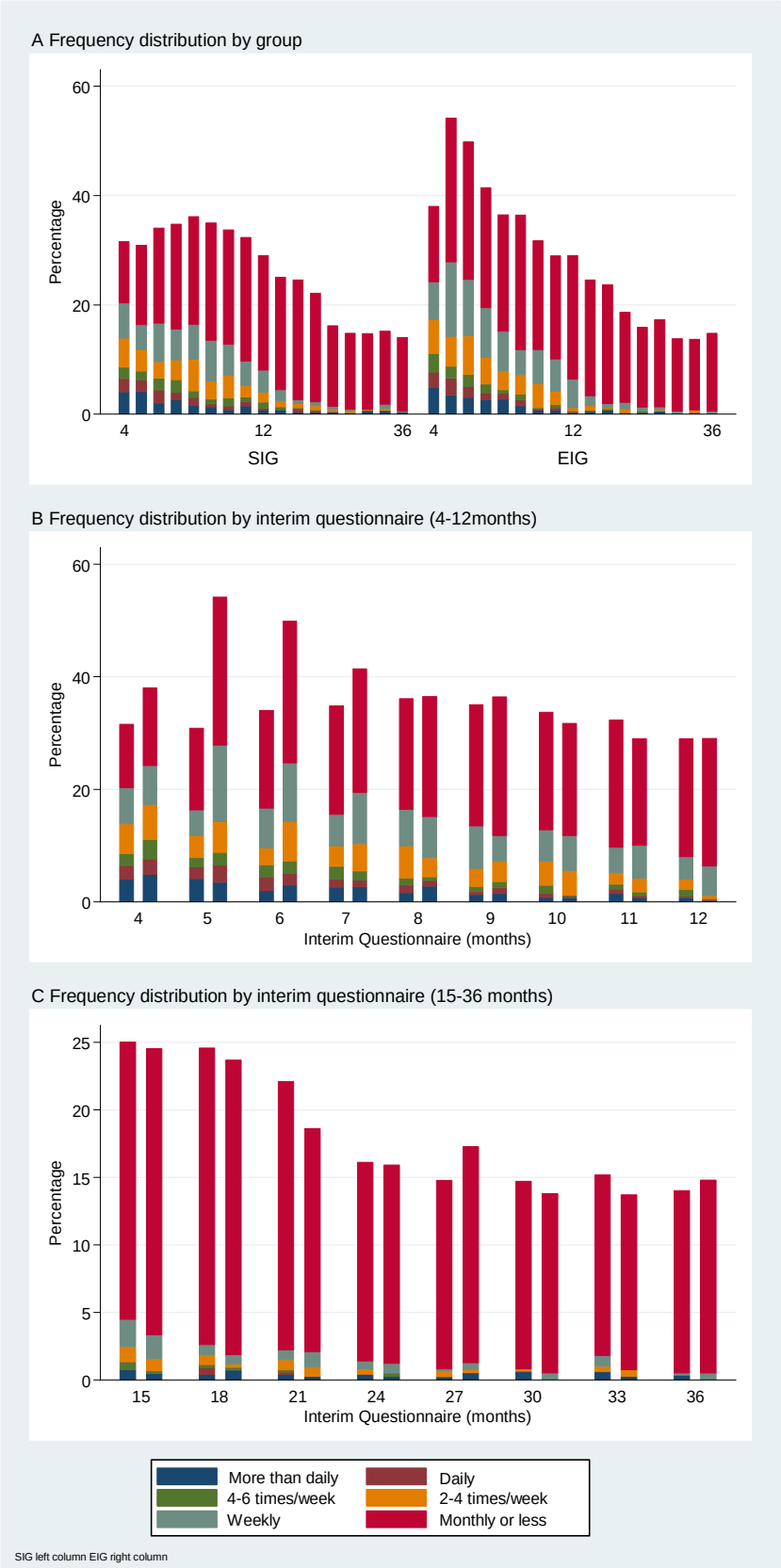


Figure 16 Adverse event: Parent Reported Vomiting

In Figure 16, Panel A it is apparent that vomiting was significantly more frequently reported in the 5 and 6 month interim questionnaires in the EIG.

This is demonstrated more clearly in the individual figures of vomiting frequency between 4 and 12 months of age in Panel B and between 12 and 36 months of age in Panel C. Note again that the y axis scale changes in Panel C.

The differences recorded in 4-6 month period were statistically significant (Table 23, $p<0.001$) and the difference remained statistically significant when the overall follow up period was considered. The difference between the two groups observed in the 5 and 6 month interim questionnaires was explained largely by an increase in the EIG for the two lowest frequency of vomiting categories ("Weekly" and "Monthly or less"), suggesting that this was not a clinically significant concern.

Table 23 Adverse Event: Parent Reported Posseting

	4-6 months		**7-12 months**		**15-36 months**		**4-36 months**	
Frequency	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**
Never	67.8 (1242)	52.9 (882)	66.6 (2264)	66.0 (1920)	81.6 (3478)	82.3 (2937)	73.6 (6954)	70.4 (5739)
Monthly or less	14.4 (263)	21.6 (361)	20.8 (709)	21.7 (630)	16.6 (705)	16.4 (584)	17.7 (1677)	19.3 (1575)
Weekly	6.0 (110)	10.3 (171)	5.6 (191)	6.4 (186)	0.7 (28)	0.7 (26)	3.5 (329)	4.7 (383)
2-4 times a week	4.1 (75)	6.2 (104)	3.4 (117)	3.1 (91)	0.5 (21)	0.3 (11)	2.2 (213)	2.5 (206)
5-6 times a week	2.0 (36)	2.6 (44)	1.3 (45)	0.7 (21)	0.1 (5)	0.1 (3)	0.9 (86)	0.8 (68)
Daily	2.3 (42)	2.6 (44)	0.9 (29)	0.7 (21)	0.1 (4)	0.0 (0)	0.8 (75)	0.8 (65)
More than daily	3.4 (62)	3.8 (63)	1.4 (47)	1.3 (39)	0.5 (19)	0.3 (10)	1.4 (128)	1.4 (112)
χ^2 for trend	<0.001		0.84		0.44		<0.001	

Responses for individual online questionnaires have been pooled across time periods to yield the total number of counts of the different categories

Colic

The overall frequency of reported colic is demonstrated in Figure 17.

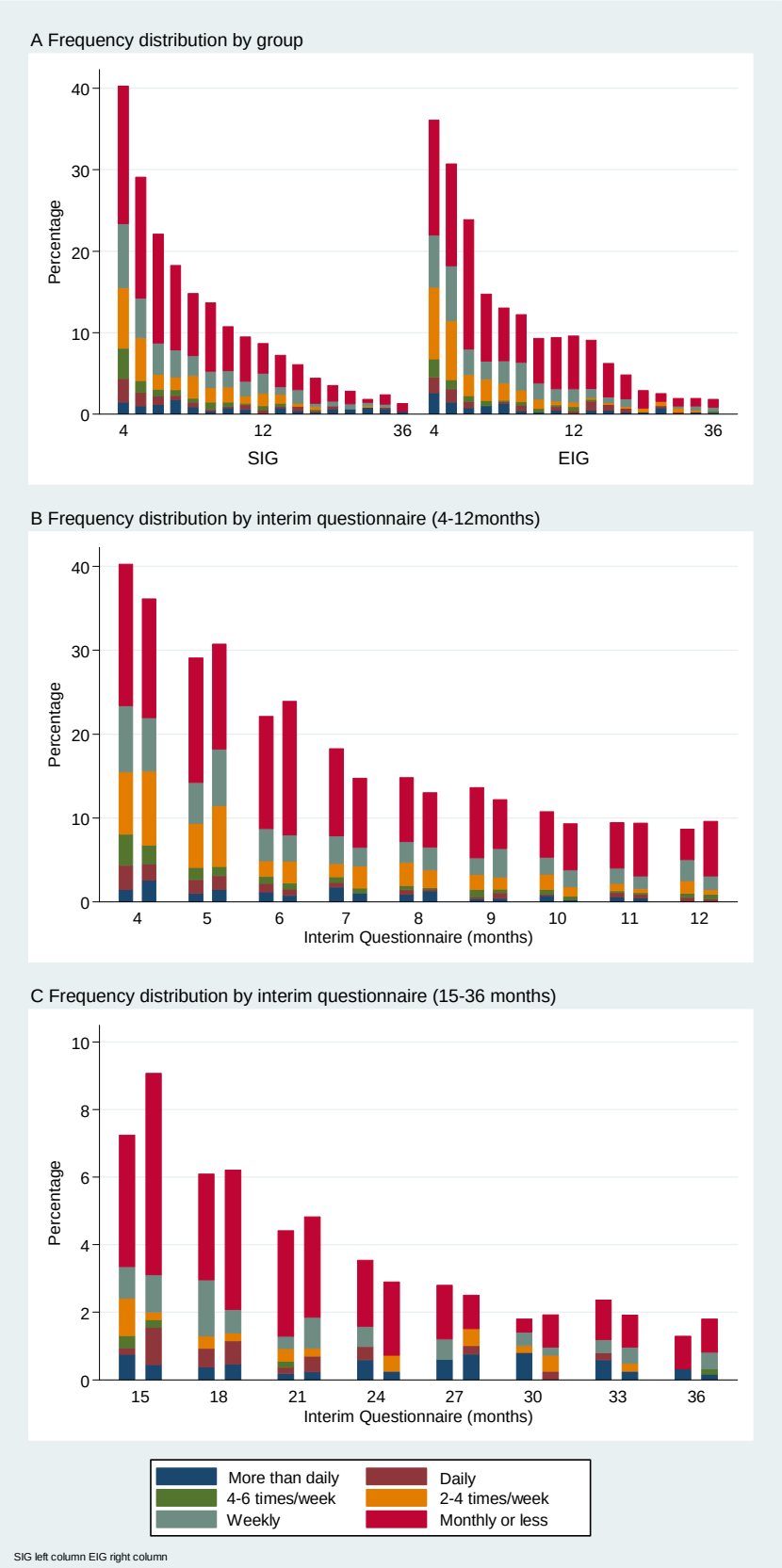


Figure 17 Adverse Event: Parent Reported Colic

The patterns are very similar, with no statistically significant differences between the two groups at any time points (Table 24).

Table 24 Adverse Event: Parent Reported Colic

	4-6 months		7-12 months		15-36 months		4-36 months	
Frequency	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**
Never	69.4 (1270)	69.6 (1162)	87.4 (2973)	88.6 (2577)	96.3 (4103)	96.1 (3433)	87.9 (8346)	88.0 (7172)
Monthly or less	15.1 (276)	14.2 (237)	6.9 (233)	6.5 (190)	2.0 (87)	2.4 (85)	6.3 (596)	6.3 (512)
Weekly	5.6 (102)	5.5 (91)	2.4 (80)	2.2 (65)	0.6 (26)	0.5 (18)	2.2 (208)	2.1 (174)
2-4 times a week	4.9 (89)	6.3 (105)	1.7 (59)	1.4 (40)	0.3 (11)	0.3 (10)	1.7 (159)	1.9 (155)
5-6 times a week	2.0 (37)	1.4 (23)	0.6 (19)	0.4 (12)	0.1 (3)	0.1 (2)	0.6 (59)	0.5 (37)
Daily	1.9 (34)	1.4 (24)	0.4 (14)	0.3 (8)	0.2 (8)	0.3 (12)	0.6 (56)	0.5 (44)
More than daily	1.2 (22)	1.6 (27)	0.7 (24)	0.6 (16)	0.5 (22)	0.3 (11)	0.7 (68)	0.7 (54)
χ^2 for trend	1.00		0.12		0.69		0.83	

Responses for individual online questionnaires have been pooled across time periods to yield the total number of counts of the different categories

WHEEZE

The question about wheeze used the ISAAC categories for positive respondents: 1-3, 4-12 and more than 12 wheezing episodes since completing the last interim questionnaire (Figure 18).

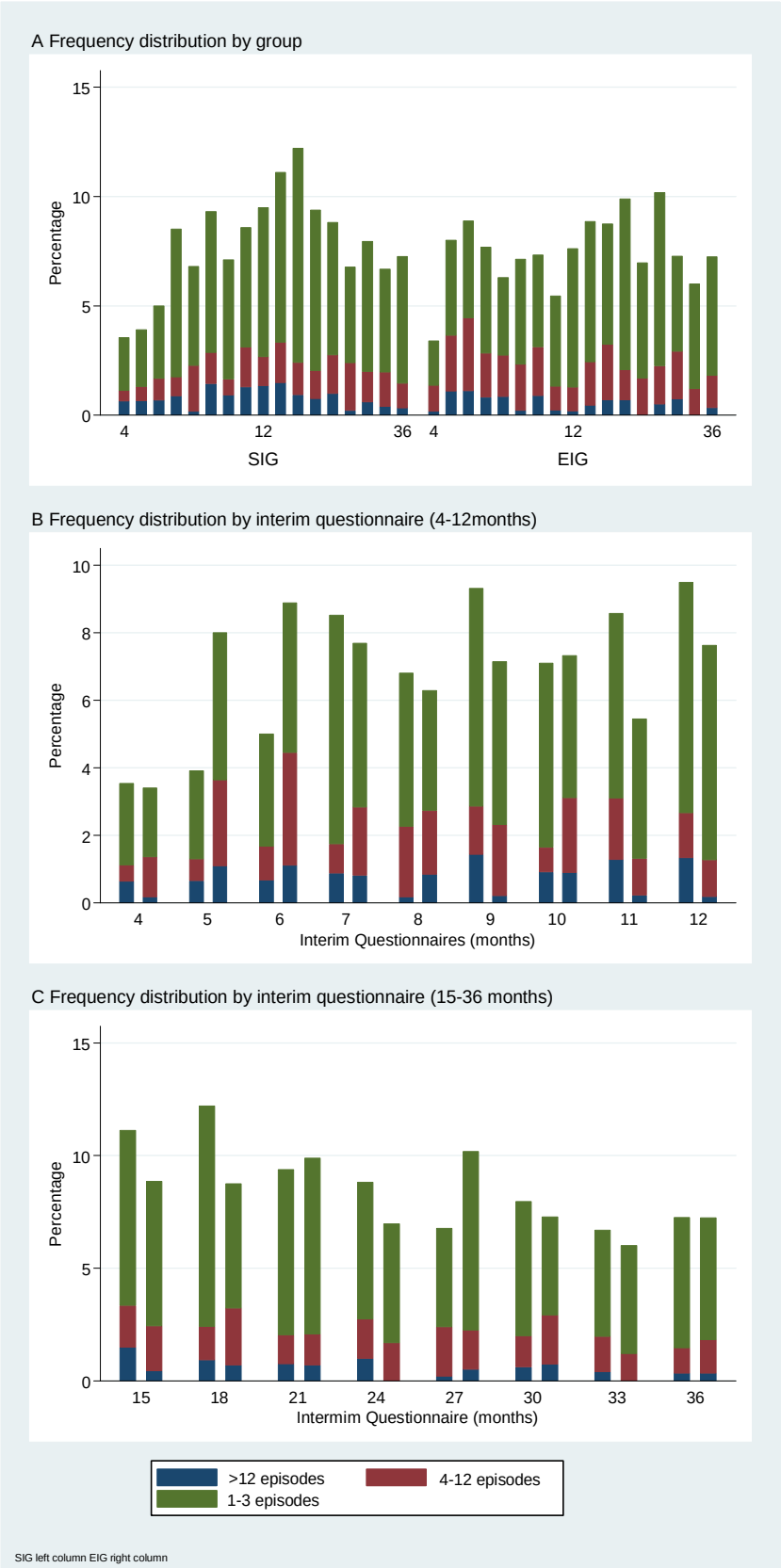


Figure 18 Adverse Event: Parent Reported Wheezing Episodes

As one might anticipate, in contrast to the preceding three gastrointestinal symptoms, the overall frequency of wheezing was considerably lower with between approximately 5 and 10 percent of participants reporting wheeze in each interim questionnaire (Table 25).

Wheezing was more commonly reported in the EIG between 4-6 months ($p<0.001$) and between 7-12 months of age ($p=0.04$), but there was no difference overall between the two groups and the absolute difference was small.

Table 25 Adverse Event: Parent Reported Wheeze

	4-6 months		**7-12 months**		**15-36 months**		**4-36 months**	
Frequency	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**
Never	95.9 (1758)	93.3 (1558)	91.7 (3121)	93.1 (2707)	91.2 (3891)	91.9 (3288)	92.3 (8770)	92.6 (7553)
1-3 episodes	2.8 (51)	3.6 (60)	5.9 (202)	4.7 (137)	6.5 (278)	5.9 (212)	5.6 (531)	5.0 (409)
4-12 episodes	0.7 (13)	2.3 (39)	1.4 (47)	1.7 (50)	1.6 (67)	1.8 (63)	1.3 (127)	1.9 (152)
>12 episodes	0.7 (12)	0.8 (13)	1.0 (34)	0.5 (15)	0.7 (30)	0.4 (15)	0.8 (76)	0.5 (43)
More than daily	95.9 (1758)	93.3 (1558)	91.7 (3121)	93.1 (2707)	91.2 (3891)	91.9 (3288)	92.3 (8770)	92.6 (7553)
χ^2 for trend	<0.001		0.04		0.28		0.45	

Responses for individual online questionnaires have been pooled across time periods to yield the total number of counts of the different categories

URTI (UPPER RESPIRATORY TRACT INFECTION)

Figure 19 shows the overall distribution of URTIs at each interim questionnaire by study group.

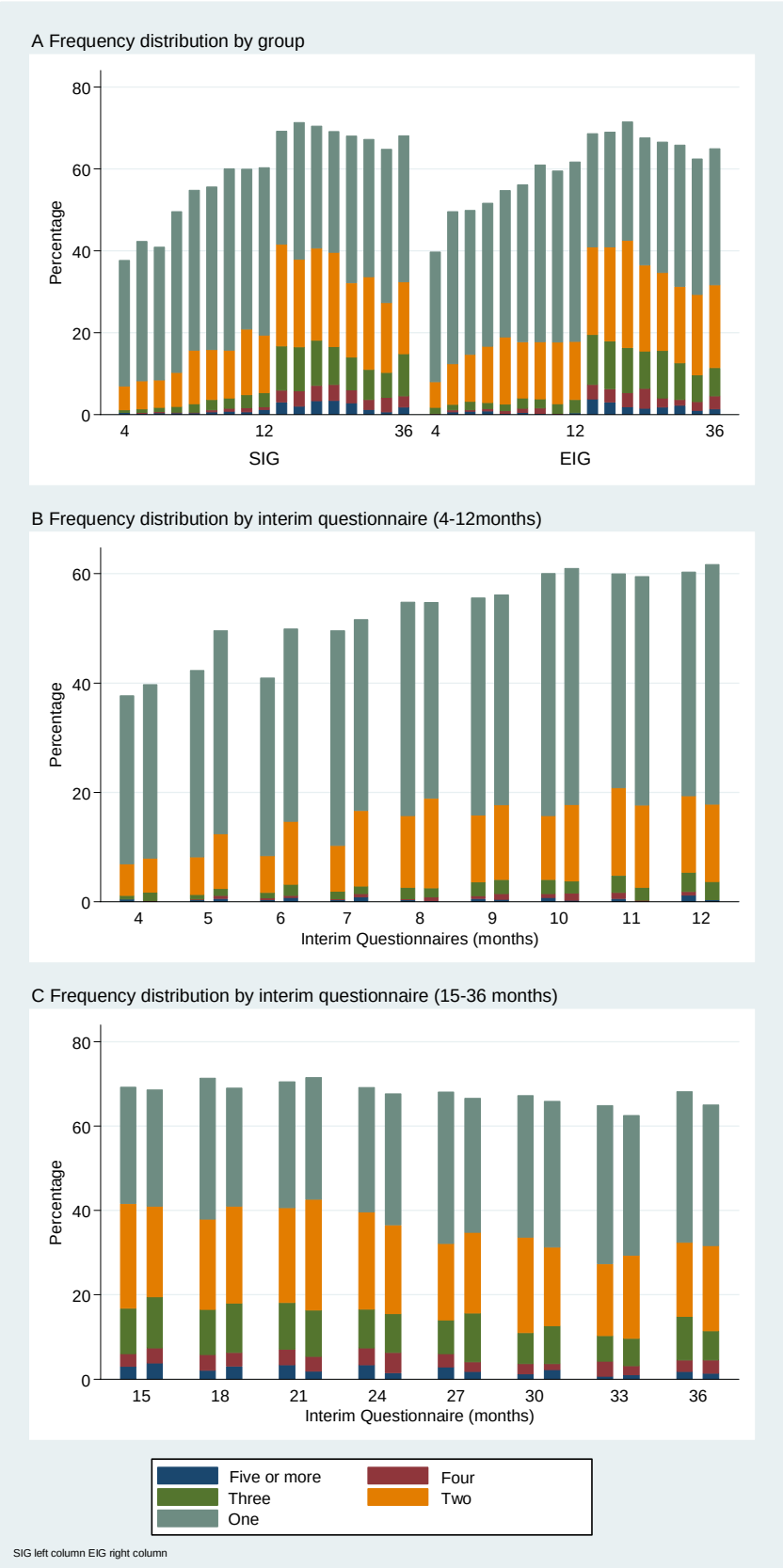


Figure 19 Adverse Event: Parent Reported Upper Respiratory Tract Infections

URTIs were more frequently reported in the EIG in the 4-6 month period (Table 26, p<0.001), but there was no difference between the two groups overall.

Table 26 Adverse Event: Parent Reported Upper Respiratory Tract Infections

	4-6 months		7-12 months		15-36 months		4-36 months	
Frequency	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**
Never	59.7 (1093)	53.8 (896)	43.3 (1472)	42.5 (1236)	31.4 (1336)	33.0 (1177)	41.1 (3901)	40.6 (3309)
Once	32.5 (594)	34.7 (578)	40.4 (1374)	39.8 (1155)	33.0 (1403)	31.2 (1113)	35.5 (3371)	35.0 (2846)
Twice	6.5 (118)	9.2 (153)	12.6 (427)	14.5 (421)	20.9 (889)	21.2 (756)	15.1 (1434)	16.3 (1330)
Three times	0.8 (15)	1.6 (27)	2.5 (86)	2.3 (66)	9.3 (395)	9.6 (344)	5.2 (496)	5.4 (437)
Four times	0.2 (3)	0.4 (6)	0.6 (19)	0.6 (18)	3.3 (139)	3.0 (108)	1.7 (161)	1.6 (132)
Five or more times	0.4 (7)	0.4 (7)	0.6 (21)	0.4 (10)	2.3 (96)	2.0 (72)	1.3 (124)	1.1 (89)
χ^2 for trend	<0.001		0.32		0.41		0.30	

Responses for individual online questionnaires have been pooled across time periods to yield the total number of counts of the different categories

LRTI (LOWER RESPIRATORY TRACT INFECTION)

LRTI rates in both groups are shown in Figure 20.

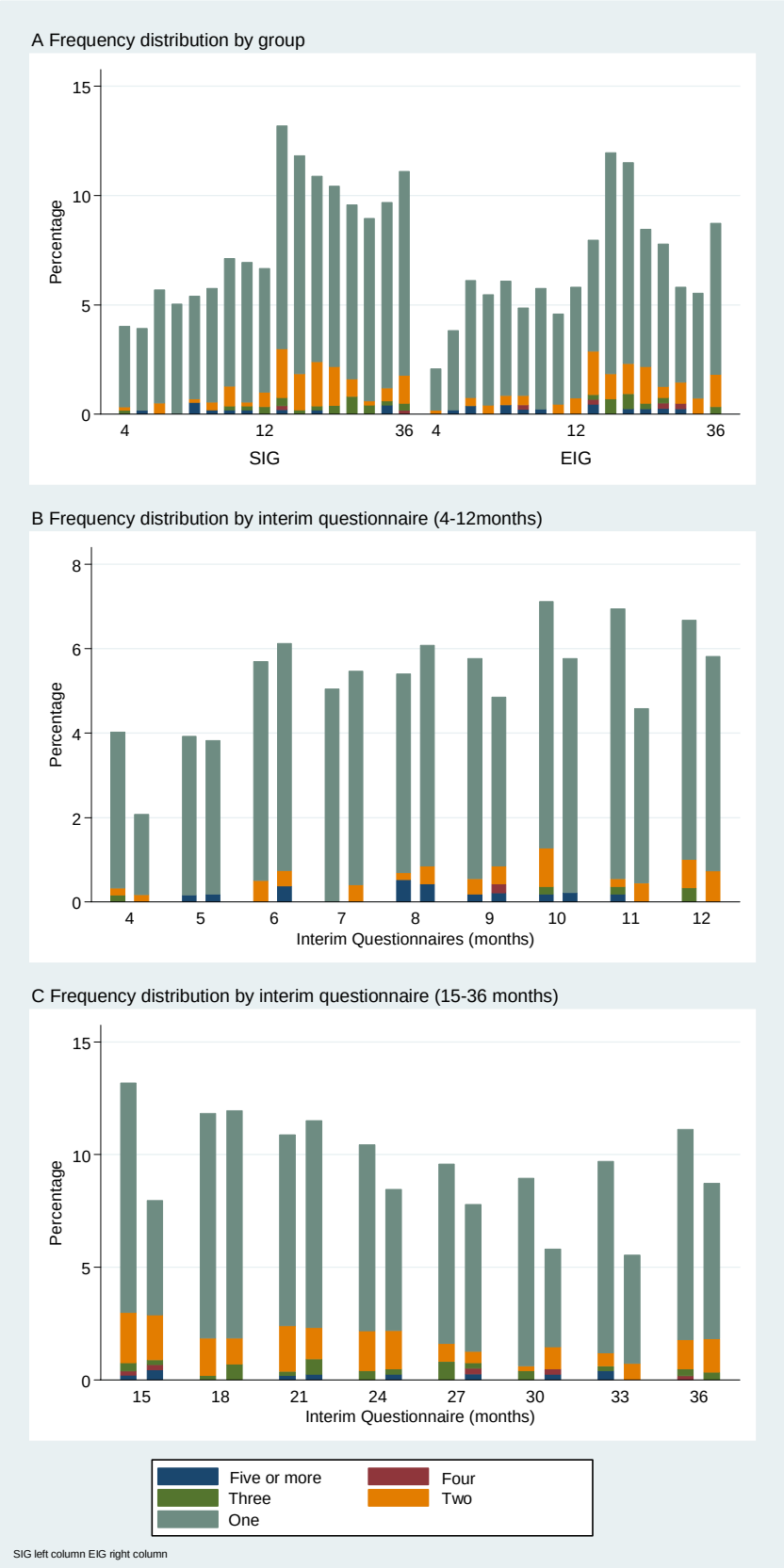


Figure 20 Adverse Event: Parent Reported Lower Respiratory Tract Infections

In contrast to URTIs, more LRTIs were reported in the SIG at every time point and overall, with the differences, whilst small, being statistically significant at 15-36 months and overall (Table 27).

The Millennium cohort found that the age of introduction of solids had no effect on risk of hospitalization for lower respiratory tract infection.[61]

Table 27 Adverse Event: Parent Reported Lower Respiratory Tract Infections

	4-6 months		7-12 months		15-36 months		4-36 months	
Frequency	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**
Never	95.5 (1747)	96.0 (1601)	93.9 (3190)	94.6 (2748)	89.2 (3800)	91.5 (3266)	92.1 (8737)	93.5 (7615)
Once	4.2 (77)	3.6 (60)	5.5 (186)	4.9 (141)	8.9 (380)	6.7 (239)	6.8 (643)	5.4 (440)
Twice	0.2 (4)	0.2 (3)	0.4 (13)	0.4 (12)	1.3 (57)	1.3 (45)	0.8 (74)	0.7 (60)
Three times	0.1 (1)	0.0 (0)	0.1 (4)	0.0 (0)	0.4 (15)	0.3 (11)	0.2 (20)	0.1 (11)
Four times	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (1)	0.1 (2)	0.1 (3)	0.0 (2)	0.1 (4)
Five or more times	0.1 (1)	0.2 (3)	0.2 (6)	0.1 (4)	0.1 (4)	0.2 (6)	0.1 (11)	0.2 (13)
χ^2 for trend	0.40		0.23		0.001		<0.001	

Responses for individual online questionnaires have been pooled across time periods to yield the total number of counts of the different categories

BRONCHIOLITIS

The frequency of reported bronchiolitis was low compared with the other infectious conditions (Figure 21).

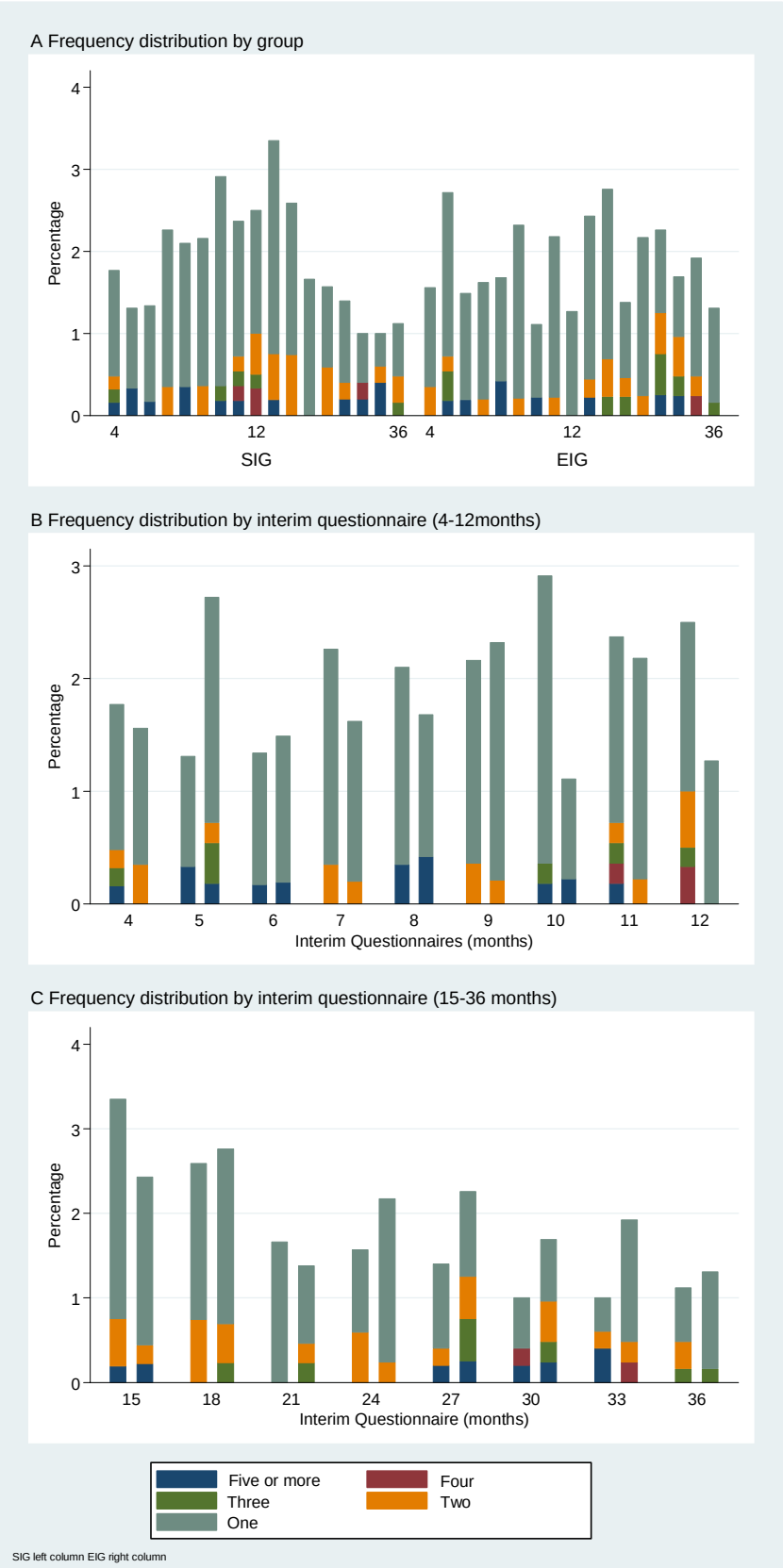


Figure 21 Adverse Event: Parent Reported Bronchiolitis

Examining the tabulation of frequency of episodes of bronchiolitis, the handful of families reporting five of more episodes in a one month period (interim questionnaires up to 12 months) or three month period (15 months onwards) are probably recording the multiple episodes of wheeze with the condition as discrete separate episodes of bronchiolitis rather than one single episode which is much more likely to be the case.

The differences between the two groups in absolute terms are tiny, with "Never" category differences ranging from 0.1 to 0.7% which is of no clinical relevance (Table 28).

Table 28 Adverse Event: Parent Reported Bronchiolitis

	4-6 months		**7-12 months**		**15-36 months**		**4-36 months**	
Frequency	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**
Never	98.5 (1803)	98.1 (1635)	97.6 (3318)	98.3 (2857)	98.3 (4185)	98.0 (3500)	98.1 (9306)	98.2 (7992)
Once	1.2 (21)	1.5 (25)	1.9 (63)	1.5 (43)	1.2 (52)	1.4 (50)	1.4 (136)	1.5 (118)
Twice	0.1 (1)	0.2 (3)	0.2 (8)	0.1 (3)	0.3 (14)	0.3 (10)	0.2 (23)	0.2 (16)
Three times	0.1 (1)	0.1 (2)	0.1 (3)	0.0 (0)	0.0 (1)	0.2 (6)	0.1 (5)	0.1 (8)
Four times	0.0 (0)	0.0 (0)	0.1 (3)	0.0 (0)	0.0 (1)	0.0 (1)	0.0 (4)	0.0 (1)
Five or more times	0.2 (4)	0.1 (2)	0.1 (4)	0.1 (3)	0.1 (5)	0.1 (3)	0.1 (13)	0.1 (8)
χ^2 for trend	0.31		0.05		0.42		0.79	

Responses for individual online questionnaires have been pooled across time periods to yield the total number of counts of the different categories

OTHER INFECTIONS

In addition to URTIs, LRTIs and bronchiolitis, families were given the opportunity to report any other infections their child had experienced (Figure 22).

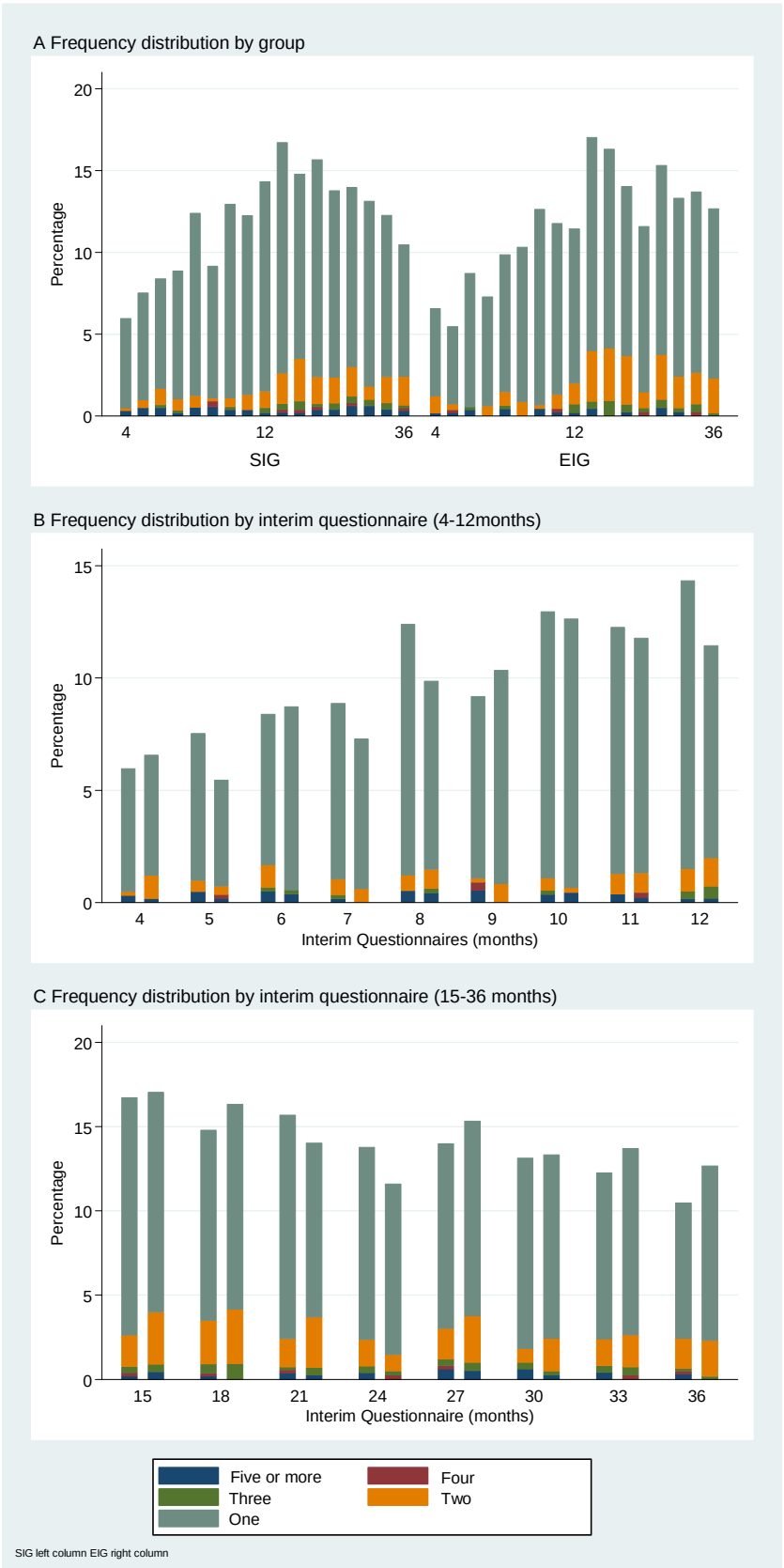


Figure 22 Adverse Events: Parent Reported Other Infections

The frequencies of these were recorded in each interim questionnaire and the family were also asked to provide a narrative of what the condition was. As one would anticipate, the responses given were therefore protean, with some obvious conditions featuring frequently (e.g. chicken pox) but others reflecting the relative prevalence of infectious diseases in childhood.

Taken as a composite, and in the grouped period comparisons in Table 29, none of differences between the two groups are statistically significant.

Table 29 Adverse Event: Parent Reported Other Infections

	4-6 months		7-12 months		15-36 months		4-36 months	
Frequency	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**	**SIG % (counts)**	**EIG % (counts)**
Never	92.7 (1697)	90.9 (1152)	88.3 (3002)	89.5 (2600)	86.2 (3670)	85.8 (3063)	88.2 (8369)	88.6 (7215)
Once	6.2 (114)	8.0 (101)	10.5 (356)	9.4 (272)	11.3 (479)	11.2 (399)	10.0 (949)	9.5 (772)
Twice	0.6 (10)	0.6 (8)	0.7 (23)	0.8 (23)	1.7 (73)	2.4 (85)	1.1 (106)	1.4 (116)
Three times	0.1 (1)	0.1 (1)	0.1 (4)	0.1 (4)	0.4 (15)	0.4 (15)	0.2 (20)	0.3 (20)
Four times	0.0 (0)	0.1 (1)	0.1 (2)	0.0 (1)	0.1 (5)	0.1 (2)	0.1 (7)	0.1 (4)
Five or more times	0.4 (8)	0.3 (4)	0.4 (12)	0.2 (6)	0.4 (16)	0.2 (6)	0.4 (36)	0.2 (16)
χ^2 for trend	0.07		0.15		0.58		0.44	

Responses for individual online questionnaires have been pooled across time periods to yield the total number of counts of the different categories

SERIOUS ADVERSE EVENTS

Serious adverse events were defined as previously described in the methods section:

- Results in death. A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up after the completion of therapy must be reported whether it is considered treatment related or not.
- Is life-threatening – refers to an event in which, in the view of the investigator, the subject was at risk of death at the time of the event
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity
- An event that requires intervention to prevent permanent impairment or damage. An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Fatalities (NCI-CTCAE Grade 5 - death)

There were no fatalities in either group during the course of the EAT study.

Life-threatening (NCI-CTCAE Grade 4 - life-threatening or disabling adverse event)

There were three Grade 4 events, all in SIG participants, which necessitated admission to a Paediatric Intensive Care Unit (PICU). One participant had a 27 night admission with heart valve damage. One had a six week admission for extensive burns. The third had a short PICU admission (2 nights) after a prolonged febrile convulsion.

Inpatient hospitalization (NCI-CTCAE Grade 3 - severe and undesirable adverse event)

In the EAT study the great majority of serious adverse events were generated by hospital admissions. Table 30 gives the number of hospital admissions each participant had during the course of the study by study group. Slightly more SIG participants were admitted and multiple admissions were more common in the SIG group as well but the differences were not statistically significant. The same pattern was seen when restricting the analysis to those participants who were evaluable for the primary outcome (data not shown).

Table 30 Serious adverse events: hospital admissions

No of admissions	SIG n (%)	EIG n (%)
0	560 (86%)	576 (88%)
1	70 (11%)	64 (10%)
2	12 (1.8%)	8 (1.2%)
3	3 (0.5%)	3 (0.5%)
4	5 (0.8%)	0 (0%)
5	1 (0.2%)	1 (0.2%)
Total	651	652

Chi-squared: p=0.28

Events requiring intervention to prevent permanent impairment or damage

In the EAT study it was determined that any participant who had an adrenaline auto-injector administered fulfilled this criterion and hence had experienced a serious adverse event. Five such serious adverse events were recorded - four in SIG participants, one in an EIG participant.

Two of these events took place on separate occasions in the community to one SIG participant. On both occasions the mother administered an EpiPen for choking episodes.
Three participants received adrenaline auto-injector administration during food challenges on the clinical trials unit, none during enrolment challenges in the EIG group (out of 553 food challenges undertaken altogether).

This is in complete contrast to the experience of the HEAP[36] and STAR[15] trials were anaphylaxis with egg introduction occurred. HEAP is particularly relevant as it recruited from the general population. 6% (23/406) were positive to egg at screening (HE specific IgE ≥ 0.35 kU/l). Of the 17 who underwent DBPCFC a remarkable 94% (16/17) were positive with 3 having anaphylactic reactions (respiratory or cardiovascular system impairment). Furthermore, in the active group, two further children reacted to the pasteurized egg white powder with first exposure at home, one with an anaphylactic reaction.

STAR recruited high risk infants with moderate to severe eczema reflected in 36% (24/67) of infants having HE specific IgE ≥ 0.35 kU/l. 31% (15/49) of the intervention group reacted to their initial consumption of the intervention food – pasteurized whole egg powder.

We had no cases of anaphylaxis with home introduction in the EIG group. The obvious explanation for the difference in EAT has to be the form of egg chosen for introduction. EAT EIG infants were introduced to well-cooked boiled egg. Its efficacy demonstrated in this trial is consistent with the mass of evidence that consumption of lower allergenicity forms of allergenic foods facilitates outgrowing allergy to those foods. This has been demonstrated for egg with baked egg consumption speeding up acquisition of tolerance to cooked egg,[62] for milk with baked milk,[63] and for peanut with boiled peanut consumption facilitating the process of sustained oral tolerance induction for peanut.[64] Raw egg is the most allergenic form of egg and clearly, introducing it to young infants, whether as pasteurized egg white powder (HEAP) or pasteurized whole egg powder (STAR) is not to be recommended.

There was no report to the study team throughout the study duration of any adverse event in a food allergic family member of an EIG participant through accidental exposure related to the participant's consumption.

A&E ATTENDANCES

Whilst A&E attendances resulting in a hospital admission became, by definition, a serious adverse event, the great majority of A&E attendances did not result in admission and were deemed to be NCI-CTCAE Grade 2 (moderate adverse event). The frequency with which these occurred in the study groups is indicated in Figure 23. There was no discernible difference between study groups. However, these data reveal the frequency of A&E attendances in contemporary young children in England & Wales. Between 15 months and 3 years of age approximately 10% of the children visit A&E in any three month period.

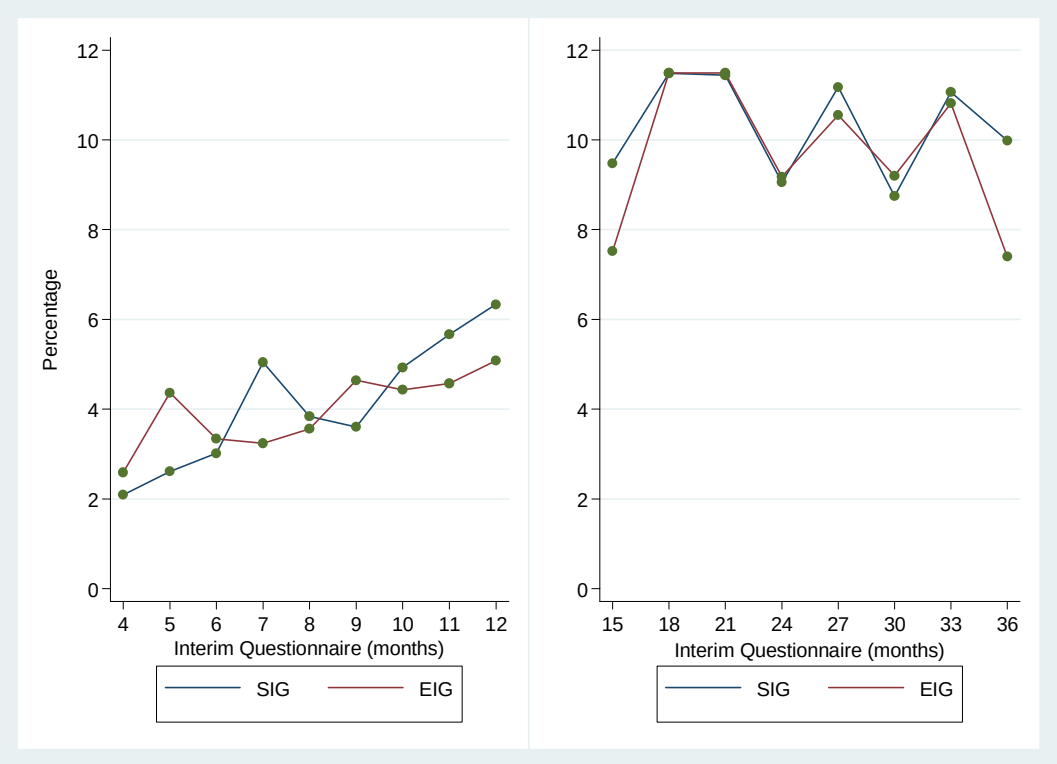


Figure 23 Adverse Event: Parent Reported A&E Attendances

GROWTH

EAT participants underwent an extensive series of anthropometric assessments. Table 31 summarises the results. Of the 30 statistical tests in the table (comparisons were not made at baseline in accordance with good trial practice) none reached statistical significance. There was a tendency towards the EIG participants at one year of age being marginally heavier (90 grams or 0.08 z-score higher) and having a higher body mass index (0.14 index points or 0.11 z-score higher) and skin fold thicknesses but the differences were not statistically significant and no longer present at three years of age.

Table 31 Anthropometry at 3, 12 Months and Three Years in the EAT Study.

	3 months		12 months			36 months		
Anthropometric outcome, mean (SD)	**SIG**	**EIG**	**SIG**	**EIG**		**SIG**	**EIG**	
1. Weight (kg)	6.29 (0.76)	6.27 (0.77)	9.94 (1.17)	10.03 (1.20)	p=0.23	15.02 (1.82)	15.01 (1.82)	p=0.88
1. Weight-for-age z-score	-0.15 (0.94)	-0.14 (0.92)	0.20 (0.92)	0.28 (0.90)	p=0.15	0.23 (0.86)	0.23 (0.86)	p=0.96
2. Length (cm)	62.16 (2.31)	62.04 (2.27)	76.64 (2.96)	76.68 (3.11)	p=0.80	96.80 (4.50)	96.89 (4.40)	p=0.72
2. Length-for-age z-score	0.26 (1.00)	0.25 (0.98)	-0.01 (1.02)	-0.02 (1.00)	p=0.94	-0.03 (0.96)	0.00 (0.93)	p=0.59
Weight-for-length z-score	-0.39 (1.02)	-0.37 (1.02)	0.28 (0.92)	0.39 (0.91)	p=0.06	0.51 (0.79)	0.50 (0.87)	p=0.91
3. BMI	16.25 (1.43)	16.26 (1.48)	16.88 (1.34)	17.02 (1.36)	p=0.09	15.98 (1.10)	15.96 (1.21)	p=0.73
3. BMI-for-age z-score	-0.40 (0.98)	-0.38 (0.99)	0.29 (0.92)	0.40 (0.91)	p=0.05	0.35 (0.80)	0.33 (0.90)	p=0.61
4. Head circumference (cm)	41.11 (1.25)	41.12 (1.30)	46.76 (1.47)	46.83 (1.51)	p=0.40	50.21 (1.62)	50.27 (1.72)	p=0.53
4. Head circumference-for-age z-score	0.51 (0.90)	0.57 (0.92)	0.65 (0.97)	0.71 (0.98)	p=0.25	0.73 (1.09)	0.78 (1.13)	p=0.41
5. MUAC (cm)	13.36 (1.09)	13.29 (1.05)	15.23 (1.10)	15.32 (1.23)	p=0.19	16.37 (1.16)	16.38 (1.16)	p=0.90
5. MUAC-for-age z-score	-0.07 (1.01)	-0.11 (0.96)	0.59 (0.88)	0.66 (1.01)	p=0.21	0.41 (0.83)	0.42 (0.84)	p=0.86
6a. Sub scapular skin fold (cm)	6.58 (1.46)	6.50 (1.51)	6.80 (1.55)	6.96 (1.69)	p=0.11	6.51 (1.57)	6.56 (1.63)	p=0.63
6a. Sub scapular skin fold-for-age z-score	-1.05 (1.29)	-1.14 (1.38)	0.14 (1.24)	0.24 (1.28)	p=0.19	0.28 (1.13)	0.29 (1.10)	p=0.85
6b. Triceps skin fold (cm)	7.55 (1.84)	7.58 (1.82)	8.70 (2.13)	8.93 (2.12)	p=0.07	8.76 (2.62)	8.85 (2.90)	p=0.62
6b. Triceps skin fold-for-age z-score	-1.59 (1.48)	-1.56 (1.47)	0.29 (1.25)	0.43 (1.24)	p=0.07	0.13 (1.40)	0.12 (1.47)	p=0.97

Key: BMI Body Mass Index MUAC Mid-Upper Arm Circumference

CHALLENGE BREAKDOWN

The EAT study design meant that any sensitised participant underwent a food challenge. The total number of challenges undertaken in the study by food is given in Table 32.

Table 32 Food challenges undertaken in the EAT study

	DBPCFC (1 year)	DBPCFC (3 year)	OFC	FCC	FPIES	Total by Food
Egg	102	31	83	37	4	257
Peanut	13	53	21	13	0	100
Milk	23	6	41	16	1	87
Wheat	1	0	11	30	0	42
Sesame	5	19	9	2	1	36
Cod	4	2	8	16	1	31
Total by type	148	111	173	114	7	553

DBPFC: Double blind placebo controlled food challenge
OFC: Open food challenge
FCC: Frequent consumer challenge
FPIES: Food protein induced entero-colitis syndrome

FOOD ALLERGY (INTENTION-TO-TREAT)

PRIMARY OUTCOME

Of 74 participants with food allergy 70 diagnoses (39 in the SIG, 31 in the EIG) were based on double-blind, placebo-controlled food challenges (primary outcome Categories 1A/B – see Table 6) and four (3 in SIG, 1 in EIG) on an allergic reaction in a participant with a skin-prick test of 5 mm or more (primary outcome Category 3) (Table 33).

Table 33 Hierarchical categorisation of the primary outcome

Category	SIG N=42	EIG N=32
1A & 1B: +ve DBPCFC	39	31
2: +ve challenge 6 months to <1 year	0	0
3: Reaction & SPT ≥5mm	3	1

For the primary outcome, 595 participants (91.4%) in the SIG and 567 participants (87.0%) in the EIG were included in the intention-to-treat analysis (Figure 9). The primary outcome was non-significantly lower in the EIG 5.6% (32/567) than the SIG 7.1% (42/595), representing a relative risk of 0.80 (95% confidence interval (CI), 0.51 to 1.25, p=0.32), with the point estimate representing a 20% reduction in prevalence (Figure 24 and Table 34).

Table 34 Primary Outcome of Allergy to One or More Foods

	SIG ITT % (n/N)	EIG ITT % (n/N)	EIG vs SIG Relative risk (95% CI)	p value
Overall	7.1 (42/595)	5.6 (32/567)	0.80 (0.51-1.25)	p=0.32[1]

[1]Chi squared

Allergy to more than one food was non-significantly lower in the EIG (p=0.17) (Table 35).

Table 35 Number of Participants with One or More Allergies to Early Introduction Foods

Number of study foods primary outcome positive to	SIG N=42 % (n)	EIG N=32 % (n)	
1	78.6 (33)	90.6 (29)	p=0.17
2	16.7 (7)	6.3 (2)	
3	2.4 (1)	3.1 (1)	
5	2.4 (1)	0.0 (0)	
Total number of food allergies	55 (1.31/+ve child)	36 (1.12/+ve child)	

A diagnosis of any food allergy was significantly associated with eczema at enrollment, non-white ethnicity and having siblings. In the dominance analysis these accounted for 92.6% of the variation in overall logistic models fit statistic (Table 36).

Table 36 Logistic Modelling and Dominance of Factors Influencing the Primary Outcome

	Primary outcome 6.4% (74/1161)		Primary outcome dominance analysis	
	OR (95% CI)	p value	Dominance statistic	Rank
Study group (EIG)	0.75 (0.46-1.24)	0.26	1.5%	6
Ethnicity (non-white)	2.09 (1.19-3.66)	0.01	11.3%	2
Visible eczema at 3m visit	6.09 (3.67-10.1)	<0.001	72.4%	1
Maternal atopy	1.49 (0.86-2.59)	0.15	3.4%	4
Maternal education (≤18 years)	0.58 (0.28-1.23)	0.16	2.7%	5
Siblings (any)	1.95 (1.11-3.42)	0.02	8.9%	3

HIGH RISK SUBGROUP

The 24.5% of EAT participants who were high risk (visible eczema at the enrolment visit) and whose primary outcome status was evaluable generated 64.9% of the primary outcome cases (48/74). Conversely therefore, a significant minority (35.1%) of the primary outcomes cases were coming from the low risk three month infants. The primary outcome was lower in the EIG group for both high risk and non-high risk participants but neither reduction was statistically significant (Table 37).

Table 37 Primary Outcome of Allergy to One or More Foods by Enrolment Eczema Status

Primary Outcome	SIG ITT % (n/N)	EIG ITT % (n/N)	EIG vs SIG Relative risk (95% CI)	p value
No visible eczema	3.6 (16/451)	2.4 (10/426)	0.66 (0.30-1.44)	p=0.30[1]
Visible eczema	18.2 (26/143)	15.6 (22/141)	0.86 (0.51-1.44)	p=0.56[1]

[1]Chi squared

SECONDARY OUTCOMES OF ALLERGY TO INDIVIDUAL FOODS

Whilst the EAT study had not been powered to assess differences in the prevalence of allergy to individual foods, the prevalence of allergy to each food was lower in the EIG for the two most prevalent allergenic foods - egg and peanut (Table 38 and Figure 24). The reduction in peanut allergy was over 50% but not statistically significant. Similarly the reduction in egg allergy did not reach statistical significance.

Prevalence of food allergy to the four other early introduction foods was low (0.7% or less) and no statistically significant differences between groups were discernible (Table 38 and Figure 25).

Table 38 Secondary Outcomes of Allergy to Individual Foods

Secondary Outcomes	SIG ITT % (n/N)	EIG ITT % (n/N)	EIG vs SIG Relative risk (95% CI)	p value
Peanut	2.5 (15/597)	1.2 (7/571)	0.49 (0.20-1.19)	p=0.11[1]
Egg	5.4 (32/596)	3.7 (21/569)	0.69 (0.40-1.18)	p=0.17[1]
Milk	0.7 (4/597)	0.5 (3/569)	0.79 (0.18-3.50)	p=1.00[2]
Sesame	0.5 (3/597)	0.5 (3.573)	1.04 (0.21-5.14)	p=1.00[2]
Fish	0.2 (1/601)	0.2 (1/573)	1.05 (0.07-16.7)	p=1.00[2]
Wheat	0.0 (0/597)	0.2 (1/572)	-	p=0.49[2]

[1]Chi squared [2]Fisher's exact test

Table 39 shows the point prevalence of food allergy at the one year assessment and three year assessments. The EAT study design meant that only milk, egg, wheat and fish could contribute to the point prevalence at one year. For both age points the prevalence was lower in the EIG and approaching statistical significance for the three year difference.

Table 39 Point Prevalence of Food Allergy at One Year (Excluding Peanut and Sesame) and Three Years (all foods)

Point prevalence of food allergy	SIG % (n/N)	EIG % (n/N)	
12 months (M E W F)	5.2 (31/601)	3.8 (21/550)	p=0.27
36 months (M E W F P S)	4.6 (27/593)	2.5 (14/563)	p=0.06

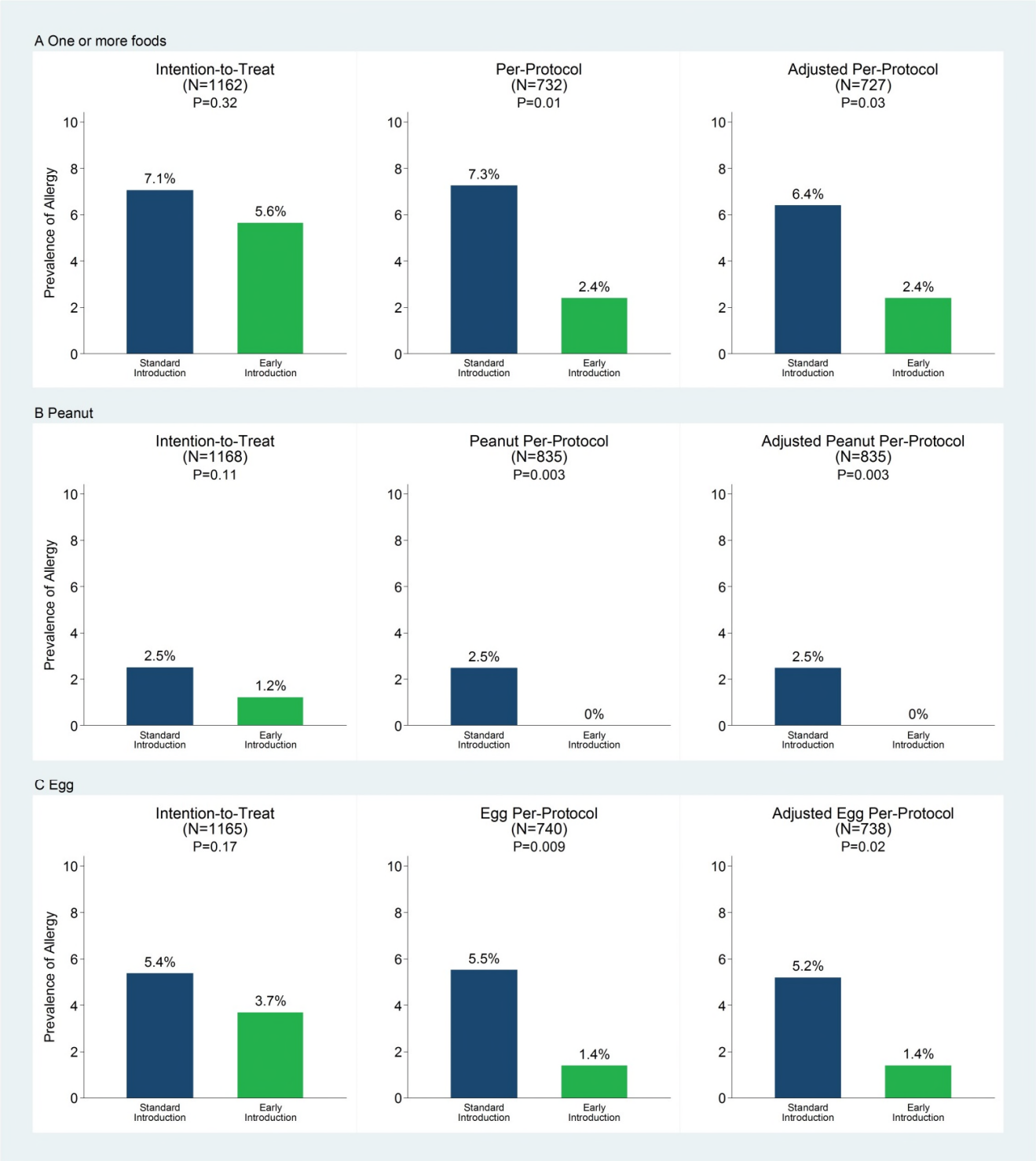


Figure 24. Primary Outcome - Food Allergy

The prevalence of IgE mediated food allergy is shown to one or more of the six intervention foods (Panel A), to peanut (Panel B) and to egg (Panel C). The first column shows the intention-to-treat analysis, the second column the per-protocol analysis and the third column an adjusted per-protocol analysis. The latter was a conservative per-protocol analysis that adjusted the SIG food allergy prevalence by subtracting the number of baseline EIG participants who were challenge positive at enrollment and completed the study with a confirmed food allergy from both the numerator (the number of allergic SIG participants) and the denominator (the number of SIG per-protocol adherent participants). P values are based on chi-square analyses (or Fisher's exact test where appropriate).

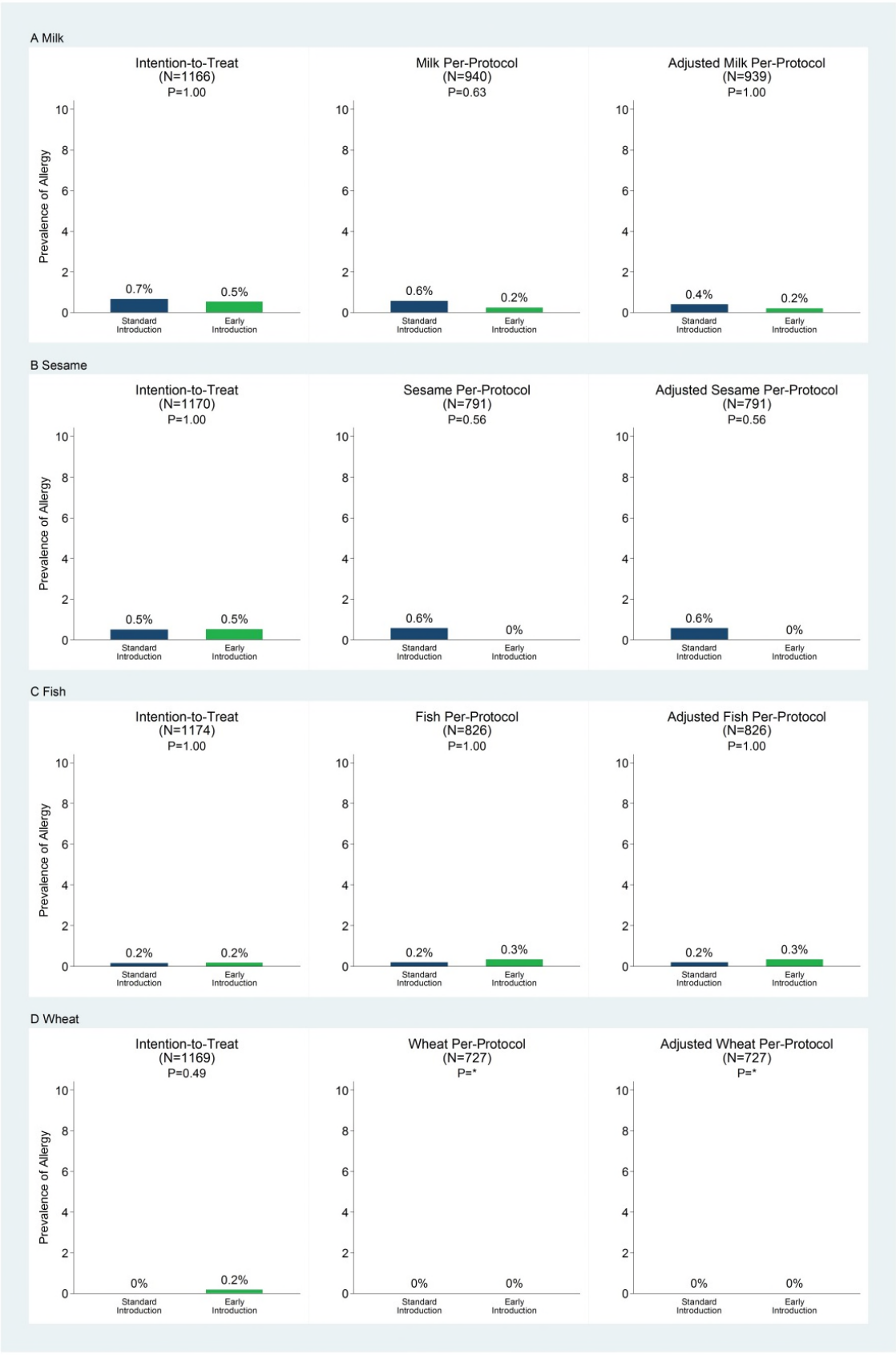


Figure 25 Secondary Outcomes of Allergy to Other Early Introduction Foods

The secondary outcomes are shown for allergy to milk (Panel A), sesame (Panel B), white fish (Panel C) and wheat (Panel D). The first column shows the intention-to-treat analysis, the second column the per-protocol analysis and the third column an adjusted per-protocol analysis. P values are based on Fisher's exact test (2 tailed).

SENSITISATION (INTENTION-TO-TREAT)

The point prevalence of sensitisation to one or more of the six intervention foods at one year and three years of age was lower in the EIG but these differences were not statistically significant (Table 40 and Figure 26).

At 12 months of age, sensitisation was lower to five of the six foods in the EIG, reaching statistical significance for wheat. By three years of age, the sensitisation rate was lower for all six foods in the EIG and again statistically significant for wheat (Table 39 and Figure 26 – peanut, egg and raw egg white, and Figure 27 – other early introduction foods).

Table 40 Sensitisation Results in the EAT Study at 12 and 36 Month of Age

	SIG ITT % (n/N)	EIG ITT % (n/N)	EIG vs SIG Relative Risk (95% CI)	p value
12 months				
Any food sensitisation	18.1 (109/601)	14.2 (78/550)	0.78 (0.60-1.02)	p=0.07[1]
Peanut	6.2 (37/601)	4.2 (23/550)	0.68 (0.41-1.13)	p=0.13[1]
Egg	13.0 (78/601)	10.4 (57/550)	0.80 (0.58-1.10)	p=0.17[1]
Milk	3.0 (18/601)	1.6 (9/550)	0.55 (0.25-1.21)	p=0.13[1]
Sesame	1.2 (7/601)	0.7 (4/550)	0.62 (0.18-2.12)	p=0.55[2]
Fish	1.2 (7/601)	2.0 (11/550)	1.72 (0.67-4.40)	p=0.25[1]
Wheat	3.2 (19/601)	1.3 (7/550)	0.40 (0.17-0.95)	p=0.03[1]
36 months				
Any food sensitisation	10.1 (61/601)	8.9 (51/572)	0.88 (0.62-1.25)	p=0.47[1]
Peanut	5.7 (34/599)	3.9 (22/569)	0.68 (0.40-1.15)	p=0.15[1]
Egg	6.2 (37/599)	5.1 (29/568)	0.83 (0.52-1.33)	p=0.43[1]
Milk	1.8 (11/599)	1.1 (6/568)	0.57 (0.21-1.53)	p=0.27[1]
Sesame	1.7 (10/599)	1.1 (6/567)	0.63 (0.23-1.73)	p=0.37[1]
Fish	0.8 (5/599)	0.7 (4/567)	0.85 (0.23-3.13)	p=1.00[2]
Wheat	3.2 (19/599)	1.4 (8/569)	0.44 (0.20-1.00)	p=0.04[1]
Raw egg white	7.2 (43/596)	5.1 (29/569)	0.71 (0.45-1.12)	p=0.13[1]

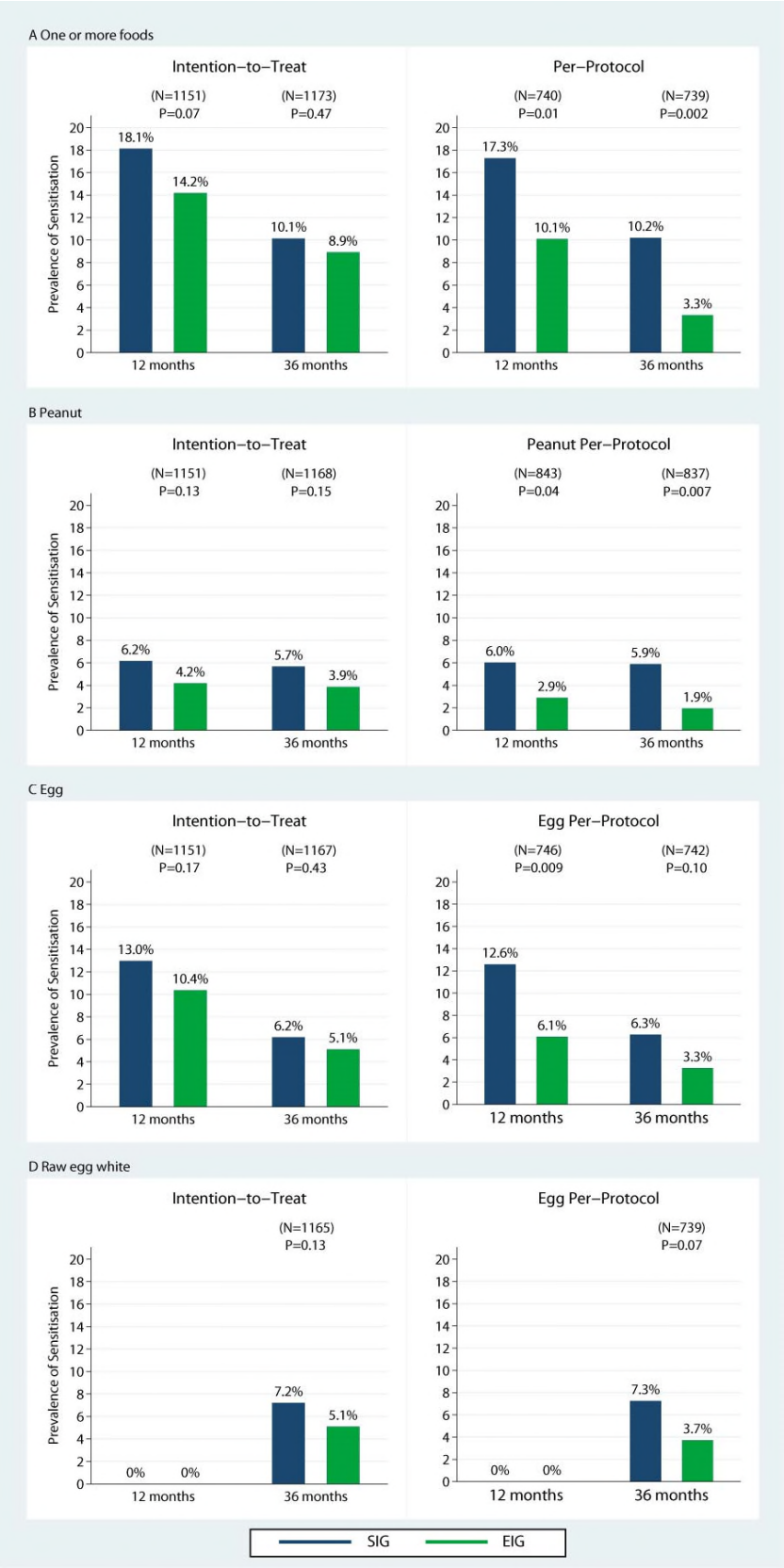


Figure 26 Secondary Outcome - Skin-prick Test Status

The prevalence of skin-prick positivity (any sized wheal) is shown for positive results to one or more of the six intervention foods (Panel A), to peanut (Panel B), to egg (Panel C) and to raw egg white (Panel D - only undertaken at the 36 months visit). The first column shows the intention-to-treat analysis, the second column the per-protocol analysis. P values are based on chi-square analyses.

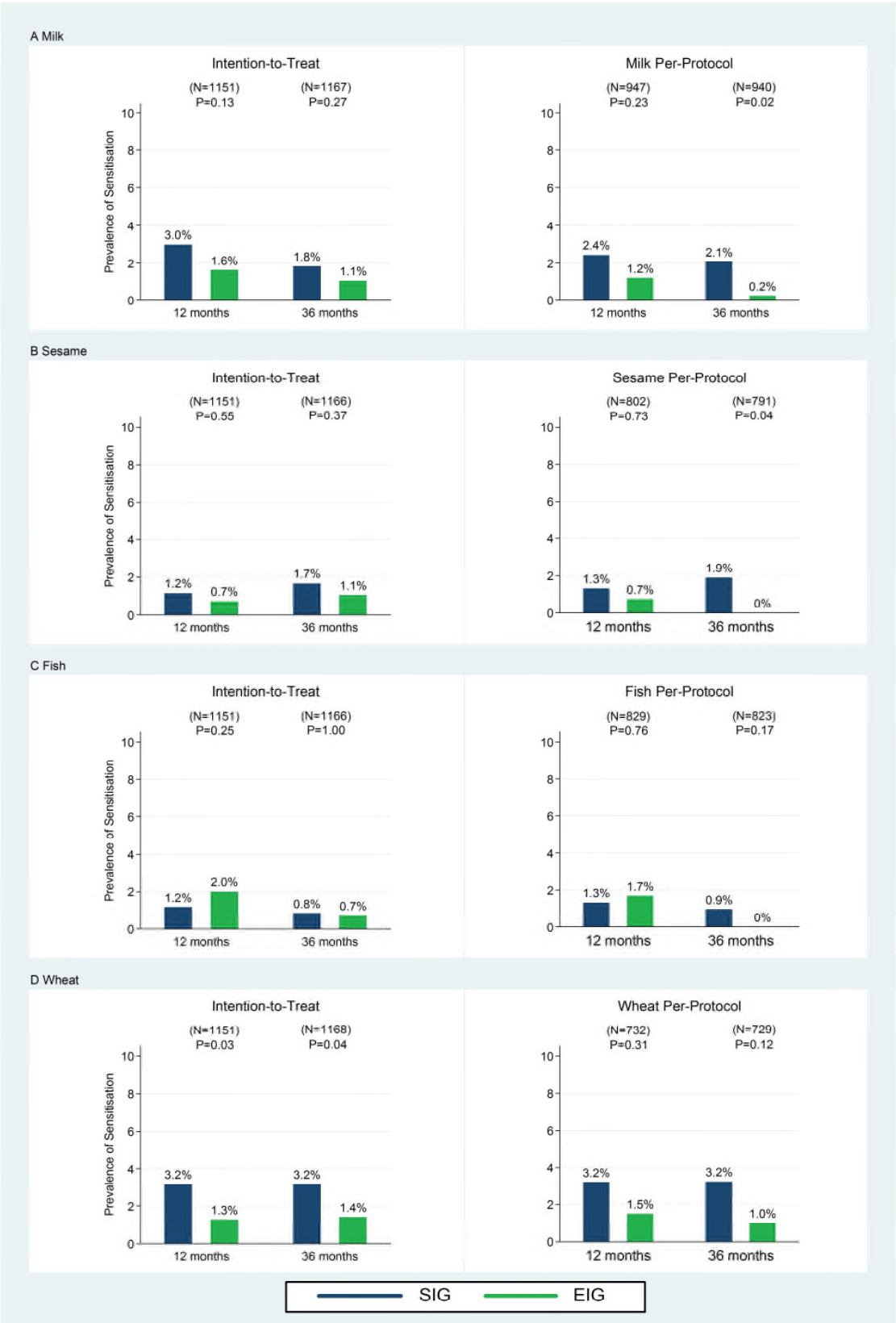


Figure 27 Secondary Outcome of Results on Skin-Prick Testing to Other Early Introduction Foods

The prevalence of a positive skin-prick test (any sized wheal) is shown to milk (Panel A), sesame (Panel B), white fish (Panel C) and wheat (Panel D). The first column shows the intention-to-treat analysis, the second column the per-protocol analysis. P values are based on chi-square analyses (or Fisher's exact test where appropriate).

OTHER ALLERGIC DISEASES (INTENTION-TO-TREAT)

INDIVIDUAL ALLERGIC CONDITIONS

Whilst visible eczema was more common in the EIG as 12 months, 36 months and the combined 12 and/or 36 months assessment the differences did not achieve statistical significance (Table 41).

Table 41 The Point Prevalence of Eczema at One Year and Three Years of Age and Cumulative Prevalence of Eczema by Three Years of Age

Prevalence of visible eczema	SIG % (n/N)	EIG % (n/N)	
12 months	24.0 (144/601)	28.4 (156/550)	p=0.09
36 months	20.1 (120/596)	23.4 (133/569)	p=0.18
Cumulative prevalence by 36 months	42.7 (245/574)	47.7 (247/518)	p=0.10

SCORAD was not significantly different comparing the two groups for all children (Table 42) or those children with visible eczema at the assessment visit (Table 43).

Table 42 The Severity of Eczema at One Year and Three Years of Age (All Participants)

SCORAD	SIG mean (SD)	EIG mean (SD)	
12 months	2.3 (6.0)	2.9 (6.4)	p=0.12
36 months	2.9 (8.3)	3.2 (8.5)	p=0.57

Table 43 The Severity of Eczema at One Year and Three Years of Age (Participants With Eczema)

SCORAD	SIG mean (SD)	EIG mean (SD)	
12 months	9.8 (9.0)	10.2 (8.4)	p=0.69
36 months	14.3 (13.4)	13.6 (13.2)	p=0.71

There was no effect on allergic rhinitis prevalence based on the ISAAC questionnaire definition (Table 44) or inhalant allergen sensitisation (Table 45).

Table 44 The Prevalence of Allergic Rhinitis at Three Years of Age

Sneezing, runny or blocked nose without cold/flu in last 12 months	SIG % (n/N)	EIG % (n/N)	
36 months	15.0 (93/618)	15.3 (93/607)	p=0.89

Table 45 The Prevalence of Inhalant Allergen Sensitization at One Year and at Three Years of Age

Inhalant allergen sensitisation*	SIG % (n/N)	EIG % (n/N)	
12 months	7.9 (47/597)	8.0 (44/550)	p=0.94
36 months	17.7 (103/583)	18.4 (101/550)	p=0.76

* Cat, dog, house dust mite, grass or tree

COMPOSITE CONDITIONS

A composite outcome of allergic rhinitis prevalence based on the ISAAC questionnaire definition and inhalant allergen sensitisation was not significantly different between the two groups (Table 46).

Table 46 The Prevalence of Parent Reported Allergic Rhinitis and Inhalant Allergen Sensitization at One Year and at Three Years of Age

Sneezing, runny or blocked nose without cold/flu in last 12 months AND inhalant allergen sensitisation*	SIG % (n/N)	EIG % (n/N)	
12 months	2.1 (12/583)	3.4 (18/533)	p=0.17
36 months	4.3 (25/578)	4.5 (24/549)	p=0.97

* Cat, dog, house dust mite, grass or tree

A composite of ISAAC defined wheezing with inhalant allergen sensitisation was the same in both groups (Table 47).

Table 47 The Prevalence of the Atopic Wheeze Phenotype at Three Years of Age (Wheezing or Whistling in the Chest and Inhalant Allergen Sensitisation)

Atopic wheeze phenotype	SIG % (n/N)	EIG % (n/N)	
36 months	2.6 (15/578)	2.6 (14/549)	p=0.96

A further composite measure of combined allergic disease (food allergy, atopic wheeze phenotype, eczema and allergic rhinitis) at three years of age was also the same in both groups (Table 48).

Table 48 The Prevalence of Combined Allergic Disease (a Composite of Cumulative IgE Mediated Food Allergy to All Foods, Atopic Wheeze Phenotype, Eczema and Allergic Rhinitis) at Three Years of Age

Combined allergic disease	SIG % (n/N)	EIG % (n/N)	
36 months	36.5 (212/581)	38.7 (216/558)	p=0.44

OTHER OUTCOMES - QUALITY OF LIFE (INTENTION-TO-TREAT)

The quality of life in mothers in EAT study at three time points are given in Table 49. Interestingly, for 9 of the 12 comparisons (including the enrolment data) the EIG had a marginally higher score than the SIG. For 2 comparisons the mean quality of life score was the same and only for one was the quality of life score marginally higher in the SIG. The distribution of quality of life scores were quite tight in general and given the range of scores in each domain is from 4 to 20, it is unlikely that differences of one or two tenths are of any clinical significance.

Table 49 Maternal Quality of Life at 3, 12 Months and Three Years

Quality of life domain score	3 months mean (SD)		12 months mean (SD)		36 months mean (SD)	
	SIG	EIG	SIG	EIG	SIG	EIG
D1	16.4 (2.0)	16.6 (1.8)	16.6 (2.1)	16.6 (2.1)	16.6 (2.2)	16.6 (2.2)
Physical health	p=0.12		p=0.73		p=0.95	
D2	15.5 (2.0)	15.6 (2.1)	15.4 (2.1)	15.5 (2.2)	15.4 (2.3)	15.5 (2.4)
Psychological	p=0.64		p=0.40		p=0.16	
D3	15.6 (2.7)	15.5 (2.8)	15.3 (3.1)	15.5 (3.0)	15.2 (3.2)	15.5 (3.2)
Social relationships	p=0.74		p=0.34		p=0.11	
D4	16.3 (2.0)	16.4 (1.9)	16.0 (2.0)	16.2 (2.3)	16.1 (2.4)	16.3 (2.4)
Environment	p=0.15		p=0.29		p=0.15	

PER-PROTOCOL ANALYSES

PER-PROTOCOL STATUS - METHODOLOGY

The SIG and EIG per-protocol criteria have been presented previously (Table 2 & 3 respectively). Criterion A for both groups, exclusive breastfeeding at the point of enrolment, was a pre-requisite to taking part in the study and hence adherence with this was complete (Table 50). The ability to determine adherence with the other individual criteria relied on data being available from the interim questionnaires.

Standard Introduction Group

For the SIG, Criterion B (continued breastfeeding up to five months) and Criterion D (no or minimal introduction of cows' milk formula between three months and six months of age) could be determined from any of the interim questionnaires, as every questionnaire asked at what age the participant stopped breastfeeding and at what age they started giving their child formula milk. Criterion C (no consumption of peanut, egg, sesame, wheat or fish before five months) required the SIG mother to have completed both the 4 month and the 5 month interim questionnaires for their adherences to this criterion to be evaluable.

Early Introduction Group

For the EIG, Criterion B was the same as for the SIG and hence could be determined from the response to any interim questionnaire. However it was Criterion C that made assessment of adherence in the EIG more difficult to achieve compared with the SIG. Criterion C was consumption of at least five of the allergenic foods in at least 75% of the recommended amount (3g allergen protein/week), for at least five weeks between three months and six months of age. In order for this to be determined the EIG family needed to have completed all three of the four, five and six month interim questionnaires.

Interim questionnaire completion rates by study group

However, this weighting towards it being more difficult to determine per-protocol status in the EIG compared with the SIG was compounded by it becoming apparent that there was a significant difference in completion of interim questionnaires between the two study groups with completion at all time points being significantly lower in the EIG (Figure 28).

This is likely to represent the impact of the additional burden for EIG families of keeping essentially a daily diary of how much of the six allergenic foods their infant was consuming. Furthermore, personal conversations with EIG families who were not completing questionnaires did suggest that there was a tendency for EIG mothers who were not meeting the EIG consumption target to feel that their participation in the study was less valuable to the study team and hence there being no or less necessity to complete the questionnaires.

The combination of the enhanced difficulty of being per-protocol assessable in the EIG and the lower questionnaire completion rate meant that there was a marked difference in the proportion whose per-protocol status was non-evaluable between the two groups (SIG 6.9%, EIG 18.9%).

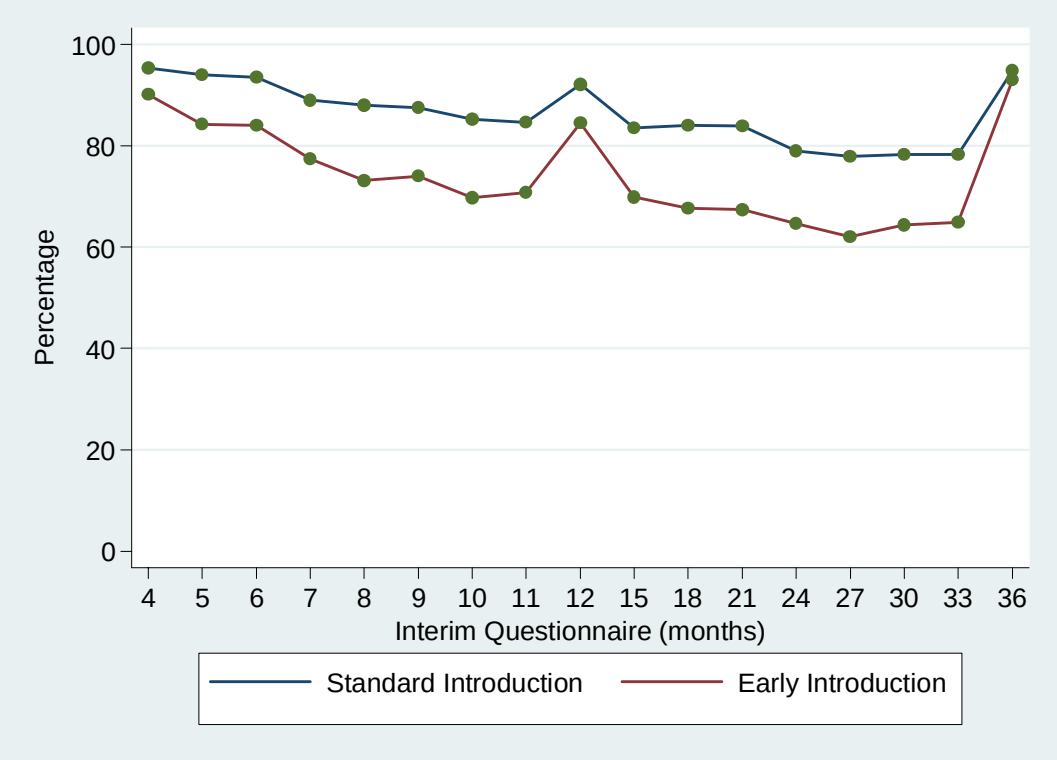


Figure 28 Interim questionnaire completion by study group

For the per-protocol non-evaluable EIG participants it is possible to look at individual interim questionnaire responses to assess how much of each allergenic food they were consuming for the questionnaires that were completed. The mean dose of allergenic protein consumed each week from enrolment to 12 months of age for each allergenic food is presented for the EIG group in Figure 29. The EIG group is divided into those who were per-protocol (34% - blue line), those non per-protocol (47% - red line) and those per-protocol status was non-evaluable (19% - green line). This clearly indicates that allergenic consumption levels in the non-evaluable children were similar to the non per-protocol EIG participants.

This per-protocol non-evaluable group therefore represents a hybrid of families completing few questionnaires and formal drop outs from the study. The distinction is important as some of the former did return for the clinical visits (and were therefore primary outcome evaluable), whereas none of the latter did.

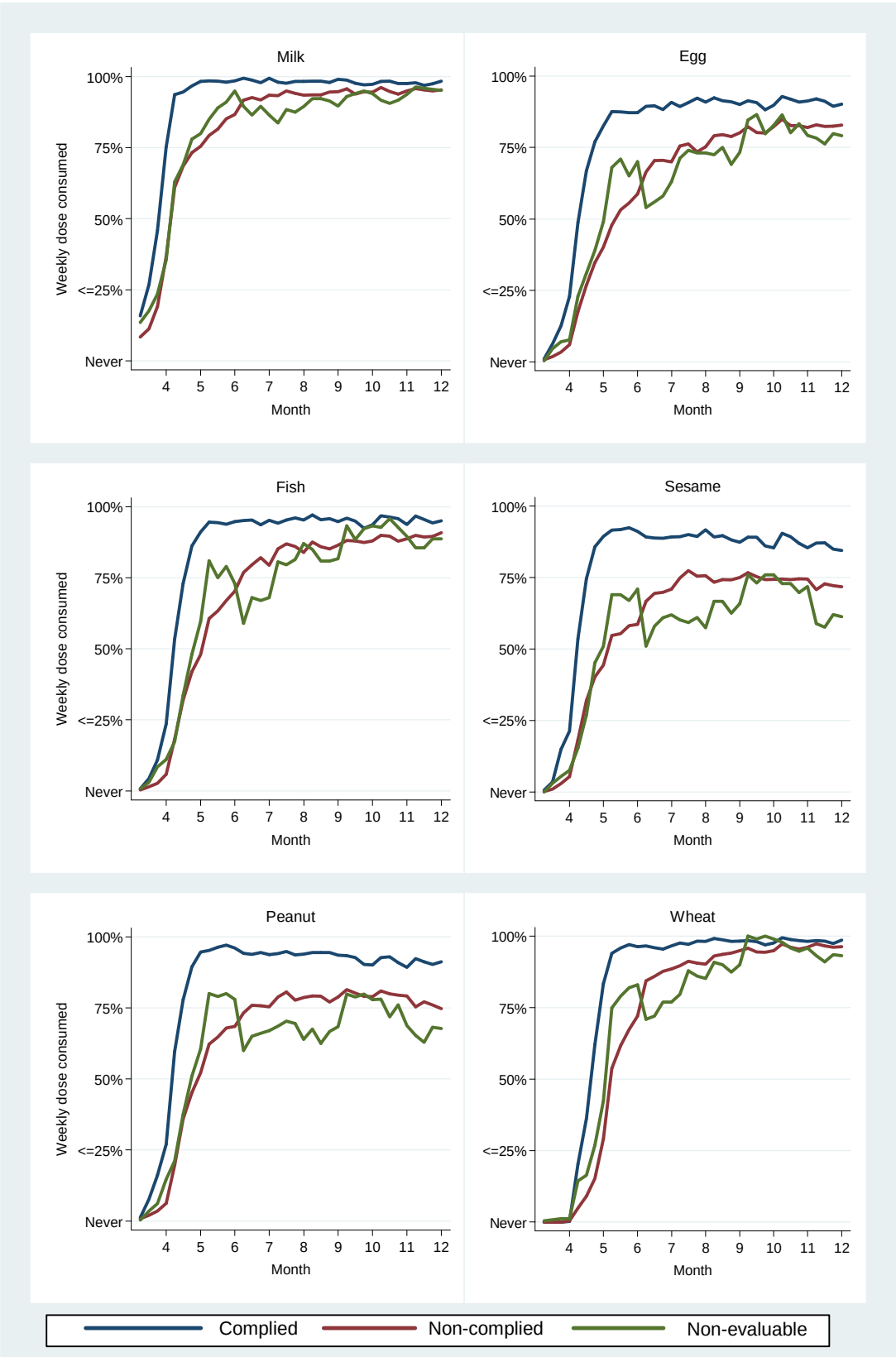


Figure 29 EIG compliance status and early introduction of allergenic foods

PER-PROTOCOL COMPLIANCE

Table 50 Per-protocol compliance criteria in the EAT study

Per-Protocol definitions	Per-protocol evaluable children meeting the per-protocol definitions
Standard Introduction Group (SIG)	
(N=606/651 children per-protocol evaluable)	
• Criterion A: Exclusive breastfeeding for at least three months duration (water and/or oral rehydration solution allowed)	100% (606/606) (A) 12.0% have had water by 3 months of age
• Criterion B: Continued breastfeeding up to five months of age	99.7% (604/606) (B)
• Criterion C: No consumption of peanut, egg, sesame, fish or wheat before five months	97.4% (590/606) (C)
• Criterion D: No introduction of cow's milk formula (or goat's milk formula) (or consumption of less than 300 mls/day) between three months and six months of age	(1) No formula pre six months 85.6% (519/606) (2) Consumption of less than 300mls/day 8.8% (53/606) *(median age of introduction of 22 weeks)* (1) or (2): 94.4% (572/606) (D)
Overall SIG per-protocol compliance (meets all criteria)	**92.1% (558/606) (A, B, C & D)**
Early Introduction Group (EIG)	
(N=529/652 children per-protocol evaluable)	
• Criterion A: Exclusive breastfeeding for three months duration (water and/or oral rehydration solution allowed)	100% (529/529) (A) 13.1% have had water by 3 months of age
• Criterion B: Continued breastfeeding up to five months of age	99.6% (527/529) (B)
• Criterion C: Consumption of at least five of the allergenic foods in at least 75% of the recommended amount (3g allergen protein/week), for at least five weeks between three months and six months of age	42.3% (224/529) (C)
Overall EIG per-protocol compliance (meets all criteria)	**42.2% (223/529) (A, B & C)**

* Per-protocol status non-evaluable for 7% (45/651) of the SIG and 19% (123/652) of the EIG participants

PER-PROTOCOL ADHERENCE

In the SIG 558 participants were per-protocol adherent: this represents 92.1% (558/606) of those in whom adherence could be determined, or 85.7% (558/651) of the enrolled SIG (Table 50).

The primary outcome status could not be determined for 42 of the 606 SIG participants in whom adherence was evaluable. Hence, 92.9% (524/564) of the SIG participants whose primary outcome status could be determined were per-protocol adherent (Figure 9). This represents 80.5% (524/651) of the enrolled SIG.

In the EIG the proportion adhering to the per-protocol criteria was much lower: 223 participants were per-protocol adherent representing 42.2% (223/529) of those in whom adherence could be determined, or 34.2% (223/652) of the enrolled EIG.

The primary outcome status could not be determined for 43 of the 529 EIG participants in whom adherence was evaluable. Hence, 42.8% (208/486) of the EIG participants whose primary outcome status could be determined were per-protocol adherent (Figure 9). This represents 31.9% (208/652) of the enrolled EIG.

PER-PROTOCOL STATUS AND PER-PROTOCOL ANALYSES

These adherence statistics are summarised in Table 51.

Table 51 Overall per-protocol status of EAT participants

	Per-Protocol Status		Per-Protocol Status AND Primary Outcome Determinable	
	Per-Protocol Status *(Per-Protocol Evaluable)* % (n/N)	**Per-Protocol Status *(All Enrolled Participants)* % (n/N)**	**Per-Protocol Status *(Per-Protocol Evaluable)* % (n/N)**	**Per-Protocol Status *(All Enrolled Participants)* % (n/N)**
Standard Introduction Group				
Per-protocol	92.1 (558)	85.7 (558)	92.9 (524)	80.5 (524)
Non Per-protocol	7.9 (48)	7.4 (48)	7.1 (44)	6.8 (44)
Missing data	-	6.9 (45)	-	12.9 (84)
Total	100.0 (606)	100.0 (651)	100.0 (564)	100.0 (651)
Early Introduction Group				
Per-protocol	42.2 (223)	34.2 (223)	42.8 (208)	31.9 (208)
Non Per-protocol	57.8 (306)	46.9 (306)	57.2 (278)	42.8 (278)
Missing data	-	18.9 (123)	-	25.5 (166)
Total	100.0 (529)	100.0 (652)	100.0 (486)	100.0 (652)

Because there were significant numbers of participants in all three categories of adherence, the per-protocol analyses sections are presented for all six categories:

- EIG per-protocol
- EIG non per-protocol
- EIG adherence non-evaluable

- SIG per-protocol
- SIG non per-protocol
- SIG adherence non-evaluable

This allows an assessment to be made as the extent to which particularly the non-evaluable group are similar or dissimilar to those participants whose compliance status was evaluable.

PEANUT PROTEIN AND ADHERENCE

Dust samples collected from participants' beds were obtained at enrollment from 538 of the 1303 study participants and at 12 months of age from 350 of the 1303 study participants to provide an index of peanut exposure independent of parental reporting. The median level of peanut detected in the bed dust at enrollment was similar in both groups: 9.7 μg per gram of dust (interquartile range, 2.6 to 40.1) in the SIG and 7.6 μg per gram of dust (interquartile range, 2.4 to 14.1) in the EIG (Figure 30). At 12 months of age, the levels were respectively 77.0 μg per gram of dust (interquartile range, 11.3 to 383) and 387.9 μg per gram of dust (interquartile range, 120 to 643) (p<0.0001). At 12 months of age the median level of peanut in the bed dust in the EIG was significantly higher in the per-protocol participants' beds compared to the non per-protocol participants' beds (p=0.04).

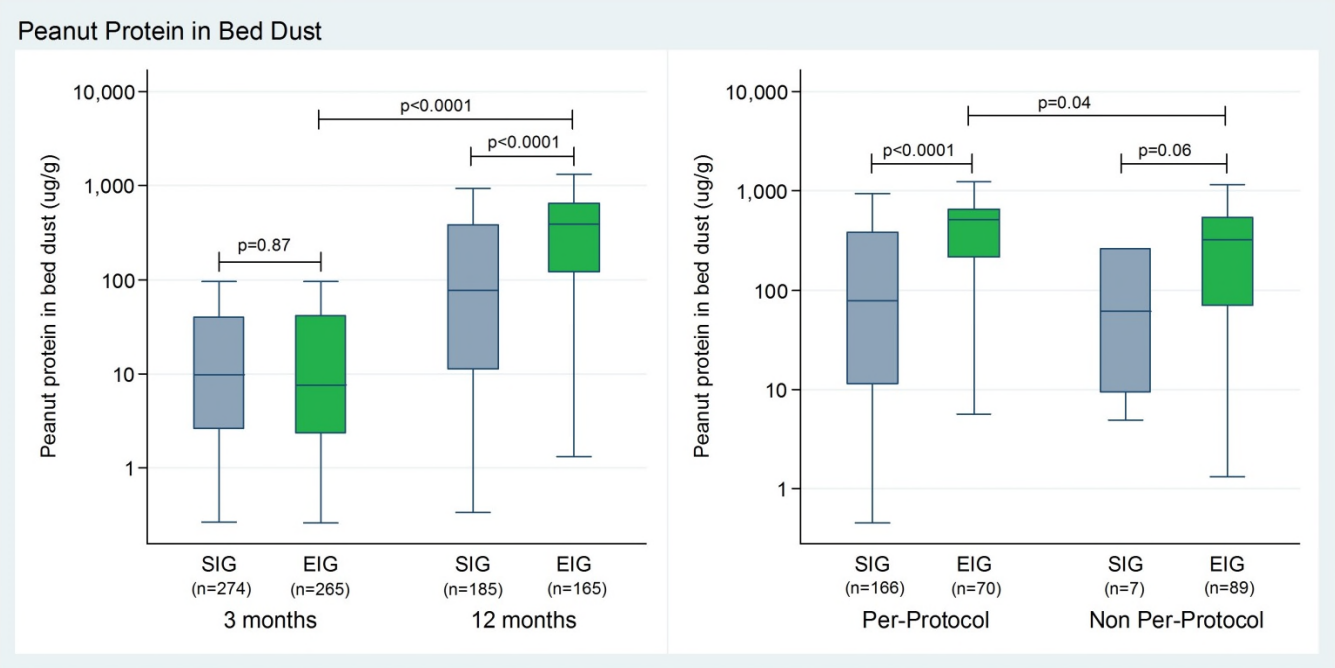


Figure 30 Peanut Protein in Bed Dust at 3 and 12 Months of Age

Peanut protein levels (µg/g) are shown from dust collected from individual participant's bed sheets that provided samples at 3 and 12 months. The box in the box and whisker plots represents the median and inter-quartile range. The whiskers represent the further point within 1.5 times the inter-quartile range from the box. In the left panel the enrollment levels of peanut protein are similar in both groups, but significantly higher in the EIG by one year of age. In the right panel, peanut protein levels were significantly higher in the EIG at one year of age when stratified by per-protocol status. Furthermore, peanut protein levels were significantly higher at one year of age in the EIG per-protocol participants compared with the non per-protocol EIG participants.

PRIMARY OUTCOME – PER-PROTOCOL ANALYSIS

In the per-protocol analysis the primary outcome was significantly lower in the EIG 2.4% (5/208) than the SIG 7.3% (38/524), a relative risk of 0.33 (95% CI, 0.13 to 0.83, P=0.01), representing a 67% reduction in prevalence (Figure 24 and Table 52). It is important to note that the EIG non per-protocol group did not display the benefits with respect to food allergy observed in the EIG per-protocol group.

The primary outcome prevalence in the EIG non per-protocol and adherence non-evaluable groups was similar to the SIG per-protocol rate at around 7.0% (Table 52). This is an important finding, suggesting that failure in the EIG to reach the level of consumption required to be defined as per-protocol adherent did not confer any increased risk of food allergy than occurred in the SIG per-protocol group. Comparisons between the SIG per-protocol group and the EIG non per-protocol and adherence non-evaluable groups were all non-significant (Table 54).

The allergy rate in the EIG adherence non-evaluable group being similar to the SIG per-protocol group is also very important as it suggests a bias did not exist with higher risk EIG participants being more likely to be adherence non-evaluable.

PRIMARY OUTCOME – ADJUSTED PER-PROTOCOL

Out of the 652 participants in the EIG, seven had one or more positive challenges at enrolment (Table 13). However, one of these was primary outcome negative (no IgE mediated food allergy to any of the six foods). Another dropped out and their primary outcome status is unknown.

The remaining five children represent primary outcome positive EIG infants who were food allergic prior to the study intervention commencing. It can therefore be assumed that there were five similar children in the SIG per-protocol group.

When making the per-protocol comparison we therefore also undertook an adjusted analysis where we compared the allergy rate in the EIG per-protocol group (5/208) with the SIG per-protocol group less five allergic children to reflect those likely to already have a food allergy at enrolment and for whom inclusion in the SIG could not have impacted on their allergic status (38-5/524-5 i.e. 33/519). As these children have already been removed from the EIG per-protocol group due to the nature of the intervention, this provides a fairer comparison of the per-protocol groups.

The results are: EIG per-protocol: 2.4% (5/208), SIG per-protocol (adjusted) 6.2% (33/519), risk ratio 0.38 (95% CI 0.15-0.96), p=0.03 (Figure 24). This shows that there remains a significant reduction in food allergy prevalence between EIG and SIG per-protocol groups even once the analysis has been adjusted for children who had an underlying food allergy at entry to the study which could not be altered by inclusion in either study group.

PRIMARY OUTCOME – PER-PROTOCOL ANALYSIS - HIGH RISK/NON-HIGH RISK

Table 53 gives the results of adherence with the study intervention, stratified by risk status (visible eczema being present at the enrolment visit). Allergy prevalence reduced 55% in the non-high risk group and 73% in the high risk group, although with the small numbers neither was statistically significant. Once again, there was no suggestion that EIG non per-protocol participants within each risk strata had a significantly increased prevalence of food allergy compared with the SIG per-protocol group (Table 54).

FOOD ALLERGY

All p values are comparing SIG compliant with EIG compliant

Table 52 Primary Outcome: Per-Protocol

Primary outcome *(one or more foods)*	SIG Per-Protocol % (n/N)	EIG Per-Protocol % (n/N)	EIG vs SIG Relative Risk (95% CI)	p value	SIG Non Per-Protocol % (n/N)	EIG Non Per-Protocol % (n/N)	SIG Adherence Non-Evaluable % (n/N)	EIG Adherence Non-Evaluable % (n/N)
Overall	7.3 (38/524)	2.4 (5/208)	0.33 (0.13-0.83)	p=0.01	7.5 (3/40)	7.6 (21/278)	3.2 (1/31)	7.4 (6/81)

Table 53 Primary Outcome: Per-Protocol (High Risk Subgroup)

Primary outcome *(one or more foods)*	SIG Per-Protocol % (n/N)	EIG Per-Protocol % (n/N)	EIG vs SIG Relative Risk (95% CI)	p value	SIG Non Per-Protocol % (n/N)	EIG Non Per-Protocol % (n/N)	SIG Adherence Non-Evaluable % (n/N)	EIG Adherence Non-Evaluable % (n/N)
Visible eczema	17.5 (22/126)	4.8 (2/42)	0.27 (0.07-1.11)	p=0.04	30.0 (3/10)	21.0 (17/81)	14.3 (1/7)	16.7 (3/18)
No visible eczema	4.0 (16/398)	1.8 (3/166)	0.45 (0.13-1.52)	p=0.30	0.0 (0/30)	2.0 (4/197)	0.0 (0/23)	4.8 (3/63)

Table 54 Primary Outcome: Comparisons between the Standard-Introduction Per-Protocol Group and the Early Introduction Non Per-Protocol and Adherence Non-Evaluable Groups

Primary outcome *(one or more foods)*	SIG Per-Protocol (A) % (n/N)	EIG Non Per-Protocol (B) % (n/N)	p value SIG PP vs EIG Non-PP (A vs B)	EIG Adherence Non-Evaluable (C) % (n/N)	p value SIG PP vs EIG Adherence Non-Evaluable (A vs C)
Overall	7.3 (38/524)	7.6 (21/278)	0.89	7.4 (6/81)	1.00
Visible eczema	17.5 (22/126)	21.0 (17/81)	0.59	16.7 (3/18)	1.00
No visible eczema	4.0 (16/398)	2.0 (4/197)	0.24	4.8 (3/63)	0.73

FOOD SPECIFIC ALLERGY – PER-PROTOCOL ANALYSIS

Individual food per-protocol adherence in the EIG varied: egg 43.1% (215/499), sesame 50.7% (266/505), fish 60.0% (297/495), peanut 61.9% (310/501) and milk 85.2% (415/487).

For food specific per-protocol consumption the protective effects were larger for that food: egg allergy was 1.4% in the egg per-protocol EIG and 5.5% in the per-protocol SIG, a relative reduction of 75% (p=0.009). There were no cases of peanut allergy in the 310 peanut per-protocol adherent EIG compared with 2.5% (13/525) in the per-protocol SIG (p=0.003) (Figure 24 and Table 55).

Per-protocol food allergy rates were lower, but not statistically significantly, for milk (p=0.63) and sesame (p=0.56). There was no wheat allergy in either group in the per-protocol analysis. Fish allergy was non-significantly increased in the EIG (p=1.00) (Figure 25 and Table 55).

Although not part of the statistical analysis plan, if these six component food tests were adjusted for multiple testing using Bonferroni the critical value for statistical significance would be 0.0085 ($1-0.95^{1/6}$); under this constraint the effect on peanut allergy remains statistically significant whilst egg remains borderline significant.

With regards to EIG non per-protocol or EIG adherence being non-evaluable, food specific allergy rates were again not significantly increased above the SIG per-protocol group (Table 56).

Public health imputation analysis – individual food allergy

Assessing individual foods to which there were positive challenges at enrolment in the EIG group, prior to attempted introduction of that food, three out of the 652 participants had positive egg challenges (0.46%), two of whom were primary outcome positive to egg and one was likely to have been. There was one such child for wheat (0.15%) and one for milk (0.15%). There were no children with a positive peanut challenge at enrolment with a subsequent confirmed primary outcome of peanut allergy.

These underlying cases of egg, wheat and milk allergy are important because they are children in whom the intervention had no possibility of being successful. This has public health implications because it means that if the early introduction regimen were to be rolled out more widely, there would still be these few cases of allergy within the population.

It is possible that intervention at an earlier age may have prevented these underlying cases of food allergy but that cannot be ascertained from the current data and there would be many practical difficulties in attempting to introduce allergenic food into the diet of infants before 3 or 4 months of age.

Table 55 Secondary Outcomes: Individual Food Allergy – Food Specific Per-Protocol

Individual Food Allergy	SIG Per-Protocol % (n/N)	EIG Food Specific Per-Protocol % (n/N)	EIG vs SIG Relative Risk (95% CI)	p value	SIG Non Per-Protocol % (n/N)	EIG Food Specific Non Per-Protocol % (n/N)	SIG Adherence Non-Evaluable % (n/N)	EIG Food Specific Adherence Non-Evaluable % (n/N)
Peanut	2.5 (13/525)	0.0 (0/310)	0.00 (-)	p=0.003	2.4 (1/41)	2.1 (4/191)	3.2 (1/31)	4.3 (3/70)
Egg	5.5 (29/525)	1.4 (3/215)	0.25 (0.08-0.82)	p=0.009	5.0 (2/40)	6.0 (17/284)	3.2 (1/31)	1.4 (1/70)
Milk	0.6 (3/525)	0.2 (1/415)	0.42 (0.04-1.04)	p=0.63	2.4 (1/41)	2.8 (2/72)	0.0 (0/31)	0.0 (0/82)
Sesame	0.6 (3/525)	0.0 (0/266)	0.00 (-)	p=0.56	0.0 (0/41)	1.3 (3/239)	0.0 (0/31)	0.0 (0/68)
Fish	0.2 (1/529)	0.3 (1/297)	1.78 (0.11-28.4)	p=1.00	0.0 (0/41)	0.0 (0/198)	0.0 (0/31)	0.0 (0/78)
Wheat	0.0 (0/525)	0.0 (0/202)	-	-	0.0 (0/41)	0.3 (1/303)	0.0 (0/31)	0.0 (0/67)

Table 56 Secondary Outcomes: Comparisons between the Standard-Introduction Per-Protocol Group and the Early Introduction Non Per-Protocol and Adherence Non-Evaluable Groups

Individual Food Allergy	SIG Per-Protocol % (n/N)	EIG Food Specific Non Per-Protocol % (n/N)	p value SIG PP vs EIG Non-PP	EIG Food Specific Adherence Non-Evaluable % (n/N)	p value SIG PP vs EIG Adherence Non-Evaluable
Peanut	2.5 (13/525)	2.1 (4/191)	1.00	4.3 (3/70)	0.42
Egg	5.5 (29/525)	6.0 (17/284)	0.79	1.4 (1/70)	0.24
Milk	0.6 (3/525)	2.8 (2/72)	0.11	0.0 (0/82)	1.00
Sesame	0.6 (3/525)	1.3 (3/239)	0.38	0.0 (0/68)	1.00
Fish	0.2 (1/529)	0.0 (0/198)	1.00	0.0 (0/78)	1.00
Wheat	0.0 (0/525)	0.3 (1/303)	0.37	0.0 (0/67)	-

FOOD SENSITISATION

In the per-protocol analyses, there was a statistically significant reduction in skin-prick positivity to any food at 12 (41.6% relative reduction, p=0.01) and 36 months (67.3% relative reduction, p=0.002) in the EIG compared to the SIG (Table 57).

Like the food allergy results, food sensitisation rates in the EIG non per-protocol group were very similar to those of the SIG per-protocol group.

There was a consistent relative reduction in skin-prick test positivity at 12 months of age in the EIG of approximately 50% (with the exception of fish), statistically significant for egg (p=0.009) and peanut (p=0.04) (Table 58).

At 36 months the effect was greater with a relative reduction in skin-prick positivity in the EIG of 67.1% for peanut (p=0.007), 48.0% for egg (p=0.10), 88.4% for milk (p=0.02), 100.0% for sesame (p=0.04) and fish (p=0.17), and 69.3% for wheat (p=0.12) (Table 58). Skin-prick positivity to raw egg white was also lower in the EIG at 36 months of age with a comparable relative reduction (48.7%, p=0.07) to that observed for commercial egg extract.

These results are an immunological corollary to the reductions in food allergy prevalence observed in the previous section.

Table 57 Any Food Sensitisation – Per-Protocol

	SIG ITT % (n/N)	EIG ITT % (n/N)	EIG vs SIG Relative Risk (95% CI)	p value	SIG Non-Adherent % (n/N)	EIG Non- Adherent % (n/N)	SIG Adherence Non-Evaluable % (n/N)	EIG Adherence Non-Evaluable % (n/N)
12 months								
Any food sensitisation	17.3 (92/532)	10.1 (21/208)	0.58 (0.37-0.91)	p=0.01[1]	28.6 (12/42)	17.1 (48/280)	18.5 (5/27)	14.5 (9/62)
36 months								
Any food sensitisation	10.2 (54/529)	3.3 (7/210)	0.33 (0.15-0.71)	p=0.002[1]	12.2 (5/41)	11.8 (33/280)	6.5 (2/31)	13.4 (11/82)

All p values are comparing SIG per-protocol with EIG per-protocol [1]Chi squared [2]Fisher's exact test

Table 58 Food Sensitisation – Food Specific Per-Protocol

	SIG ITT % (n/N)	EIG ITT % (n/N)	EIG vs SIG Relative Risk (95% CI)	p value	SIG Non-Adherent % (n/N)	EIG Non- Adherent % (n/N)	SIG Adherence Non-Evaluable % (n/N)	EIG Adherence Non-Evaluable % (n/N)
12 months								
Peanut	6.0 (32/532)	2.9 (9/311)	0.48 (0.23-0.99)	p=0.04[1]	9.5 (4/42)	6.9 (13/189)	3.7 (1/27)	2.0 (1/50)
Egg	12.6 (67/532)	6.1 (13/214)	0.48 (0.27-0.85)	p=0.009[1]	16.7 (7/42)	13.8 (40/289)	14.8 (4/27)	8.5 (4/47)
Milk	2.4 (13/532)	1.2 (5/415)	0.49 (0.18-1.37)	p=0.23[2]	7.1 (3/42)	4.1 (4/78)	7.4 (2/27)	0.0 (0/57)
Sesame	1.3 (7/532)	0.7 (2/270)	0.56 (0.12-2.69)	p=0.73[2]	0.0 (0/42)	0.9 (2/230)	0.0 (0/27)	0.0 (0/50)
Fish	1.3 (7/532)	1.7 (5/297)	1.28 (0.41-4.00)	p=0.76[2]	0.0 (0/42)	3.0 (6/198)	0.0 (0/27)	0.0 (0/55)
Wheat	3.2 (17/532)	1.5 (3/200)	0.47 (0.14-1.58)	p=0.31[2]	4.8 (2/42)	1.3 (4/304)	0.0 (0/27)	0.0 (0/46)
36 months								
Peanut	5.9 (31/527)	1.9 (6/310)	0.33 (0.14-0.78)	p=0.007[1]	4.9 (2/41)	6.8 (13/190)	3.2 (1/31)	4.4 (3/69)
Egg	6.3 (33/527)	3.3 (7/215)	0.52 (0.23-1.16)	p=0.10[1]	4.9 (2/41)	6.4 (18/282)	6.5 (2/31)	5.6 (4/71)
Milk	2.1 (11/527)	0.2 (1/413)	0.12 (0.02-0.89)	p=0.02[2]	0.0 (0/41)	5.3 4/75)	0.0 (0/31)	1.3 (1/80)
Sesame	1.9 (10/527)	0.0 (0/264)	0.00 (-)	p=0.04[2]	0.0 (0/41)	2.1 (5/236)	0.0 (0/31)	1.5 (1/67)
Fish	0.9 (5/527)	0.0 (0/296)	0.00 (-)	p=0.17[2]	0.0 (0/41)	2.1 (4/194)	0.0 (0/31)	0.0 (0/77)
Wheat	3.2 (17/527)	1.0 (2/202)	0.31 (0.07-1.32)	p=0.12[2]	4.9 (2/41)	2.0 (6/301)	0.0 (0/31)	0.0 (0/66)
Raw egg white	7.3 (38/524)	3.7 (8/215)	0.51 (0.24-1.08)	p=0.07[1]	7.3 (3/41)	6.4 (18/283)	6.5 (2/31)	4.2 (3/71)

All p values are comparing SIG per-protocol with EIG per-protocol [1]Chi squared [2]Fisher's exact test

PRIMARY OUTCOME – DOSE AND FREQUENCY

The effect of altering the number of foods eaten, the quantity and the frequency during this period is shown in Panel A of Table 59. Compliance with the different permutations ranged from 6% to 81% depending on how stringent the criteria used were.

Food allergy prevalence was reduced in concert with increases in any of these parameters.

Panel B of Table 59 shows the corresponding primary outcome prevalence for these permutations. Compared with the SIG per-protocol group's primary outcome allergy prevalence of 7.3%, the highest prevalence observed in Table 59 is 3.8% in the top left cell of the ≥4 foods grid representing ≥50% consumption for ≥4 weeks. This was a statistically significant reduction in food allergy prevalence, in part due to the fact that this level of consumption was achieved by the great majority of the EIG group (81%).

For higher levels of consumption, the prevalence of the primary outcome was proportionately lower and statistically significant. The exceptions being for a few permutations were the number of EIG participants achieving that level of consumption was small and hence there was insufficient power to show a statistically significant effect despite the low allergy prevalence rates.

Table 59 illustrates that there are primary outcome benefits across a wide range of adherence levels. Although this is not necessarily indicative of a dose-response relationship, it is important to note that the more foods a child ate, for the more weeks and for the greater amount, then the less the number of participants in the EIG who ended up with a food allergy.

Figure 31 is a graphical representation of the data in Panel B of Table 59 and serves as a precursor for the presentation of the same analyses and grids, but restricted to the high risk subgroup, displayed in Table 60 and Figure 32. These high risk data demonstrates the dose response relationship much more clearly. In Figure 32 it can be seen how effective an incremental rise in number of weeks or in dose of allergenic food, results in a stepwise reduction in food allergy prevalence. The general reduction in food allergy prevalence as adherence increases from ≥4 foods, to ≥5 foods and then 6 foods is obvious. Even amongst high risk infants, consumption of the six foods in 5 of the 9 permutations presented resulted in a complete absence of food allergy.

Table 59 Influence of Number of Foods Consumed, Quantity and Frequency of Consumption on Adherence and Food Allergy in the EIG

SIG primary outcome allergy prevalence: SIG Per-Protocol 7.3% (38/524) SIG Non Per-Protocol 7.5% (3/40)

A

	≥4 foods			≥5 foods			6 foods		
	≥50%	≥75%	100%	≥50%	≥75%	100%	≥50%	≥75%	100%
≥4 weeks	81% (393/483)	69% (333/480)	54% (256/474)	74% (358/484)	58% (280/481)	40% (189/475)	57% (279/488)	41% (201/485)	24% (117/479)
≥5 weeks	68% (327/483)	54% (262/484)	35% (169/483)	58% (282/485)	**43%** (208/486)	25% (120/485)	42% (208/496)	25% (123/496)	12% (60/494)
≥6 weeks	57% (277/488)	42% (207/491)	25% (123/490)	45% (222/494)	26% (131/496)	16% (77/494)	25% (126/500)	13% (67/501)	6% (32/498)

B

	≥4 foods			≥5 foods			6 foods		
	≥50%	≥75%	100%	≥50%	≥75%	100%	≥50%	≥75%	100%
≥4 weeks	3.8%* (15/393)	3.3%* (11/333)	3.1%* (8/256)	3.1%* (11/358)	2.9%* (8/280)	1.6%** (3/189)	2.5%** (7/279)	2.5%* (5/201)	0.9%** (1/117)
≥5 weeks	3.7%* (12/327)	2.7%* (7/262)	3.0% (5/169)	3.2%* (9/282)	2.4%* (5/208)	2.5% (3/120)	3.4% (7/208)	0.8%** (1/123)	0.0%* (0/60)
≥6 weeks	3.2%* (9/277)	1.9%** (4/207)	1.6%* (2/123)	2.3%** (5/222)	2.3%* (3/131)	2.6% (2/77)	0.8%** (1/126)	1.5% (1/67)	0.0% (0/32)

*p<0.05 p<0.01

Panel A of Table 59 shows the percentage, and corresponding numbers, of EIG participants achieving varying levels of study food consumption amongst those EIG participants in whom the primary outcome was determined (NB the numerators and denominators differ from the grid shown in Fig. E3 of our previous publication on the EAT study[65] because of the additional requirement in Table 59 to be primary outcome evaluable. The effect on the actual percentages in each cell is minimal). The grid varies by number of foods being consumed, the amount of food being consumed and the number of weeks this level of consumption was achieved. ≥50%, ≥75% and 100% categories represent consumption of ≥ 2 g, ≥ 3 g and 4 g of allergenic protein per week respectively. Consumption is measured over a 12 week period from enrollment to 6 months of age. The shaded blue square represents the level of consumption defined as per-protocol adherent, i.e. consumption of 5 or more study foods, at 75% or greater volume for 5 or more weeks before 6 months of age. Panel B presents the primary outcome allergy prevalence for the corresponding level of consumption in the respective cells in the grid in Table 59. The shaded blue square represents the allergy prevalence among those EIG participants complying with the study protocol, i.e. among the 43% of children in Panel A who consumed 5 or more study foods, at 75% or more of the weekly recommended dose of allergenic protein, for 5 or more weeks before 6 months of age. P values are based on Fisher's exact test (2 tailed) comparing each allergy prevalence rate in the EIG with the allergy prevalence rate in the SIG per-protocol group where 7.3% (38/524) were found to meet the primary outcome.

Table 59 (Panel B) Primary Outcome by Number of Foods Consumed, Quantity and Frequency of Consumption in the EIG

SIG primary outcome allergy prevalence: SIG Per-Protocol 7.3% (38/524) SIG Non Per-Protocol 7.5% (3/40)

B

≥4 foods

	≥50%	≥75%	100%
≥4 weeks	3.8%* (15/393)	3.3%* (11/333)	3.1%* (8/256)
≥5 weeks	3.7%* (12/327)	2.7%* (7/262)	3.0% (5/169)
≥6 weeks	3.2%* (9/277)	1.9%** (4/207)	1.6%* (2/123)

*p<0.05 p<0.01

≥5 foods

	≥50%	≥75%	100%
≥4 weeks	3.1%* (11/358)	2.9%* (8/280)	1.6%** (3/189)
≥5 weeks	3.2%* (9/282)	2.4%* (5/208)	2.5% (3/120)
≥6 weeks	2.3%** (5/222)	2.3%* (3/131)	2.6% (2/77)

6 foods

	≥50%	≥75%	100%
≥4 weeks	2.5%** (7/279)	2.5%* (5/201)	0.9%** (1/117)
≥5 weeks	3.4% (7/208)	0.8%** (1/123)	0.0%* (0/60)
≥6 weeks	0.8%** (1/126)	1.5% (1/67)	0.0% (0/32)

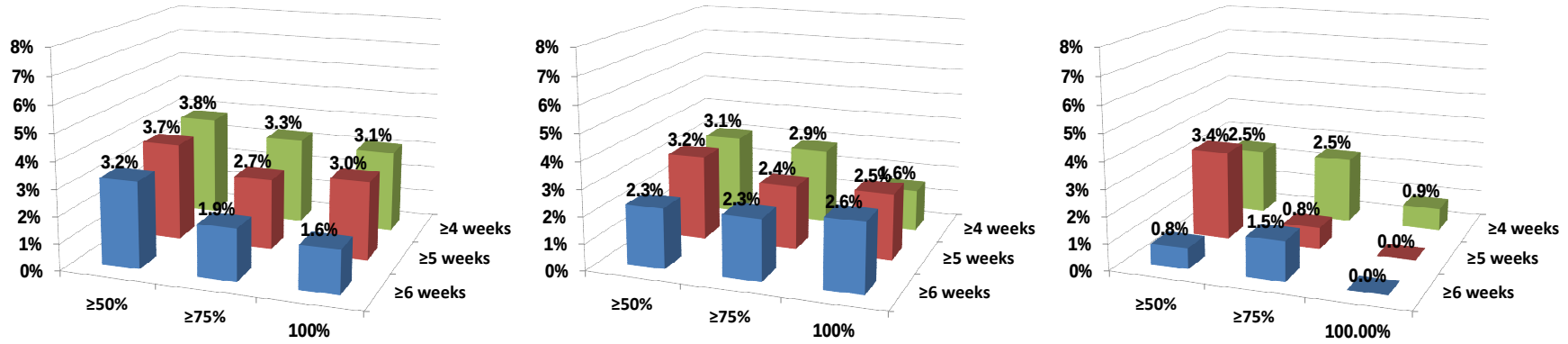


Figure 31 Graphical Representation of the Influence of Number of Foods Consumed, Quantity and Frequency of Consumption on the Primary Outcome

Figure 31 is a graphical representation of the corresponding grids shown in Panel B of Table 59. The three axes show the allergy prevalence rate in the EIG, the volume of foods being consumed and the number of weeks that consumption occurred for. The allergy prevalence rates are also indicated above each column. The results illustrate the primary outcome benefits across a wide range of compliance levels and demonstrate that the more foods a child ate, for the more weeks and for the greater amount, then the less the number of participants in the EIG who ended up with a food allergy.

Table 60 Primary Outcome by Number of Foods Consumed, Quantity and Frequency of Consumption in the EIG (Atopic Participants - Visible Eczema at Enrolment)

SIG primary outcome allergy prevalence: SIG Per-Protocol 17.5% (22/126) SIG Non Per-Protocol 30.0% (3/10)

≥4 foods

	≥50%	≥75%	100%
≥4 weeks	12.6% (11/87)	9.6% (7/73)	7.1% (4/56)
≥5 weeks	11.1% (8/72)	5.5%* (3/55)	3.2%* (1/31)
≥6 weeks	9.1% (5/55)	2.3%* (1/43)	0.0%* (0/22)

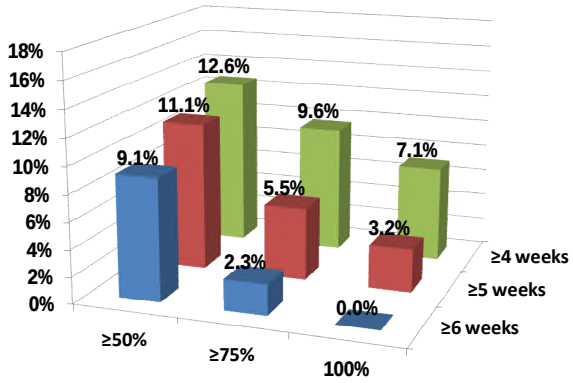
*p<0.05 p<0.01

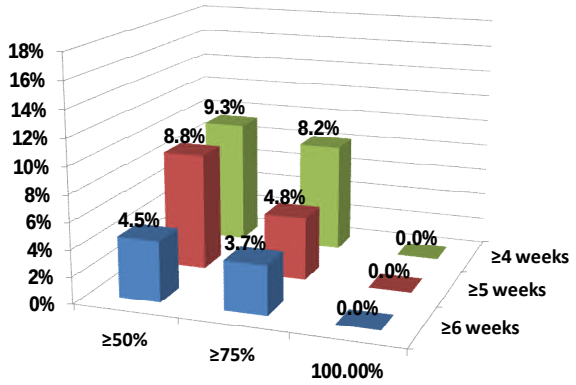
≥5 foods

	≥50%	≥75%	100%
≥4 weeks	9.3% (7/75)	8.2% (5/61)	0.0%** (0/36)
≥5 weeks	8.8% (5/57)	4.8%* (2/42)	0.0%* (0/21)
≥6 weeks	4.5%* (2/44)	3.7% (1/27)	0.0% (0/17)

6 foods

	≥50%	≥75%	100%
≥4 weeks	7.4% (4/54)	9.8% (4/41)	0.0%* (0/21)
≥5 weeks	10.0% (4/40)	0.0%* (0/26)	0.0% (0/13)
≥6 weeks	0.0%* (0/25)	0.0% (0/14)	0.0% (0/9)





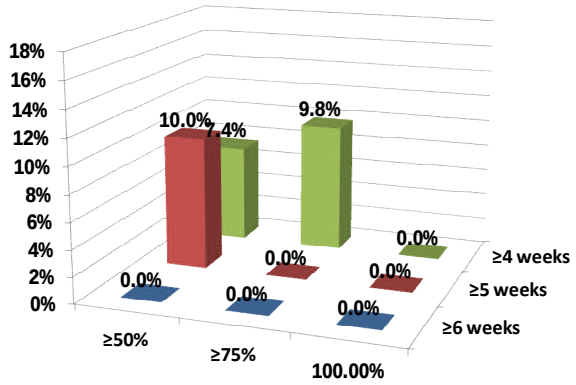


Figure 32 Graphical Representation of the Influence of Number of Foods Consumed, Quantity and Frequency of Consumption on the Primary Outcome (Atopic Participants - Visible Eczema at Enrolment)

FOOD SPECIFIC ALLERGY – DOSE AND FREQUENCY

We have presented already the consumption data for each individual allergenic food during the key period up until six months of age and shown that the ability to consume the requested amount varied by food. The following grids explore the extent to which the same dose response relationship was observed for each individual food.

MILK

Dairy was the first food introduced into the infant's diet in the EAT early introduction regimen and hence the one for which the most weeks were available for it to be consumed in from commencement of allergenic food introduction through to six months of age. Furthermore, dairy is a complementary food which mothers would naturally feel confident about offering their infant as reflected in IFS 2010 data with dairy (cheese, yoghurt or fromage frais) being the allergenic food given most frequently in 8-10 month old infants (80% at least once a day and 10% 1-6 times a week).[14] The result was that the great majority of the EIG were offering their infant at least 50% of the recommended weekly dose on at least 4 weeks (95%) (Table 61). At the top end of consumption, over two thirds of EIG infants received the full dose on six or more weeks.

Cows' milk allergy was minimal in the EAT study. 0.6% of SIG per-protocol infants had a milk allergy as compares with only 1 infant in any of the nine permutations presented (a prevalence ranging from 0.2-0.3% depending on the size of the denominator).

Milk allergy – per-protocol (adjusted for baseline challenge positive participants)

Four EIG infants were sensitised and had positive milk challenges at enrolment but only one of these was primary outcome positive for milk. The adjusted analysis is: EIG milk complied 0.2% (1/415), SIG complied (adjusted) 0.4% ((3-1)/(525-1)), risk ratio 0.63 (95% CI 0.06-6.94), p=1.00.

Table 61 Influence of milk

Milk consumption

	≥50%	≥75%	100%
≥4 weeks	95% (478/504)	91% (449/495)	86% (421/492)
≥5 weeks	90% (441/488)	85% (415/487)	77% (374/488)
≥6 weeks	87% (425/489)	78% (385/492)	70% (344/493)

Milk allergy

SIG per-protocol: 0.6% (3/525)

SIG Non per-protocol: 2.4% (1/41)

	≥50%	≥75%	100%
≥4 weeks	0.2% (1/478)	0.2% (1/449)	0.2% (1/421)
≥5 weeks	0.2% (1/441)	0.2% (1/415)	0.3% (1/374)
≥6 weeks	0.2% (1/425)	0.3% (1/385)	0.3% (1/344)

*p<0.05 **p<0.01

EIG Low/non consumer of milk allergy rate:

No milk pre 6 months: 2/6, 33.3%**

More than zero consumption but less than 4 weeks at ≥50% of recommended dose: 0/20, 0%

EGG

Egg was one of the two foods (along with sesame) that mothers appeared to have more difficulty with achieving the consumption target (Figure 11). However, 76% managed to achieve four or more week's consumption of at least 50% of the recommended dose. This contrasts with the IFS 2010 data where 12% of mothers of 8-10 month olds avoided egg completely and 73% of these infants were consuming egg less than once a week.[14]

What was noteworthy was the extent to which consumption was successful in reducing egg allergy. Every single permutation of egg consumption was associated with a statistically significant reduction in egg allergy compared with the SIG per-protocol group with the exception of the numerically smallest group of 100% consumers for six or more weeks.
At a consumption level of 2 g per week of allergenic protein for 4 or more weeks, egg was consumed by 76% (370/490) of the EIG participants in whom adherence could be determined, with a corresponding rate of egg allergy of 1.9% (Table 62).

Egg allergy – per-protocol (adjusted for baseline challenge positive participants)
Three EIG infants were sensitised and had positive egg challenges at enrolment. Two of these were subsequently proven to have a primary outcome egg allergy. The third dropped out of the study and their primary outcome egg allergy status is unknown. The adjusted analysis is: EIG egg complied 1.4% (3/215), SIG complied (adjusted) 5.2% ((29-2)/(525-2)), risk ratio 0.27 (95% CI 0.08-0.88), p=0.02.

In addition to these three children there were a further 10 EIG infants whose mothers fed them no egg at all prior to six months of age. There was also a notably larger egg allergy rate in the mothers giving more than zero egg but less than 4 weeks at 50% or more of the recommended dose: of 8.2% (9/110), but the difference was not statistically significant compared with the SIG complied group.

Table 62 Influence of egg

Egg consumption

	≥50%	≥75%	100%
≥4 weeks	75% (370/494)	59% (286/488)	43% (207/482)
≥5 weeks	62% (306/493)	43% (215/499)	28% (142/502)
≥6 weeks	49% (246/501)	33% (165/502)	21% (106/507)

Egg allergy
SIG per-protocol: 5.5% (29/525)
SIG Non per-protocol: 5.0% (2/40)

	≥50%	≥75%	100%
≥4 weeks	1.9%** (7/370)	2.1%* (6/286)	1.0%** (2/207)
≥5 weeks	2.3%* (7/306)	1.4%* (3/215)	1.4%* (2/142)
≥6 weeks	0.8%** (2/246)	1.2%* (2/165)	1.9% (2/106)

*p<0.05 **p<0.01

EIG Low/non consumer of egg allergy rate:
No egg pre 6 months: 2/13, 15.4%
More than zero consumption but less than 4 weeks at ≥50% of recommended dose: 9/110, 8.2%

PEANUT

The peanut results were the most significant in the EAT study (Table 63). For a food that only 8% of infants were consuming in the IFS 2010 by 8-10 months of age (and only 2% weekly or more), consumption rates were remarkable. 85% of EIG families were able to feed their infant at least half the recommended dose for at least four or more weeks with a corresponding rate of peanut allergy of 0.2%. Furthermore, 310 families met the peanut per-protocol compliance target (75% or more for five or more weeks). In this latter group there was not a single case of peanut allergy. For peanut every single permutation of peanut consumption was associated with a statistically significant reduction in peanut allergy.

Peanut allergy – per-protocol (adjusted for baseline challenge positive participants)
No EIG infant had a positive peanut challenge at enrolment and went on to have a primary outcome peanut allergy, hence there is no adjustment to be made to the per-protocol comparison between the groups.

The peanut allergy prevalence of 0.2% observed in the EIG infants consuming at least 50% of the recommended dose (i.e. 1g twice weekly) for at least 4 weeks are particularly interesting. This dose is almost identical to that consumed by the Israeli children whose median monthly consumption amount was 7.1g in a median frequency of consumption of 8 times a month (i.e. about 1g approximately twice weekly).[13] This level of consumption was associated with a tenfold reduction in peanut allergy from 1.85% in Jewish children in the UK to 0.17% in Israeli children. This is almost identical to our results with a tenfold reduction from 2.2% in the SIG complied group to 0.2%.

Table 63 Influence of peanut

Peanut consumption

	≥50%	≥75%	100%
≥4 weeks	85% (419/495)	74% (363/492)	63% (304/486)
≥5 weeks	72% (359/497)	62% (310/501)	50% (252/501)
≥6 weeks	64% (320/499)	53% (266/503)	39% (196/505)

Peanut allergy
SIG per-protocol: 2.5% (13/525)
SIG Non per-protocol: 2.4% (1/41)

	≥50%	≥75%	100%
≥4 weeks	0.2%** (1/419)	0.0%** (0/363)	0.0%** (0/304)
≥5 weeks	0.3%* (1/359)	0.0%** (0/310)	0.0%* (0/252)
≥6 weeks	0.3%* (1/320)	0.0%* (0/266)	0.0%* (0/196)

*p<0.05 **p<0.01

EIG Low/non consumer of peanut allergy rate:
No peanut pre 6 months: 1/14, 7.1%
More than zero consumption but less than 4 weeks at ≥50% of recommended dose: 2/62, 3.2%

SESAME

Sesame was the other food (along with egg) that families had greater difficulty achieving the consumption target (Table 64). The prevalence of sesame allergy was low in the EAT study (0.6% in the SIG per-protocol group). However any permutation of sesame consumption in the grid below results in complete avoidance of a sesame allergy developing.

Sesame allergy – per-protocol (adjusted for baseline challenge positive participants)
No EIG infant had a positive sesame challenge at enrolment and went on to have a primary outcome sesame allergy, hence there is no adjustment to be made to the per-protocol comparison between the groups.

Table 64 Influence of sesame

Sesame consumption

	≥50%	≥75%	100%
≥4 weeks	78% (385/494)	66% (323/491)	51% (248/485)
≥5 weeks	67% (334/499)	53% (266/505)	37% (188/503)
≥6 weeks	57% (290/507)	42% (213/510)	28% (145/510)

Sesame allergy
SIG per-protocol: 0.6% (3/525)
SIG Non per-protocol: 0% (0/41)

	≥50%	≥75%	100%
≥4 weeks	0.0% (0/385)	0.0% (0/323)	0.0% (0/248)
≥5 weeks	0.0% (0/334)	0.0% (0/266)	0.0% (0/188)
≥6 weeks	0.0% (0/290)	0.0% (0/213)	0.0% (0/145)

*p<0.05 **p<0.01

EIG Low/non consumer of sesame allergy rate:
No sesame pre 6 months: 0/18, 0.0%
More than zero consumption but less than 4 weeks at ≥50% of recommended dose: 3/92, 3.3%*

FISH

Fish allergy was very unusual in the EAT study with only one child positive in the SIG per-protocol group (0.2%) (Table 65). Fish consumption in the EIG group was associated either with complete protection from fish allergy (for four of the permutations) or affected a single child (prevalence ranging from 0.2-0.3% depending on the denominator).

Fish allergy – per-protocol (adjusted for baseline challenge positive participants)
No EIG infant had a positive fish challenge at enrolment and went on to have a primary outcome fish allergy, hence there is no adjustment to be made to the per-protocol comparison between the groups.

Table 65 Influence of fish

Fish consumption

	≥50%	≥75%	100%
≥4 weeks	84% (419/497)	74% (367/494)	58% (283/486)
≥5 weeks	73% (361/495)	60% (297/495)	42% (212/501)
≥6 weeks	62% (309/500)	46% (232/504)	34% (171/507)

Fish allergy
SIG per-protocol: 0.2% (1/529)
SIG Non per-protocol: 0% (0/41)

	≥50%	≥75%	100%
≥4 weeks	0.2% (1/419)	0.3% (1/367)	0.0% (0/283)
≥5 weeks	0.3% (1/361)	0.3% (1/297)	0.0% (0/212)
≥6 weeks	0.3% (1/309)	0.0% (0/232)	0.0% (0/171)

EIG Low/non consumer of fish allergy rate:
No fish pre 6 months: 0/13, 0.0%
More than zero consumption but less than 4 weeks at ≥50% of recommended dose: 0/96, 0.0%

WHEAT

Wheat allergy was the least common allergy in the EAT study (Table 66). No participant in the EIG or SIG per-protocol groups had a wheat allergy. Food specific per-protocol consumption for wheat in the EIG was less high than one might have anticipated, but this simply reflected the study protocol design with wheat being the last of the six intervention foods to be introduced into the infant's diet and hence there being less weeks available to achieve the five or more week's consumption target.
The absence of any difference in wheat allergy also overlooks the statistically significant reductions in wheat sensitisation that were observed in the EIG in the intention-to-treat analyses at both 12 and 36 months of age (Table 40).

Wheat allergy – per-protocol (adjusted for baseline challenge positive participants)
One EIG participant had a positive wheat challenge at enrolment and had a primary outcome wheat allergy subsequently confirmed (in addition to other foods – Table 13). It is not possible to subtract a child from the numerator in the SIG complied group as it is already zero (0/491). Furthermore it is not possible to undertake a statistical test comparing the two groups when the numerator is zero in both groups (EIG wheat complied 0/202 versus SIG complied 0/491).

Table 66 Influence of wheat

Wheat consumption

	≥50%	≥75%	100%
≥4 weeks	75% (371/494)	64% (314/492)	50% (244/489)
≥5 weeks	56% (278/500)	40% (202/505)	26% (132/505)
≥6 weeks	37% (186/504)	26% (131/508)	16% (80/507)

Wheat allergy
SIG per-protocol: 0% (0/525)*
SIG Non per-protocol: 0% (0/41)

	≥50%	≥75%	100%
≥4 weeks	0.0% (0/371)	0.0% (0/314)	0.0% (0/244)
≥5 weeks	0.0% (0/278)	0.0% (0/202)	0.0% (0/132)
≥6 weeks	0.0% (0/186)	0.0% (0/131)	0.0% (0/80)

* No p values calculable as prevalence 0% in both EIG & SIG

EIG Low/non consumer of wheat allergy rate:
No wheat pre 6 months: 0/16, 0.0%
More than zero consumption but less than 4 weeks at ≥50% of recommended dose: 1/92, 1.1%

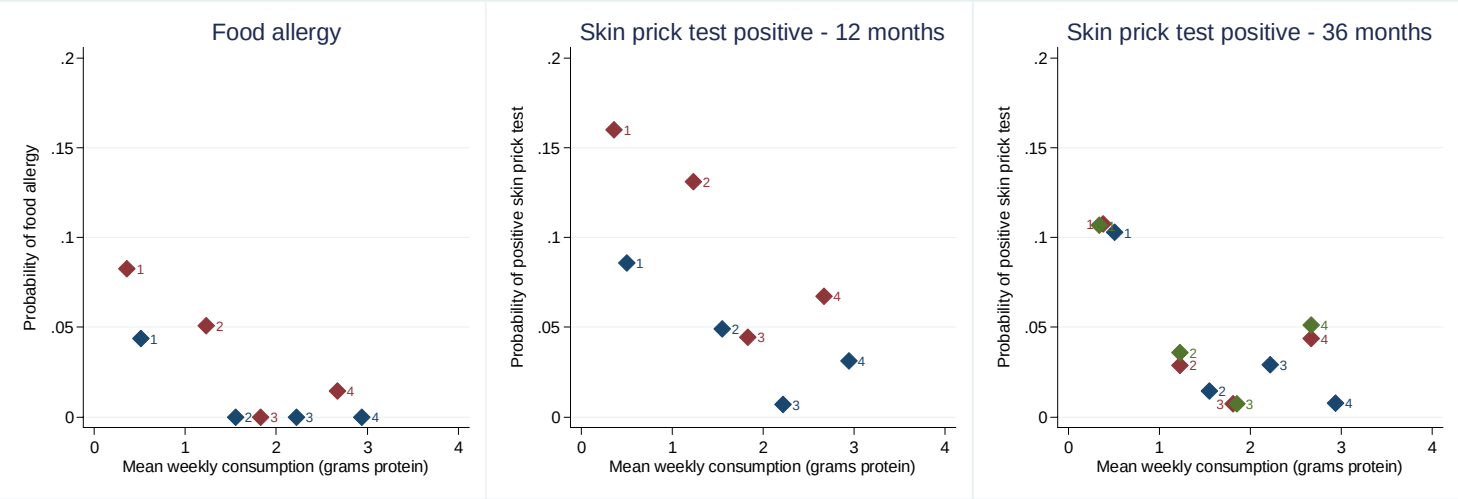
DOSE-RESPONSE ANALYSIS

Whilst the grid results give an indication of a dose-response relationship between level of consumption and protection from developing food allergy, the variation in levels of consumption allowed a more formal dose-response analysis to be undertaken. The mean weekly consumption of egg and peanut protein between enrollment and six months of age was calculated and divided into quartiles (Figure 33). In the Panel A allergy and skin-prick responses to peanut, egg and raw egg white diminished with increasing quartile levels of consumption.

In the Panel B the mean weekly consumption data were used to generate predictive probability plots based on logistic modelling showing that higher consumption was associated with a lower prevalence of allergy to that food. Mean weekly consumption of 2 g of peanut protein and 4 g of egg protein (equivalent to 2 g of egg white protein) are associated with prevention of these two food allergies respectively.

Cooked egg consumption was equally effective in inhibiting skin-prick test reactivity to raw egg white protein and egg extract at 3 years of age.

A Food allergy/skin prick test positive status: by quartiles of weekly allergen consumption



B Food allergy/skin prick test positive status: predicted probability plots by quartiles of weekly allergen consumption

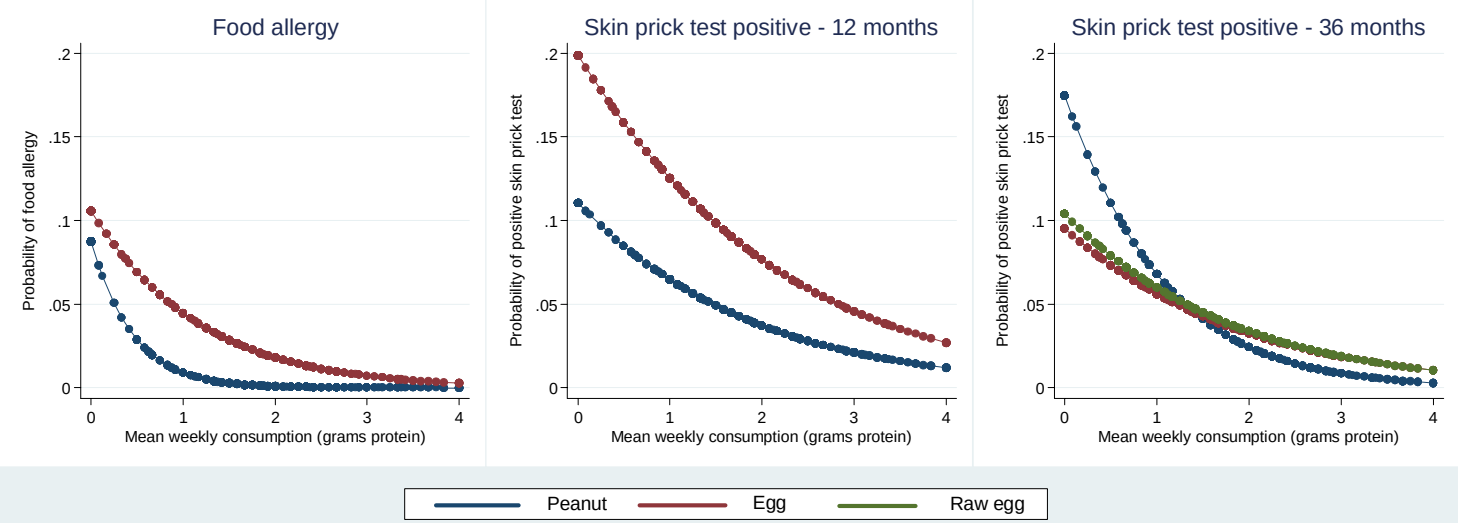


Figure 33 (overleaf) Dose-Response Analysis of the Relationship between Mean Weekly Dose of Peanut or Egg Protein Consumed and Allergy or Positive Result on Skin-Prick Testing to Peanut, Egg, and Raw Egg White.

Panel A shows the prevalence of peanut and egg allergy (left column) and skin-prick test positivity to peanut and egg at 12 months (middle column) and to peanut, egg and raw egg white at 36 months (right column) by quantity of mean weekly consumption between enrollment and six months of age of peanut and egg protein. Diamond symbols represent quartiles of mean weekly consumption of peanut protein (blue diamonds) and egg protein (red diamonds for the association with egg allergy and commercial egg extract skin-prick positivity at 12 and 36 months and green diamonds for the association with raw egg white skin-prick positivity at 36 months) and are denoted 1 to 4 for each quartile in the panel. Both food allergy and skin-prick positivity diminish with increasing levels of mean weekly consumption.

Panel B shows predictive probability plots based on logistic modelling of the same data. The outcome in the logistic models is food allergy or skin-prick test positivity to peanut (blue), egg (red) and raw egg white (green) and the independent variable is the mean weekly grams of protein consumed between enrollment and six months of age as a continuous variable.

PARENT REPORTED FOOD ALLERGY SYMPTOMS

EIG families were significantly more likely to report both IgE and non-IgE type symptoms to one of the early introduction foods between enrollment and 6 months of age (Figure 34 and Table 67).

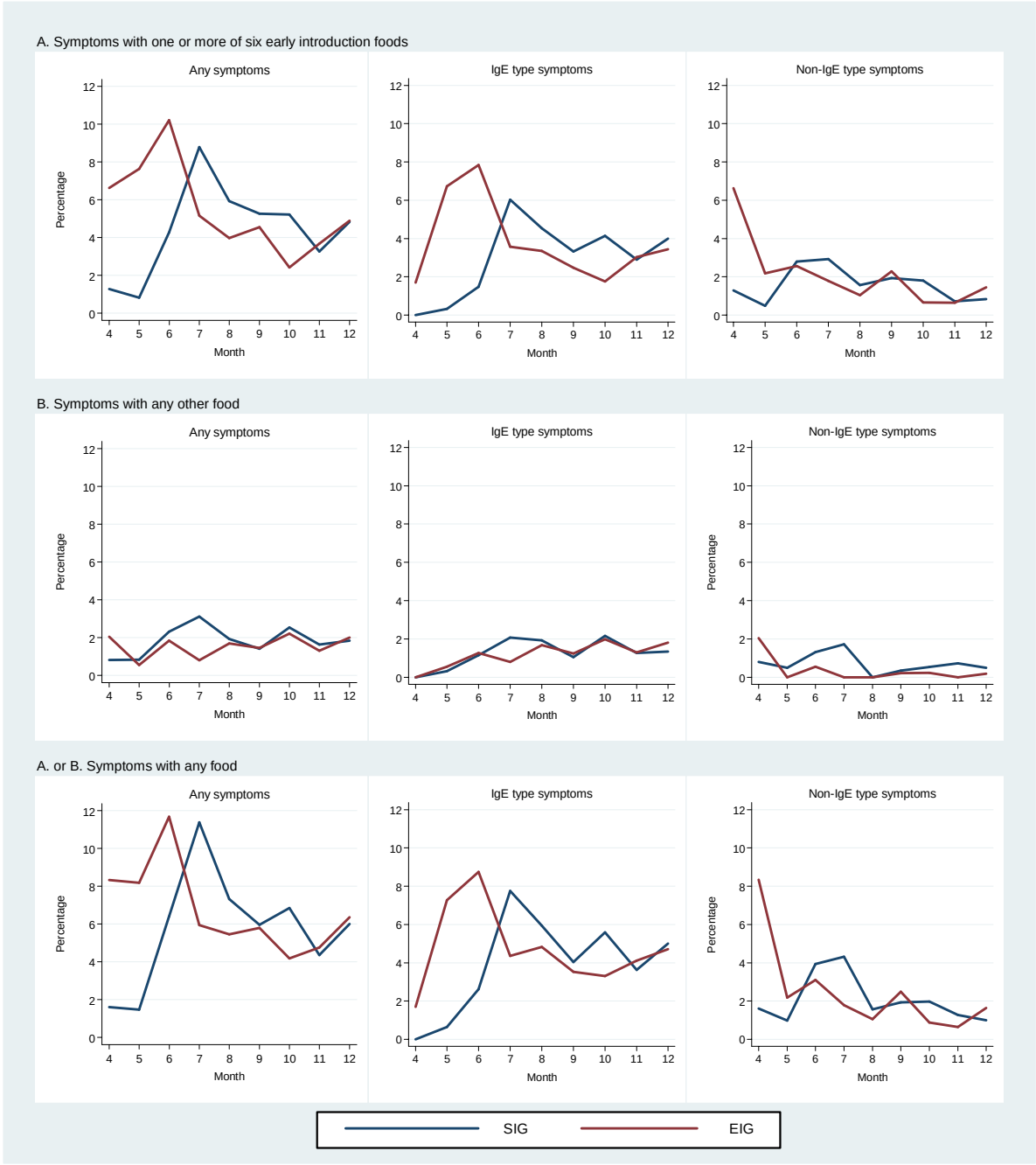


Figure 34 Parent Reporting of IgE and non-IgE Type Symptoms to Early Introduction Foods or Any Other Food by Monthly Interim Questionnaire

However the situation reversed in the subsequent time periods with significantly more reports occurring in the SIG in the interim questionnaires completed from 7 to 9 months of age and in the questionnaires completed from 10 to 12 months of age. The result was that

for the overall period between enrollment and one year of age there were no significant differences in the reporting of any food symptoms (IgE or non-IgE type) to any food (early introduction or any other food): SIG 25.7% versus EIG 26.5% (p=0.72).
This strongly suggests that the process of introducing foods leads to both IgE and non-IgE type symptoms being observed, irrespective of the age of introduction, but that this is a relationship with the process of food introduction rather than being causally linked with food allergy as the percentage reporting any food symptoms to any food (bottom right cell of Table 67) at 26% in both groups, significantly exceeds the rate of food allergy that we confirmed in the two groups.

FOOD PROTEIN INDUCED ENTEROCOLITIS SYNDROME

There were 10 participants whose families reported food protein induced enterocolitis syndrome like reactions (Table 68), seven in the EIG (six reporting egg as the trigger, one sesame) and three in the SIG (one fish and prawn, one milk and one milk, soya and rice). The difference between the two groups was not statistically significant (p=0.34). When challenges were undertaken, of the seven EIG participants, five had negative challenges, one was positive and one did not return for the challenge. Of the three SIG participants, two had positive challenges and one had a negative challenge.

PROCTOCOLITIS

There were three cases suggestive of proctocolitis, all in the SIG and all to cow's milk.

Table 67 Grouped Comparison of Parental Reporting of IgE and Non-IgE Type Symptoms

		4-6m % (n/N)	7-9m % (n/N)	8-12m % (n/N)	4-12m % (n/N)
(A) IgE type symptoms					
(1) To one or more of early introduction foods	**EIG**	11.7 (72/615)	6.7 (37/551)	5.6 (32/571)	16.0 (101/633)
	SIG	1.6 (10/638)	10.4 (64/614)	7.5 (46/616)	14.6 (94/643)
	p value	<0.001	0.03	0.20	0.51
(2) To any other food	**EIG**	1.6 (10/615)	2.9 (16/551)	4.0 (23/571)	7.0 (44/633)
	SIG	1.3 (8/638)	4.4 (27/614)	3.6 (22/616)	7.9 (51/643)
	p value	0.58	0.21	0.76	0.51
(1 or 2) To any food	**EIG**	12.9 (79/615)	8.9 (49/551)	8.4 (48/571)	19.8 (125/633)
	SIG	2.8 (18/638)	13.8 (85/614)	9.3 (57/616)	19.4 (125/643)
	p value	<0.001	0.01	0.68	0.89
(B) Non-IgE type symptoms					
(1)To one or more of early introduction foods	**EIG**	8.6 (53/615)	4.4 (24/551)	1.8 (10/571)	11.9 (75/633)
	SIG	3.8 (24/638)	5.4 (33/614)	2.8 (17/616)	9.6 (62/583)
	p value	<0.001	0.50	0.33	0.20
(2) To any other food	**EIG**	2.4 (15/615)	0.2 (1/551)	0.4 (2/571)	2.8 (18/633)
	SIG	2.2 (14/638)	1.8 (11/614)	1.3 (8/616)	4.8 (31/643)
	p value	0.77	0.007	0.11	0.07
(1 or 2) To any food	**EIG**	10.7 (66/615)	4.5 (25/551)	2.1 (12/571)	13.9 (88/633)
	SIG	5.0 (32/638)	6.4 (39/614)	3.4 (21/616)	12.3 (79/643)
	p value	<0.001	0.20	0.22	0.39
(A or B) Any food symptoms					
(1)To one or more of early introduction foods	**EIG**	16.4 (101/615)	10.2 (56/551)	7.2 (41/571)	21.8 (138/633)
	SIG	5.2 (33/638)	14.3 (88/614)	8.8 (54/616)	20.1 (129/643)
	p value	<0.001	0.03	0.34	0.45
(2) To any other food	**EIG**	3.9 (24/615)	3.1 (17/551)	4.4 (25/571)	9.3 (59/633)
	SIG	3.1 (20/638)	5.4 (33/614)	4.2 (26/616)	10.6 (68/643)
	p value	0.46	0.06	1.00	0.45
(1 or 2) To any food	**EIG**	19.4 (119/615)	12.3 (68/551)	10.3 (59/571)	26.5 (168/633)
	SIG	7.2 (46/638)	17.8 (109/614)	11.0 (68/616)	25.7 (165/643)
	p value	<0.001	0.01	0.71	0.72

Table 68 Adverse Event: Food Protein Induced Enterocolitis Syndrome

ID	Group	Parent reported symptoms	Onset of symptoms	Food	Age presented	Treatment	Challenge age	Challenge result
1	SIG	"Violent" vomiting (cod) Recurrent vomiting - (?after prawn cracker at nursery)	2 hours	Fish (cod) Seafood (prawn)	7 & 11m (cod) 31m (prawn)	Admitted to hospital for IV fluids on both occasions	3yr (cod)	Positive (vomiting x4)
2	EIG	"Violent" recurrent vomiting, diarrhoea, pale and floppy	2 hours	Egg	5m	Attended hospital, no treatment, not admitted	18m	Negative
3	EIG	Recurrent vomiting 9-10 times, floppy and listless	2 hours	Sesame	4m	Attended community clinic, given oral rehydration solution, not admitted	8m	Negative
4	EIG	Recurrent vomiting 5 times and lethargic	1 hour	Egg	4m	Attended hospital, no treatment, not admitted	21m	Negative
5	EIG	Recurrent vomiting, pale and listless	2 hours	Egg	4m	None	16m	Negative
6	EIG	"Violent" vomiting	1-2 hours	Egg	5m	None	6m & 20m	Both positive (vomiting x3 6m) (vomiting x2 20m)
7	SIG	Severe diarrhoea and blood in stools	2 hours	Milk	6m	None	19m	Negative
8	SIG	Blood in stools and diarrhoea (cow's milk & soya in maternal breastmilk) "Huge" vomits, pale, subdued (rice)	2 hours	Milk Soya Rice	3m (cow's milk) 4m (soya) 5m (rice)	None	6m (soya)	Positive (diarrhoea)
9	EIG	"Profuse" vomiting and sleepy	1 hour	Egg	5m	None	DNA	DNA
10	EIG	Diarrhoea and vomiting	2 hours	Egg	5m	None	19m	Negative

Fisher exact test: SIG 3/651 EIG 7/652, p=0.34

QUESTIONNAIRE COMPLETION AND COMPLIANCE

In addition to varying by study group (see Figure 35), the questionnaire response rate also varied with adherence with the protocol in both groups. Non per-protocol participants in both groups were less likely to be completing interim questionnaires. Questionnaire completion was lowest in the minority of participants in both groups whose per-protocol status was non-evaluable.

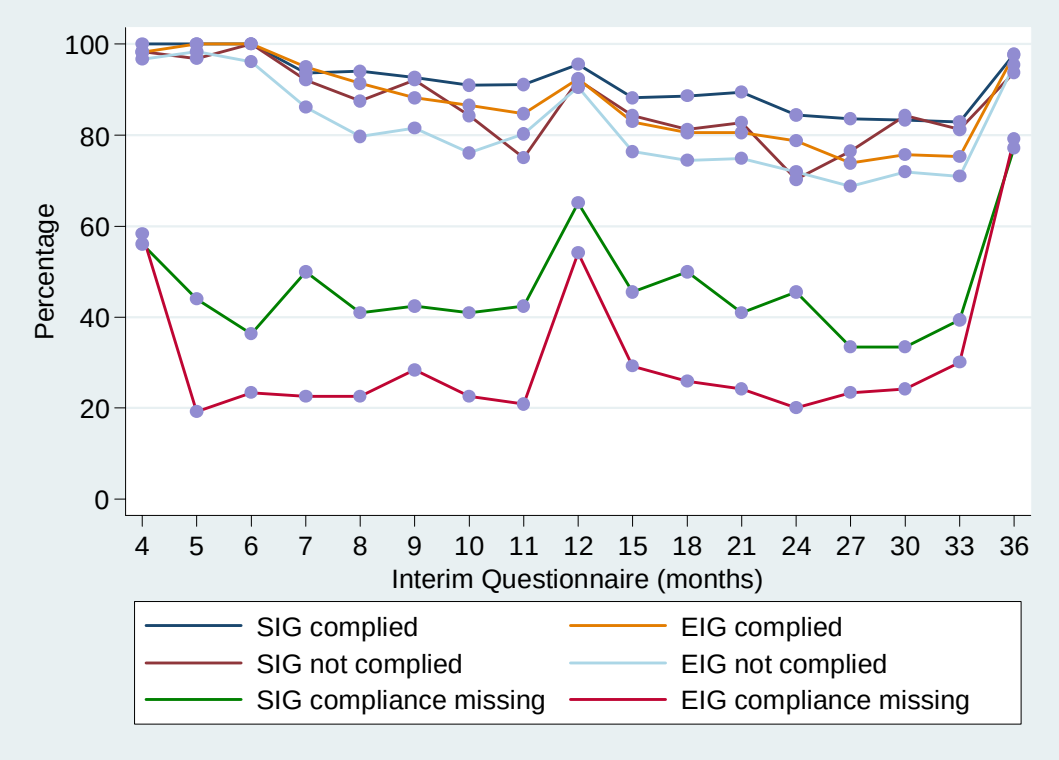


Figure 35 Questionnaire Completion Rate by Per-Protocol Status

PER-PROTOCOL ADHERENCE AND BASELINE CHARACTERISTICS

STANDARD INTRODUCTION GROUP

Ethnicity was related to SIG per-protocol status with a higher proportion of non-white participants in the non per-protocol and adherence non-evaluable groups, being statistically significant for the latter ($p<0.05$) (Table 71 overleaf). Maternal quality of life at enrolment was significantly lower in every domain for the SIG adherence non-evaluable group. As might be anticipated questionnaire completion rates were lower in the SIG non per-protocol group and considerably lower in the adherence non-evaluable group.

Logistic modelling of SIG non per-protocol status

Table 69 shows the results of logistic modelling of non-adherence to the protocol in the SIG (versus SIG per-protocol status). In the dominance analysis it was two social variables, low maternal education and maternal smoking that had the greatest contribution to the overall model fit statistic. Low maternal education was associated with being less likely to be non-adherent to the SIG protocol (but the result was not statistically significant), whilst maternal smoking increased the likelihood of being non-adherent to the SIG protocol and the association was statistically significant.

Table 69 Logistic Modelling and Dominance Analysis of Factors Influencing SIG Non-Adherence

	SIG non-adherence 7.9% (48/606)		SIG dominance analysis	
	OR (95% CI)	p value	Dominance statistic	Rank
Ethnicity (non-white)	0.99 (0.43-2.25)	0.97	6.4%	5
Visible eczema at 3m visit	1.02 (0.51-2.04)	0.97	1.6%	6
Maternal atopy	0.92 (0.50-1.70)	0.80	1.8%	4
Maternal education (≤18 years)	0.65 (0.27-1.52)	0.32	15.6%	2
Maternal smoking	4.23 (1.27-14.1)	0.02	72.3%	1
Siblings (any)	0.80 (0.44-1.45)	0.48	9.4%	3

EARLY INTRODUCTION GROUP

Ethnicity was more strongly related to EIG per-protocol status with a much higher proportion of non-white participants in the non per-protocol and adherence non-evaluable groups, both being statistically significant (Table 71 overleaf). Infants who were non per-protocol in the EIG were significantly more likely to have had visible eczema at enrolment.
Quality of life at enrolment influenced adherence, with EIG non per-protocol and adherence non-evaluable mothers having lower scores for the psychological domain (Table 71 overleaf). Similarly questionnaire completion rates were statistically significantly lower in both these groups compared with the EIG per-protocol group (Table 71 overleaf.

Logistic modelling of EIG non per-protocol status

Two factors were statistically significantly associated with EIG non-adherence (Table 70). Non-white ethnicity was associated with an over a doubling of risk of EIG non per-protocol status. Families who reported symptoms to any of the six foods during the early introduction period were more likely to be non-adherent with the EIG regimen.

Table 70 Logistic Modelling and Dominance Analysis of Factors Influencing EIG Non-Adherence

	EIG non-adherence 56.6% (286/505)		EIG dominance analysis	
	OR (95% CI)	p value	Dominance statistic	Rank
Ethnicity (non-white)	2.20 (1.17-4.13)	0.01	26.9%	1
Visible eczema at 3m visit	1.38 (0.87-2.19)	0.18	10.7%	4
New onset eczema (4-6m)	1.35 (0.76-2.42)	0.31	3.8%	6
Maternal atopy	1.23 (0.84-1.79)	0.29	5.0%	5
Maternal education (≤18 years)	1.12 (0.69-1.83)	0.65	0.5%	13
Maternal smoking	0.78 (0.27-2.27)	0.65	1.4%	11
Caesarean delivery	1.20 (0.79-1.83)	0.39	3.7%	7
Sex (female)	1.21 (0.84-1.75)	0.31	3.2%	8
Siblings (any)	1.11 (0.76-1.62)	0.60	1.7%	9
QOL psychological domain (>mean)	0.67 (0.46-0.97)	0.04	19.2%	3
Skin-prick test positive at 3m visit	1.01 (0.39-2.60)	0.98	0.6%	12
Any symptoms to EIG foods(4-6m)	1.70 (1.01-2.85)	0.04	21.7%	2
Any symptoms to other foods (4-6m)	1.34 (0.53-3.35)	0.54	1.6%	10

Table 71 Baseline Characteristics by Per-Protocol Status

	SIG			EIG		
	Per-Protocol status			Per-Protocol status		
	Per-Protocol (N=558)	Non Per-Protocol (N=48)	Adherence Non-Evaluable (N=45)	Per-Protocol (N=223)	Non Per-Protocol (N=306)	Adherence Non-Evaluable (N=123)
Primary outcome evaluable %(n)	93.9 (524)	83.3 (40)†	68.9 (31)‡	93.3 (208)	90.8 (278)	65.9 (81)‡
Demography						
Sex (male) (%)	49.5	45.8	31.1*	49.3	53.6	52.0
Siblings (any) (%)	62.0	56.3	64.4	59.6	64.1	64.0
Ethnicity (non-white) (%)	15.1	16.7	26.7*	7.2	16.3†	23.6‡
Pet ownership (any) (%)	43.4	58.3*	45.5	45.7	39.5	33.6*
Maternal education (≤18 years) (%)	19.5	14.6	29.6	16.6	17.3	22.0
Smoking						
Maternal smoking (%)	2.3	8.3	6.8	3.6	2.6	4.9
Father smoking (%)	9.5	16.7	22.7†	11.2	10.5	10.7
Birth history						
Birth weight (mean kg)	3.55	3.53	3.54	3.57	3.57	3.58
Caesarean delivery (%)	21.9	20.8	35.6*	24.7	29.1	29.3
Enrollment atopy status						
Visible eczema at 3m visit (%)	24.2	25.0	22.7	20.2	28.1*	23.6
Scorad at 3m visit (median) *(infants with eczema)*	7.4	9.4	15.7	7.4	8.6	7.1
Skin-prick positive at 3m visit (%)	-	-	-	4.0	5.2	6.5
Eczema natural history						
New onset eczema (4-6m) (%)	11.3	8.3	5.9	10.4	12.6	2.4
amily atopy status						
Maternal asthma (%)	27.1	22.9	27.3	26.5	28.1	18.9
Maternal atopy (%)	63.3	60.4	65.9	60.1	64.7	58.2
Paternal atopy (%)	57.0	50.0	45.5	51.1	51.0	48.4

Maternal factors						
Maternal QOL at 3m mean (SD)						
Physical QOL	16.4 (2.0)	16.8 (1.7)	15.6 (2.6)*	16.7 (1.9)	16.5 (1.7)	16.4 (1.9)
Psychological QOL	15.6 (1.9)	15.6 (1.7)	14.8 (2.4)*	16.0 (2.1)	15.4 (2.0)†	15.2 (2.2)†
Social QOL	15.7 (2.7)	15.6 (2.6)	14.3 (2.8)†	15.8 (2.8)	15.4 (2.8)	15.3 (2.6)
Environment QOL	16.3 (2.0)	16.6 (1.6)	15.2 (2.4)‡	16.6 (2.0)	16.3 (1.7)	16.3 (1.9)
Maternal age (mean years)	34	32	33	33	34	33
Participation measures						
Number of IQ completed median (IQR) (max 17)	17 (15-17)	16 (14-17)	6 (1-12)‡	17 (13-17)	16 (12-17)‡	4 (2-7)‡

*p<0.05 †p<0.01 ‡p<0.001

P-values comparing non per-protocol or adherence non-evaluable group with the per-protocol group for SIG or EIG as appropriate

PRIMARY OUTCOME EVALUABILITY

Of the original 1303 enrolled participants 125 were primary outcome non-evaluable. Table 73 overleaf investigates what factors were associated with being non-evaluable in both groups combined and then splitting the non0evaluable participants by group to see if there were group specific factors associated with primary outcome non-evaluable status.

Primary outcome non-evaluable - both groups

Statistically significant positive associations were seen with the following baseline characteristics: study group (primary outcome non-evaluable participants being more likely to be in the EIG), having siblings, ethnicity (non-white), lower maternal education, maternal smoking, and younger maternal age. With regards to atopy, visible eczema at enrolment had no influence on being non-evaluable, whilst maternal atopy decreased the likelihood of being non-evaluable.

In terms of subsequent participation in the study, primary outcome non-evaluable participants had a shorter duration of both any breastfeeding and were less likely to have had interim questionnaires completed and less likely to be per-protocol compliant in both the SIG and the EIG.

Logistic modelling of primary outcome non-evaluable status – both groups

In the logistic analysis (Table 72), ethnicity (non-white) remained strongly associated with being non-evaluable, as did lower maternal education, maternal atopy and having siblings. Study group was also important with EIG participants being significantly more likely to be primary outcome non-evaluable.

Table 72 Logistic Modelling of Factors Influencing Primary Outcome Evaluation Status

	Primary outcome non-evaluable 9.5% (123/1300)	
	OR (95% CI)	p-value
Ethnicity (non-white)	2.12 (1.35-3.32)	0.001
Visible eczema at 3m visit	0.93 (0.59-1.46)	0.76
Maternal atopy	0.64 (0.44-0.94)	0.02
Maternal education (≤18 years)	1.67 (1.08-2.58)	0.02
Maternal smoking	1.98 (0.87-4.53)	0.11
Caesarean delivery	0.83 (0.53-1.30)	0.41
Sex (female)	1.22 (0.83-1.79)	0.31
Siblings (any)	1.67 (1.09-2.56)	0.02
Study group (EIG vs SIG)	1.66 (1.13-2.44)	0.01

Primary outcome non-evaluable – group specific factors

The associations with social factors were stronger in the EIG primary outcome non-evaluable group with having siblings, non-white ethnicity, lower maternal education and maternal smoking all remaining statistically significant. In contrast, two of the baseline quality of life factors (social relationships and environment domains) were statistically significantly lower in the SIG primary outcome non-evaluable participants.

Table 73 Baseline Characteristics of Cohort by Primary Outcome Evaluation Status

	Primary outcome evaluable (N=1178)*	Both groups Primary outcome non-evaluable (N=125)	Primary outcome evaluable vs non-evaluable p value	SIG Primary outcome non-evaluable (N=49)	Primary outcome evaluable vs SIG non-evaluable p value	EIG Primary outcome non-evaluable (N=76)	Primary outcome evaluable vs EIG non-evaluable p value
	A	B + C	A vs (B + C)	B	A vs B	C	A vs C
Study Group (EIG)	48.9	60.8	0.01	-	-	-	-
Demography							
Sex (male) (%)	50.5	46.4	0.38	57.1	0.36	39.5	0.06
Siblings (any) (%)	61.0	73.6	0.006	71.4	0.14	75.0	0.02
Ethnicity (non-white) (%)	14.2	25.6	0.001	20.4	0.22	29.0	0.001
Pet ownership (any) (%)	43.0	39.0	0.40	43.8	0.91	36.0	0.24
Maternal education (≤18 years) (%)	17.9	28.2	0.005	25.0	0.21	30.3	0.007
Smoking							
Maternal smoking (%)	2.9	6.5	0.03	4.2	0.61	8.0	0.02
Father smoking (%)	10.6	13.0	0.42	14.6	0.38	12.0	0.71
Birth history							
Birth weight (mean kg)	3.56	3.57	0.59	3.67	0.13	3.53	0.62
Caesarean delivery (%)	25.4	23.2	0.59	20.4	0.43	25.0	0.94
Participant enrollment atopy status							
Visible eczema at 3m visit (%)	24.5	23.2	0.75	20.4	0.52	25.0	0.92
Scorad at 3m visit (median) *(infants with eczema)*	7.6	7.3	0.78	7.5	0.82	7.2	0.85
Skin-prick positive at 3m visit (%)	4.9	6.6	0.52	-	-	6.6	0.52
Participant post-enrollment atopy status							
Visible eczema at 12m visit (5)	26.3	21.6	0.45	17.4	0.34	25.0	0.88
Skin-prick positive at 12m visit (%)	15.8	25.5	0.07	30.4	0.06	21.4	0.42
Food allergy at 12m visit (%) **	4.7	0.0	0.17	0.0	0.62	0.0	0.24

	Primary outcome evaluable (N=1178)*	Both groups Primary outcome non-evaluable (N=125)	Primary outcome evaluable vs non-evaluable p value	SIG Primary outcome non-evaluable (N=49)	Primary outcome evaluable vs SIG non-evaluable p value	EIG Primary outcome non-evaluable (N=76)	Primary outcome evaluable vs EIG non-evaluable p value
	A	B + C	A vs (B + C)	B	A vs B	C	A vs C
Family atopy status							
Maternal asthma (%)	26.6	23.6	0.47	22.9	0.57	24.0	0.62
Maternal eczema (%)	35.2	27.6	0.09	31.3	0.57	25.3	0.08
Maternal atopy (%)	63.7	52.0	0.01	50.0	0.05	53.3	0.07
Paternal atopy (%)	52.6	58.5	0.20	64.6	0.10	54.7	0.72
Maternal factors							
Maternal QOL at 3m mean (SD)							
Physical	16.5 (1.9)	16.4 (2.1)	0.70	16.1 (2.2)	0.22	16.6 (2.0)	0.60
Psychological	15.6 (2.0)	15.5 (2.5)	0.63	15.5 (2.5)	0.69	15.5 (2.5)	0.75
Social	15.6 (2.7)	15.4 (2.7)	0.49	14.6 (2.7)	0.02	16.0 (2.5)	0.30
Environment	16.4 (1.9)	16.1 (2.2)	0.29	15.5 (2.3)	0.005	16.6 (2.1)	0.36
Maternal age (mean years)	34	32	0.001	31	0.002	33	0.04
Participation measures							
Number of IQ completed (median - max 17)	16 (13-17)	6	0.001	8 (3-15)	0.001	4 (1-9)	0.001
Breastfeeding data							
Duration of any breastfeeding (median weeks)	52	49	0.13	50.5	0.22	49	0.33
Per-protocol adherence							
EIG per-protocol	43.1 (212/492)	29.7 (11/37)	0.11	-	-	29.7 (11/37)	0.11
SIG per-protocol	92.6 (528/570)	83.3 (30/36)	0.05	83.3 (30/36)	0.05	-	

* 1178 participants primary outcome evaluable: SIG 595 (+7 outside visit window), EIG 567 (+9 outside visit window)
IQ Interim Questionnaires

ETHNICITY

Ethnicity played a significant role in the EAT study both in relationship to the likelihood of having food allergy but also the likelihood of complying with the EIG intervention regimen and being evaluable for the primary outcome (Table 74).

ETHNICITY AND PRIMARY OUTCOME - INTENTION-TO-TREAT

Food allergy showed a stepwise increase from white participants (5.3%), to mixed ethnicity participants (9.4%) and with the highest prevalence being observed in the Asian, black or Chinese participants (19.3%) ($p<0.0005$). The same pattern was seen both in the SIG group and the EIG group.
The intention-to-treat analysis showed a lower rate of food allergy in the EIG compared with the SIG amongst white and mixed participants but a slightly higher rate in the EIG Asian, black or Chinese participants.
The same stepwise trend was also seen for being primary outcome non-evaluable.

ETHNICITY AND PER-PROTOCOL ADHERENCE

There was no statistically significant difference in likelihood of adhering to the protocol in the SIG between the three ethnic groups, but a very strong trend in the EIG group. The highest rates of EIG adherence were in the white participants (44.3%), intermediate in the mixed participants (32.4%) and very low in the Asian, black or Chinese group (13.3%).

ETHNICITY AND PRIMARY OUTCOME - PER-PROTOCOL

Despite the low rates of per-protocol adherence in the EIG in the ethnic minority groups, there was no suggestion that the intervention was not successful in these children. In fact no per-protocol EIG child in either the mixed group or the Asian, black or Chinese group developed a food allergy (albeit with there being very small numbers of EIG per-protocol children in these groups). However, with the small numbers of ethnic minority children adhering to the study intervention it is impossible to say if there was definitely a similar reduction in food allergy prevalence with early introduction of allergenic foods as is seen in the wider cohort.
Interestingly, excluding non-white ethnic groups with their very high rates of food allergy from the per-protocol analysis led to the per-protocol analysis in the white participants no longer being statistically significant although the order of reduction was broadly similar (54% reduction in the white per-protocol EIG participants versus 66% in the per-protocol EIG participants overall).

ETHNICITY AND DEMOGRAPHY

The question arises as to the extent to which the differences in food allergy prevalence, adherence with the EIG regimen and being non-evaluable for the primary outcome could be explained by differences in other demographic variables between the three ethnic groups (Table 75).
Asian, black and Chinese participants were more likely to come from families with siblings. Smoking rates, both in mothers and fathers, were highest in the mixed ethnicity participants.

Birth weight significantly diminished across the ethnic categories, with Asian, black or Chinese participants having the lowest birth weight.

With regards to atopy there was a stepwise increase in visible eczema across ethnic groups with it being highest in the Asian, black or Chinese group. The eczema that was present was also more severe for the Asian, black or Chinese participants compared with the other two groups. The trend in visible eczema was matched by a similar increase in sensitisation rates at enrolment in the EIG with it being 3.6% in the white participants but 23.4% in the Asian, black or Chinese participants.

Conversely, the opposite trend was seen with regards to parental atopy. Maternal asthma, maternal and paternal atopy all showed a stepwise reduction from white, to mixed, to Asian, black and Chinese participants. Maternal eczema was also significantly lower in the latter group compared with the other two groups.

Maternal quality of life scores for three of the four domains (physical, social and environment) were significantly lower in the mixed group and for two domains (physical and environment) in the Asian, black or Chinese mothers, compared with white mothers.

Table 74 Influence of Ethnicity on the EAT Study Primary Outcome and Compliance with Protocol

	White (N=1104)	Mixed (N=119)	Asian/Black/Chinese (N=80)	Between race p value
Primary outcome (Intention-to-Treat)				
All participants	5.3 (53/998)	9.4 (10/106)	19.3 (11/57)	<0.0005
SIG	6.0 (30/502)	10.9 (7/64)	17.9 (5/28)	0.03
EIG	4.6 (23/496)	7.1 (3/42)	20.7 (6/29)	0.001
SIG vs EIG p value	p=0.35	p=0.51	p=0.79	
Primary outcome non-evaluable	8.4 (93/1104)	10.1 (12/119)	25.0 (20/80)	<0.0005
Per-protocol adherence				
SIG per-protocol rate	89.3 (444/497)	88.5 (54/61)	85.2(23/27)	0.79
EIG per-protocol rate	44.3 (206/465)	32.4 (12/37)	13.3 (4/30)	0.002
Primary outcome (Per-Protocol)				
SIG per-protocol	5.7 (24/419)	11.8 (6/51)	26.3 (5/19)	0.001
EIG per-protocol	2.6 (5/193)	0.0 (0/10)	0.0 (0/4)	0.83
SIG vs EIG p value	p=0.09	p=0.25	p=0.25	

Table 75 Association of Ethnicity with Demographic Variables in the EAT Study

	White (N=1104)	Mixed (N=119)	Asian/Black/Chinese (N=80)	Between race p value
Demographic				
Sex (male) (%)	50.5	47.9	48.8	0.84
Siblings (any) (%)	61.7	58.8	75.0	0.04
Maternal education (≤18 years) (%)	19.3	17.7	15.0	0.60
Smoking				
Maternal smoking (%)	3.2	5.9	0.0	0.07
Father smoking (%)	10.2	17.7	8.9	0.04
Birth history				
Birth weight (mean kg)	3.58	3.43	3.33	
p value vs white		0.005	<0.0005	
Caesarean delivery (%)	24.3	30.3	30.0	0.21
Participant enrolment atopy status				
Visible eczema at 3m visit (%)	22.6	30.3	39.2	0.001
Scorad at 3m visit (median)*	7.25	7.35	15.2	
p value vs white		0.40	<0.0005	
Any sensitisation at 3m visit (%)	3.6	4.2	23.4	<0.0005
Family atopy status				
Maternal asthma (%)	27.3	26.1	12.7	0.02
Maternal eczema (%)	34.9	38.7	22.8	0.06
Maternal atopy (%)	63.6	62.2	49.4	0.04
Paternal atopy (%)	54.3	51.3	39.2	0.03

	White (N=1104)	Mixed (N=119)	Asian/Black/Chinese (N=80)
Maternal factors			
Maternal QOL at 3m mean (SD)			
Physical	16.6 (1.9)	16.1 (1.9)	15.4 (2.4)
p value vs white		0.004	<0.0005
Psychological	15.6 (2.0)	15.4 (1.7)	15.5 (2.5)
p value vs white		0.22	0.58
Social	15.7 (2.7)	15.0 (3.0)	15.0 (3.0)
p value vs white		0.01	0.06
Environment	16.5 (1.9)	15.7 (1.9)	15.3 (2.1)
p value vs white		0.0001	<0.0005
Maternal age (mean years)	33	34	33
		0.12	0.14
Participation measures			
Number of IQ completed (median - max 17)	16	16	11.5
p value vs white		<0.0005	<0.0005
Breastfeeding data			
Duration of any breastfeeding (mean weeks)	50	52	52
		0.13	0.85
Duration of exclusive breastfeeding (mean weeks)	18	21	18
p value vs white		0.009	0.81

CHAPTER 4 – DISCUSSION AND IMPLICATIONS

EARLY ALLERGENIC FOOD CONSUMPTION

The infant diet in developed countries such as the UK is one where consumption of many of the principal allergenic foods is minimal or absent during the first 6 months of life. Amongst 8-10 month infants in the IFS2010, egg and fish were being consumed less than once a week or never in 73% and 44% of infants respectively.[14] Remarkably, 45% of all mothers in the IFS2010 actively avoided giving at least one particular ingredient, the most common allergenic food avoided being: nuts (peanuts and tree nuts) (41% of all mothers), eggs 12%, dairy 11%, fish/seafood 8% and gluten/wheat 3%. Concern about allergies (36%) was the most common reason for avoidance overall, but this varied by food: egg 40%, dairy 47% and nuts 63%. Concern about their infant being too young for the food and the presence of eczema were also common reasons for avoidance.

There are however countries where the early allergenic food exposure is different. Observational evidence has emerged from both developed countries, e.g. Israel,[18] and developing countries, e.g. Ghana,[66] where high amounts of peanut are consumed in a variety of forms during infancy, yet peanut allergy rates remain very low, suggesting a possible route of tolerance induction. Amongst Jewish children genetic influences are not responsible as the prevalence of peanut allergy in Jewish children in the UK at 1.85% was significantly higher than the Israel prevalence of 0.17%.[67] It is interesting to note that the incidence of food allergy is believed to be now increasing in Africa,[68] and a delay in introduction and reduced quantity of consumption of peanut has been postulated as a possible cause.[69,70]

Despite the fear of allergy expressed in the IFS2010 survey, particularly with regards to peanut, the EAT study has demonstrated that parents were prepared to introduce peanuts and other allergenic foods into their infant's diet under six months of age.

EAT PRIMARY RESULTS

The EAT study did not show efficacy in an intention-to-treat analysis with a non-significant 20% relative reduction in food allergy prevalence in the EIG. In the per-protocol analysis there was a significant 67% relative reduction in overall food allergy.

Unexpectedly, statistically significant reductions to peanut (p=0.003) and egg (p=0.009) allergy were observed in the per-protocol EIG. We anticipated seeing our principal effect for the primary outcome which we estimated would have a prevalence of 8% in the SIG, whereas individual food allergy prevalence rates are much lower. Therefore we expected to see significance for overall food allergy rather than for individual food allergy. That this was not the case, is due to the fact that the proportion of the EIG that were known to have adhered to the protocol (34%) was much lower than anticipated whereas food specific per-protocol adherence was significantly higher for several foods and particularly peanut. The trade-off between a high numerator for food allergy rate versus a high denominator for per-protocol sample size favoured our ability to detect significant differences for individual food allergies and particularly peanut.

The rates of other food allergies were too low to discern any effects. Milk allergy, was very low in both groups. One potential explanation for the low rate of milk allergy in both groups is the possibility that both groups were consuming significant quantities of dairy. For pragmatic reasons we allowed SIG participants to remain in the per-protocol analysis if they had consumed up to 300mls of cow's milk formula per day at any point between 3 and 6 months of age. We were concerned that families would not enrol onto the study if they were told that all formula milk consumption was precluded after three months of age. Formula consumption in the SIG before six months of age, however, proved to be minimal and thus could not have accounted for the low rate of cow's milk allergy in this group.

At 36 months of age, for the six individual foods the average relative reduction in skin-prick test positivity was 79% and statistically significant for peanut (p=0.007), milk (0.02) and sesame (0.04). Efficacy of the intervention was related to duration of specific food consumption and quantity of food consumed between three and six months of age.

BREASTFEEDING IN THE EAT STUDY

Whilst overall compliance with the UK breastfeeding recommendations remains poor, the IFS2010 showed a continued increase in exclusive breastfeeding in the UK, with 69% of mothers exclusively breastfeeding at birth, up from 65% in 2005.[71] Exclusive breastfeeding until 6 months remains rare with only 1% achieving this but rates of non-exclusive breastfeeding have increased from 25% at 6 months in 2005 to 34% in 2010. Within this context, breastfeeding rates at the completion of the key early introduction period at 6 months of age remained extremely high, significantly exceeding equivalent IFS2010 data, with no difference between the two groups. This is particularly important because murine research has suggested that breastfeeding may be a vital component in the mechanism to induce tolerance in allergic disease[72] and hence the fact that 97% of EIG mothers continued to breastfeed while introducing allergenic foods may be a key part of our study findings.

SAFETY

We did find that early introduction of allergenic foods was safe with no cases of anaphylaxis during the initial introduction regimen. All positive food challenges at baseline (mainly egg challenges) resulted in mild allergic reactions but the role of supervised food challenges to guide early introduction of allergenic foods in such infants sensitised by SPT requires further research and debate.

There were no differences between the two groups in any of the anthropometric parameters studied.[65] Importantly, introduction of such foods did not result in obesity. Partial adherence among EIG participants was not associated with any increase in allergy prevalence. Seven EIG participants had baseline positive food challenges and hence complete adherence to the EAT early introduction protocol would not have prevented all food allergy from occurring.

While we do not know whether consumption in the EIG of cooked egg caused a reduction in allergy to raw egg white (food challenges were not undertaken to raw egg white), this is likely to be the case since per-protocol consumption of cooked egg resulted in a comparable level of reduction in skin-prick test reactivity to both raw egg white (49%) and to commercial egg extract (48%) at 3 years of age. This suggests that the possible protective effect is not

confined to the form in which the individual food is consumed. The Hen's Egg Allergy Prevention (HEAP) study, which enrolled patients from the general population[36] and the Solids Timing for Allergy Research (STAR) study, which enrolled high risk patients[15] introduced raw egg powder but experienced significant side-effects. The likely explanation for the difference in reaction severity is the form of egg chosen for introduction. EAT infants were introduced to well-cooked boiled egg. Raw egg and pasteurized egg white powder or whole egg powder are more allergenic forms of egg than cooked egg. In our study in the per-protocol EIG there was a great than 75% reduction in the prevalence of egg allergy by age 3

ETHNICITY

Consistent with the literature, food allergy rates were higher in non-white participants and those with eczema at enrollment whereas study adherence in the early-introduction participants was much lower in these groups.[42,73,74] Adherence was also reduced where parents perceived symptoms with the early introduction of the foods and where mothers had a lower psychological quality of life at enrollment. These results raise the question whether targeted clinical and dietetic support to these families at the earliest stages of food introduction could possibly augment adherence and this requires further consideration were early introduction to be considered as a policy to reduce food allergies.

The strengths of our findings are as follows; a high retention rate; nearly all allergy was double-blind, placebo-controlled challenge confirmed; an unselected population of exclusively breastfed infants was enrolled; and all children with a positive skin-prick test were challenged. The main weakness of the study was the low per-protocol adherence in the EIG.

LOW EIG PER-PROTOCOL ADHERENCE

Consumption data from the early interim questionnaires that were completed in the EIG demonstrates that their consumption pattern was similar to the non-compliant EIG participants and hence the true overall per-protocol compliance target in the EIG group was likely to have been closer to 34% than 42% (Figure 29).

This difficulty in achieving the overall per-protocol target of five or more foods at 3 grams of allergenic protein or more per week for five or more weeks was not a clear dichotomy of no consumption versus per-protocol target consumption as we have demonstrated that amongst EIG families completing the six month questionnaire the percentage who had never tried each of the allergenic foods was minimal. However clearly for at least 58% of EIG participants the amount consumed during this early period was less than the overall per-protocol target that we had set. For four foods at 5 months of age and 2 foods at six months of age 25% of EIG participants were not consuming the foods twice weekly as requested making it significantly harder to achieve the per-protocol target in only one meal per week (Figure 12). However the proportion of EIG participants not reaching the 3 gram per week per-protocol target by six months was greater than 25% for egg and sesame, suggesting that whilst once weekly consumption might partly explain why 58% did not meet the target, for other EIG participants, the amount being consumed at their two (or more) weekly meals clearly was not sufficient to meet the 3 gram per-protocol target when the consumption for that week was combined.

Despite the low figure for overall EIG per-protocol compliance, at an individual food level, for evaluable EIG participants, compliance with our per-protocol target varied from 42% for

egg to 84% for milk. Wheat compliance was lower than egg but was distorted by the introduction regimen which did not allow wheat introduction before four months, hence leaving less weeks available to achieve the target level of consumption by six months of age.
We deliberately set the bar for overall per-protocol compliance in the EIG high as the amount of allergen protein needed to potentially induce oral tolerance is unknown. We wanted to ensure that the majority of those not meeting the 3 gram per-protocol weekly target were still consuming allergenic food protein in a quantity that may induce tolerance (1g of peanut protein twice weekly in our previous research).[67] Our weekly per-protocol target had to balance the need to be recommending portion sizes appropriate for young infants with a frequency of consumption that was manageable for families given six foods were being introduced. Eighty one percent of compliance evaluable EIG children were consuming at least 2g of protein a week (1g of protein twice weekly) from at least four allergenic foods for at least four weeks between four and six months of age (Table 59).

INTENTION-TO-TREAT VERSUS PER-PROTOCOL FINDINGS IN THE EAT STUDY

There are a number of explanations for there being efficacy at the per-protocol level as opposed to the intention-to-treat level:

1. THE EIG INTERVENTION WAS EFFECTIVE

The first explanation is that the early introduction of allergenic foods prevented food allergy developing. This has some plausibility given the food specific findings and an apparent dose-response relationship for protection against peanut and egg allergy.

2. REVERSE CAUSALITY

In the EAT study it is possible that the individuals in the EIG who did not follow the protocol did so because of low level symptoms and therefore more food allergy was concealed in this group. Indeed food aversion is a common early manifestation of food allergy in young infants even in the absence of overt clinical symptoms. This would produce an artefactual decrease in the EIG per-protocol food allergy rate by shifting food allergic patients early on towards non per-protocol adherence.
In order to address this issue we compare the rates of overall food allergy and individual food allergies in the non per-protocol EIG to the standard introduction per-protocol group to ensure that the former is not concealing a higher rate of food allergy. This is the appropriate comparison to make since the per-protocol SIG, which constitutes 93% of the evaluable SIG participants, represents the spontaneous rate of food allergy in the normal exclusively breastfed population.
For the primary outcome, allergy to one or more foods, the comparison is 7.6% in the early-introduction non per-protocol group and 7.3% in the standard-introduction per-protocol group (p=0.89) (Table 54).
For four of the individual foods the rate is higher in the early-introduction non per-protocol group (for egg, milk, sesame and wheat) and lower for two (peanut and fish). None of the differences are statistically significant (Table 56).
The same arguments are applicable to the early-introduction adherence non-evaluable group who had very similar rates of overall food allergy to the standard-introduction per-protocol group (Table 54). At an individual food allergy level, there were insufficient EIG adherence non-evaluable participants to accurately determine individual food allergy rates

but none of the comparisons with the per-protocol SIG were statistically significant (Table 56).

These findings are reassuring because one would have expected, as a result of the study design, that an increased prevalence of food allergy would have been observed in the non per-protocol EIG participants. This is because only the EIG participants were likely to manifest and have their food allergy diagnosed between three and six months of age. Such participants with a confirmed food allergy during this period were told to cease consumption of the food. This therefore rendered them more likely to be in the non per-protocol group. We would therefore have expected an ascertainment bias towards more food allergy in the non per-protocol EIG compared with the per-protocol EIG. Despite this potential bias, Tables 52 and 55 indicate a bias towards increased food allergy in the early introduction non per-protocol group did not exist.

That EIG participants who were non per-protocol were not concealing raised levels of food allergy is further illustrated by the adherence grids in Tables 61 to 66. Whilst the food specific per-protocol adherence rate for egg was 43.1% (215/499) and for peanut 61.9% (310/501) (blue highlighted cells in Tables 62 and 63 respectively), at a lower adherence threshold of having consuming at least 2 g of allergenic food protein per week for at least 4 weeks, adherence increased to 75% for egg (370/494) and 85% for peanut (419/495). These increased levels of adherence were still associated with statistically significant reductions in both allergies (1.9% for egg and 0.2% for peanut).

Another argument against reverse causation is that the children who were skin-prick test positive at 3 months in the EIG who were therefore at highest risk for developing food allergies and reacting to the consumption of allergenic foods, had surprisingly low rates of food allergy. If indeed early consumption of foods would have resulted in mild symptoms of food allergy and prevented per-protocol adherence, one would have expected to find the highest rate of food allergy and lowest per-protocol adherence in this group. This was not the case. Consumption of the allergenic food to which the participant had a negative challenge by six months of age was good (Table 14) as was overall per-protocol adherence. Of the 22 baseline sensitised and challenge negative EIG participants, their per-protocol status was determinable in 19 of who 9 were adherent (47%) as compared with 42% in the EIG adherence evaluable participants overall.

The same argument is true for the LEAP findings, which showed that per-protocol adherence in the children who were skin test positive to peanut at baseline (or skin prick negative to peanut at baseline but with specific IgE to peanut already present) had excellent adherence in the consumption group and a significantly reduced rate of peanut allergy.[35]

3. BIAS

A third potential explanation is that of bias leading to increased atopy and food allergy in children outside the per-protocol analysis. This is an important consideration given that only 34.2% (223/652) of all the enrolled EIG participants were per-protocol-evaluable versus 85.7% (558/651) in the SIG.

There are three levels at which attrition of the enrolled population occurred:

A. **Participants non-evaluable for the primary outcome (EIG: 85, SIG 56)**
B. **Participants whose per-protocol status was non-evaluable (EIG 81, SIG 31)**
C. **Participants who were non per-protocol (EIG 278, SIG 40)**

The differential attrition at all three categories was higher in the EIG than the SIG all potentially contributing towards a bias between the two groups.

A. Participants non-evaluable for the primary outcome (EIG: 85, SIG 56)

By definition we do not know the prevalence of the primary outcome and individual food allergies in this group of participants. We can, however, compare their baseline demographics to see whether primary outcome non-evaluable EIG participants were more atopic at baseline. This is important because atopic infants, especially those with eczema, have a higher rate of food allergy and if such a differential drop out did occur this could have accounted for a lower rate of food allergy in the remaining EIG participants.

Table 73 shows that primary outcome non-evaluable participants had equivalent levels of atopy compared to evaluable participants in both groups combined. Maternal atopy was lower in the non-evaluable participants in both groups and therefore provides no evidence of a bias that would explain our findings.

Moreover, although we do not have primary outcome data on this category of participants we do nevertheless have data from those who remained in the study to at least the one year assessment. Table 73 shows that there was no food allergy as determined by challenge in any of the non-evaluable participants in both groups at 12 months of age, by which point we would have expected most cases of food allergy, particularly in the EIG participants, to be apparent.

B. Participants whose per-protocol status was non-evaluable (EIG 81, SIG 31)

C. Participants who were non per-protocol (EIG 278, SIG 40)

We can also compare the baseline characteristic of the EIG and SIG participants by per-protocol adherence status (Category B - adherence non-evaluable and Category C - per-protocol and non per-protocol) and this data is presented in Table 71. This indicates that non per-protocol and adherence non-evaluable EIG participants were statistically significantly more likely to be non-white. Non per-protocol EIG participants were also statistically significantly more likely to have visible eczema at enrollment. Non-white ethnicity and visible eczema at enrollment were both associated in the EAT study with being likely to have food allergy (Table 36). However, there was no significantly increased rate of food allergy in both the non per-protocol and adherence non-evaluable participants in the EIG (Tables 52 and 54). Thus the differential atopic status did not lead to a bias in the primary outcome.

4. ARTEFACT OF STUDY DESIGN

Finally, we eliminated the possibility of our results occurring consequent to an artefact of study design - the selective removal of baseline food allergic participants exclusively from the EIG. At three months of age we only evaluated food allergy in the EIG. Those participants with confirmed food allergy at this point were unable to be per-protocol adherent, thus artificially reducing the rate of food allergy in this group. We therefore undertook an adjusted per-protocol analysis where we subtracted the same number of food allergic individuals from the SIG. This did not alter the significance of our results (Figure 24). Nevertheless we cannot be certain that unmeasured sources of bias may still exist.

DOSE-RESPONSE RELATIONSHIP

Modelling determined that 2 g or more of peanut or egg white protein per week may prevent these allergies respectively. In Israeli infants this level of consumption was associated with a tenfold reduction in peanut allergy: 0.17% in Israel compared with 1.85% in Jewish children in the United Kingdom.[67] In the EAT study, this level of peanut consumption for at least 4 weeks also reduced peanut allergy tenfold, from 2.2% to 0.2%, mirroring the du Toit *et al.* findings. Furthermore, this level of consumption is one-third of

the weekly dose that participants consumed in the LEAP study with the implicit suggestion that this lower dose might have been effective in that study as well.

INDIVIDUAL FOOD ADHERENCE

Some foods were introduced with greater ease than others. Individual food per-protocol adherence in the EIG varied from 43.1% for egg to 85.2% for milk (yogurt). It is possible that this discrepancy may be related to oral motor development, with the most easily consumed food, milk, being given as yogurt. Egg, a more textured food, had the lowest adherence. Strong taste might also have been a factor with a number of mothers reporting that their infant seemed to dislike the taste of the tahini.

The number of foods given may also have played an important role with regards to adherence. Given that the majority of the food allergic burden in the SIG comprised the three foods, peanut, egg and milk, focussing an intervention directly on these three foods might have achieved greater adherence. Three foods would involve less parental effort as well as the foods being able to be introduced more rapidly into the infants' diet at an earlier time point. Future strategies might therefore incorporate giving fewer foods, in liquid form.

ISSUES SURROUNDING ADJUSTMENT FOR MULTIPLE OUTCOMES

The study design as shown in the protocol and statistical analysis plan has a single primary outcome, the period prevalence of IgE mediated food allergy to the six intervention foods between one and three years. In the intention-to-treat analysis this outcome was not statistically significant.

This primary outcome is a composite of six separate outcomes, made up of allergy to the six foods such that if a participant was allergic to any food, then the overall composite outcome was positive. The separate food analyses are regarded as secondary outcomes, and interpreted as such. The components of the composite are not usually corrected for multiple testing.[75]

Another reason for not adjusting for multiple endpoints is that the overall primary outcome and the individual secondary food outcomes are looking at different biological hypotheses. The former is the hypothesis the early introduction of multiple allergenic foods induces overall tolerance to a wide range of foods extending beyond those that have been specifically consumed. The second hypothesis is that oral tolerance induction to a specific food is antigen specific to consumption of that specific food.

In this study we have reported the primary outcome to be not statistically significant in the intention-to-treat analysis. We also tested and reported the individual foods which were not statistically significant.

A potential issue surrounding adjustment for multiple outcomes arises from the interpretation of the same composite primary outcome in the per-protocol population. This showed that the primary outcome, i.e. any allergy, was statistically significant (p=0.01) and two of the six foods were also significant (peanut: p=0.003, egg: p=0.009). If these six component food tests were adjusted for multiple testing using Bonferroni, known to be conservative, the critical value for statistical significance would be 0.0085 which is 0.009 to 3 decimal places, ($1-0.95^{1/6}$) and so peanut remains statistically significant whilst egg remains borderline significant.

WINDOW OF OPPORTUNITY FOR ORAL TOLERANCE INDUCTION

The window of opportunity to induce tolerance to peanut may be narrow. In the LEAP screening study a significant number of infants with severe eczema and/or egg allergy could not enter the study or adhere to the study protocol because of potential or proven pre-existing peanut allergy (skin prick test greater than 4mm and those infants who reacted at baseline.)[42] The possibility of earlier introduction of peanut (as early as 3 months of age) could potentially enhance prevention of peanut allergy in the general population by inducing tolerance in those children who would otherwise develop peanut allergy early in the first year of life. It remains unknown whether the window of opportunity to induce tolerance varies by food.. Observational studies have suggested a protective effect of introducing egg between four to six months of age[3] and for introducing cow's milk protein based formula milk before 14 days of age.[12] Amongst the randomised controlled trials published so far, the STAR study introduced egg to four month old infants with a non-significant reduction in egg allergy incidence,[15] and the LEAP study achieved peanut tolerance with introduction between 4 and 10 months of age.[35]

EAT STUDY IS COMPLEMENTARY TO THE LEAP STUDY

The results of EAT are complementary to LEAP. Only 9 out of the 1303 participants in EAT would have been considered sufficiently high risk to enrol in LEAP. Notably, 76% of the SIG did not have eczema at 3 months of age and yet they accounted for 38% of the overall burden of food allergy (Table 76).

Both the SPT negative and SPT positive groups in the LEAP study were considerably more atopic than in the EAT cohort with higher levels of total peanut specific IgE and baseline food allergies, as well as the majority having had a history of severe eczema. The LEAP study showed that high adherence was achievable in these participants and this is most likely a consequence of the intense dietary follow up and interaction between patients, dietitians, and nurses with weekly phone calls occurring during the infant's first year of life between the study team and the families. This would suggest from a public health perspective that implementation of the EAT findings will need early support from midwives, health visitors and General Practitioners as well as more targeted advice to children at high risk for allergies and reduced compliance.

CONCLUSION

The EAT study failed to show efficacy in an intention-to-treat analysis. Further analysis suggests that the possibility of food allergy prevention through the early introduction of multiple allergenic foods in normal breastfed infants may depend on adherence and dosage.

Table 76. Distribution of Cases of Food Allergy in the SIG by Eczema Status and Severity at Enrollment

Standard Introduction Group	Cases	No eczema at enrollment 76% of SIG (451/594)	New onset eczema from 4-6 months 11% of SIG (66/587)	No eczema by 6 months 78% of SIG (355/458)	No visible eczema at enrollment or 12 months 66% of SIG (352/532)	Any visible eczema at enrollment 24% of SIG (143/594)	SCORAD 1-14 18% of SIG (110/143)	SCORAD 15-40 5% of SIG (30/143)	SCORAD >40 1% of SIG (3/143)
		A	A1	A0	A00	B	B1	B2	B3
		Cases (% of total cases)							
One or more foods	42	16 (38.1%)	6 (14.3%)	8 (19.0)	11 (26.2)	26 (61.9%)	11 (26.2%)	14 (33.3%)	1 (2.4%)
Peanut	15	5 (33.3%)	2 (13.3%)	3 (20.0)	3 (20.0)	10 (66.7%)	5 (33.3%)	4 (26.7%)	1 (6.7%)
Egg	32	11 (37.5%)	5 (15.6%)	5 (15.6)	7 (21.9)	21 (65.6%)	7 (21.9%)	13 (40.6%)	1 (3.1%)
Milk	4	1 (25.0%)	0 (0%)	0 (0%)	1 (25.0)	3 (75.0%)	1 (25.0%)	2 (50.0%)	0 (0%)
Sesame	3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (100.0%)	2 (66.6%)	1 (33.3%)	0 (0%)
Fish	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	1 (100%)	0 (0%)
Wheat	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

This table allows one to determine where the cases of food allergy developed, depending on eczema status, in the SIG participants. Each column represents a different category of eczema status described in detail below. Within the column the number of cases of the respective allergy that occurred in the SIG is given. The percentage of the total number of cases for that allergy is also given. Hence it can be seen in the first column, top cell that 38% of all the cases of food allergy to one or more foods occurred in those SIG participants who had no eczema, who constitute 76% of the whole SIG.

A and **B** are the SIG participants whose visible eczema status was assessed at enrollment and whose primary outcome status could be determined
A is those with no eczema at enrollment who constitute 76% of the SIG, **B** is those with visible eczema at enrollment, constituting 24% of the SIG
A1 is a subgroup of **A**, and represents SIG participants without eczema at enrollment (**A**), but whose parents then reported in the interim questionnaires that they had developed new onset eczema by six months of age. This group constitutes 11% of the SIG.
A0 is a subgroup of **A,** and represents SIG participants who had no visible eczema at enrollment and whose parents did not report new onset eczema in any of the 4, 5 or 6 month interim questionnaires. To be evaluable for this category, families needed to have completed all three of these questionnaires, hence the denominator dropping to 458. 78% of SIG participants who could be evaluated for this category had no eczema by six months. The lower denominator explains why the percentage with no eczema reported by six months can be greater than the percentage reported with no visible eczema at enrollment in category **A**
A00 is a subgroup of **A**, and includes participants who had no visible eczema at either the enrollment or the 12 month assessment constituting 66% of SIG.
B1/B2/B3 are subgroups of **B** and represent all the participants in **B** divided by categories of SCORAD ranging from **B1** mild, **B2** moderate and **B3** severe. Respectively these constitute 18%, 5% and 1% of the SIG participants.

CHAPTER 5 – KEY FINDINGS

- ***No significant reduction in food allergy in the intention-to-treat analysis***

The EAT study did not show efficacy in an intention-to-treat analysis with a non-significant 20% relative reduction in food allergy prevalence in the EIG.

- ***Early regular consumption of allergenic foods does protect against developing food allergy.***

If EIG participants introduced allergenic foods early at the recommended per-protocol level there was a significant 67% relative reduction in overall food allergy.

- ***Early introduction of allergenic foods is safe for the child***

There was not a single case of anaphylaxis with the initial introduction regimen in any of the EIG participants. Of the 29 baseline sensitised EIG participants who underwent enrolment challenges, 76% of such participants (22/29) had negative challenges. Reactions in the seven participants with one or more positive challenges were mild, half requiring no treatment at all.

- ***Effect present in high risk/low risk and all ethnic groups***

The rate of food allergy associated with per-protocol introduction of allergenic foods was lower in both high risk and non-high risk infants and across all ethnic groups compared to the equivalent SIG per-protocol participants.

- ***Effect is potentially allergen specific***

Whilst per-protocol adherence in the EIG resulted in a 67% reduction in overall food allergy, food specific per-protocol adherence resulted in larger reductions in allergy to the respective food. There was no peanut allergy recorded among peanut per-protocol adherent participants (100% reduction) and egg per-protocol adherence resulted in a 75% reduction in egg allergy. Neither did allergy to sesame or wheat occur among sesame and wheat per-protocol adherent participants respectively.

- ***Effect suggests a dose dependent relationship***

The effectiveness of the intervention increased with the number of weeks the food was eaten and the percentage of the recommended dose that was eaten. For the EAT primary outcome, the same increase in effectiveness was seen as the number of foods that were eaten increased. If half the recommended dose or more was eaten for all six foods for six or more weeks, under one percent of such participants developed a food allergy.
The effect at a food specific level was most striking for peanut. Of the 419 EIG participants who ate at least half the recommended dose of peanut for as little as four weeks or more, only one participant developed a peanut allergy (0.2%), an over tenfold reduction compared with the SIG group (2.5%, 13/525).

- ***Modelling suggests 2g per week consumption of peanut or egg white protein prevents their respective food allergies developing.***

The LEAP study achieved similar levels of reduction in peanut allergy to that observed in the EAT peanut per-protocol population but in a high risk cohort. However, LEAP could not

answer any issues about dose as the great majority of participants met or exceeded the 6g/week target for peanut consumption. The spectrum of adherence in the EIG participants allowed modelling of the data to be undertaken and it was determined that a mean consumption of 2g of peanut or egg white protein per week prevented development of these allergies. The peanut figure is remarkably consistent with the original Israeli data.

- ***Protective effect of early wheat consumption on wheat sensitisation in the intention-to-treat analysis***

Wheat skin prick positivity was statistically significantly lower at both 12 and 36 months of age in the EIG in an intention-to-treat analysis.

- ***Reduction in prevalence of sensitisation to foods***

The reduction of food allergy prevalence seen in the per-protocol analysis is mirrored in the analysis of sensitisation prevalence both overall and for individual foods at 12 and 36 months of age.

- ***No effect of early introduction on other atopic disease***

In contrast to the reductions in food allergy prevalence and sensitisation, there was no protective effect of early food introduction on other atopic diseases including eczema, rhinitis and wheeze phenotype.

- ***Early introduction of allergenic foods is safe for the family***

There was no report to the study team throughout the duration of the project of any adverse event in a food allergic family member of an EIG participant through accidental exposure related to their consumption.

- ***Adherence with the per-protocol EIG regimen varied. Partial adherence was associated with no increase in allergy prevalence.***

EAT was a pragmatic trial. We did not have the infrastructure to telephone participant families on a regular basis to ensure they complied with the intervention. Furthermore, compared with all the other early intervention studies currently underway, EAT involved asking families to feed their infants multiple foods in an age appropriate quantity. The end result was that we had a spectrum of compliance reflecting what would happen in the real world. This has provided some extremely reassuring data regarding the allergy prevalence in EIG participants who did not comply with the per-protocol requirement. Both for the primary outcome and at an individual food allergy specific level the rates of food allergy in EIG participants who were not in the EIG per-protocol group were similar to the SIG per-protocol group.

- ***Adverse event data (AE/SAE)***

The early introduction of allergenic foods occurred without clinically significant sequelae. Differences between the groups, were present, were generally small. Admissions to hospital were more common, but not statistically significantly so, in the SIG.

- ***Confident that this is an accurate reflection of situation as retention rate high***

EAT retention rates were high. Over 90% of participants returned for the final EAT study visit and 94% completed the final questionnaire.

- ***Egg allergy most prevalent***

Egg allergy had the highest prevalence in the EAT study (5.4% in the SIG), followed by peanut allergy (2.5%), then milk allergy (0.7%). The most obvious comparator is the HealthNuts study.[76] This recruited a general population, undertook skin prick testing with commercial skin prick tests solutions for peanut, sesame and cows' milk and raw egg white in all participants and confirmed food allergy by challenge for three of the foods. The mean age of testing in HealthNuts was 12.7 months. Comparisons of the skin prick sensitization rates (≥1mm) in HealthNuts versus the EAT SIG results from the one year visit were as follows: peanut HealthNuts 8.9%, EAT SIG 6.2%; sesame 2.5% vs 1.2%; cows' milk 5.6% vs 3.0%. In the EAT study, skin prick testing with raw egg white was undertaken at the three year visit and the comparative sensitisation rates were: HealthNuts 16.5%, EAT SIG (3 year) 7.1%.
Comparing challenge proven allergy rates, the results for peanut were: HealthNuts 3.0%, EAT SIG 2.5%; and for sesame 0.8% vs 0.5%. HealthNuts undertook raw egg challenges (prevalence rate 8.9%) whereas EAT did not. Conversely HealthNuts did not undertake challenges to cows' milk. Hence whilst sensitisation rates were in general lower in the EAT SIG, proven allergy rates in the EAT SIG were broadly similar to those in HealthNuts.

- ***IgE mediated cows' milk allergy prevalence was very low***

The prevalence of IgE mediated cows' milk allergy in the EAT study was low with only 7 cases in the whole cohort and a prevalence of 0.7% in the SIG. Interestingly the recently published systematic review and meta-analysis of the prevalence of common food allergies in Europe concluded that the pooled estimate for food-challenge-defined cows' milk allergy was 0.61% (95% CI 0.47-0.75).[1] In this meta-analysis there were only two studies found with documented challenge proven rates of cows' milk allergy for 2-5 year olds and the pooled estimate for these was 0.35% (95% CI 0.14-0.55).

- ***Marked influence of race in the EAT Study - much more allergic, much less likely to adhere to the EAT protocol***

Food allergy rates were much higher in non-white participants with a stepwise increase from white (5.3%), to mixed race (9.4%), to Asian/black/Chinese participants (19.3%). Conversely, there was a statistically significant stepwise reduction in per-protocol adherence most notable in the EIG with less than one in five Asian/black/Chinese participants complying with the EIG protocol.

- ***No effect on breastfeeding***

Breastfeeding rates in the EAT study were well above national figures, even when comparator figures were based on women having exclusively breastfed to three months as a baseline. Half of all EAT mothers were still breastfeeding at one year.

- ***No effect on growth***

The intervention showed no adverse effect on growth of the infants.

- ***Compliance with the EAT study intervention- initial exploration of factors identifies ethnicity and reporting of non-IgE type symptoms.***

Ethnicity had the strongest influence on non-adherence with the EIG regimen, followed by reporting any symptoms with the introduction of the EIG foods between 4 and 6 months of age. Low maternal quality of life in the psychological domain also appeared to play a role in

non-adherence in the EIG. Eczema at enrolment and the new onset of eczema between 4 and 6 months of age were associated with an increased likelihood of being non-adherent in the EIG but the effects were not statistically significant.
In the SIG, maternal smoking was the only statistically significant factor associated with increased non-adherence.

- ***Retention and participation associated with study group***

The EAT early introduction regimen required a high level of commitment from the families particularly when set within the context of a clinical trial where such mothers were being asked to record their infant's allergenic food consumption on essentially on a day by day basis. It seems likely that this burden contributed to the differential retention and participation rates observed in the study with these rates being lower in the EIG.

CHAPTER 6 – FUTURE WORK

The EAT cohort represents an extraordinarily closely studied group of breastfed children. A wealth of data has been collected of which this report only touches on a small part. There is scope for a large body of work going forward some of which would fall under the remit of the FSA's areas of interest.

- EAT study – adherence

"The EAT study failed to show efficacy in an intention-to-treat analysis. Further analysis suggests that the possibility of food allergy prevention through the early introduction of multiple allergenic foods in normal breastfed infants may depend on adherence and dosage." Perkin et al. NEJM.

The EAT study was not a negative study, but is imperative that we attempt to establish to the best of our ability why there was such a variation in adherence. The EAT data set is very rich and we have not by any means explored all avenues for attempting to understand this issue. This has the most significant public health implications of any future work on the EAT study data.

- EAT study – other atopic outcomes

The EAT study did not find a protective effect on other atopic outcomes but this will produce a paper in its own right.

- EAT study – allergen specificity

The analyses done to date suggest that food specific consumption had a more powerful effect on reducing specific food allergy than food allergy in general. However this requires more careful analysis. This is not easy as food consumption levels are likely to be highly correlated.

- EAT food related immunology

Samples were taken at 3 months, 1 and 3 years. High sensitivity specific IgE has already been measured to the six EAT early introduction foods. IgG and IgG4 are planned to be measured as well as peanut component responses in those sensitised to peanut.

- EAT coeliac results

Coeliac antibodies were measured (Tissue Transglutaminase Antibodies - tTG-IgA) at 3 years of age and these can be analysed in relation to early wheat introduction

- Vitamin D

The EAT cohort provides a unique opportunity to establish vitamin D reference ranges in EBF infants at 3 months of age which do not currently exist. We propose measuring vitamin D2 & D3 in all participants. Furthermore, the link between vitamin D and health can be explored

- Haematinics

The initial WHO systematic review on the benefits of prolonged exclusive breastfeeding included the haematinic status of children as a key outcome. We propose measuring ferritin in the EAT participants.

- EAT cytokine assays

We will be undertaking an analysis of the cytokine profiles in the control arm of the study up to one year of age in relation to eczema (yes/no) and severity, with and without food sensitisation/FLG carriage/raised TEWL along with Dr Carsten Flohr.

- EAT other serological analyses

Several further tests are under consideration dependent on volumes of serum available and include IgA and hs-CRP.

- EAT - Validation of the EAT FFQ

We are completing the validation study of the FFQ used in the EAT study. An initial validation study was done some time ago as part of an MSc in Human Nutrition by Maria-Christina Alexopoulou in 2009 and supervised by TSC member Professor Christine Edwards. This was then replicated by Dr Sophie Vaughan as part of her Imperial Allergy MSc. 47 diaries had been used with a target of 50. The remaining 3 diaries are due to be selected for coding and data entry into WISP for the analysis to be completed and prepared for publication.

- EAT - Validation of the online food diary

An immense amount of work has gone into validating the online food diary that was uniquely developed by the dieticians working on EAT for use in the study. A validation of the online food diary is being completed for submission for publication. This work has significant implications for future research collecting food diary data by confirming that on line food diary completion is an effective and reliable means of collecting dietary data.

- EAT - Food challenge protocol development in EAT

A manuscript has been drafted by Bunmi Raji with Anna Tseng's input outlining the work that went into the development of the challenge regimen in EAT. The process of undertaking food challenges to infants from 3 months of age to multiple foods was unique to EAT and there is much interest in the dietician community as to who our protocols were developed and performed.

- EAT - use of dietetic support during the key early intervention period

We can analyse the extent to which families used the available dietetic support during the key early introduction period and the extent to which this influenced adherence. This has important implications for advocating early introduction in the wider population without this support available.

- Food challenge data

The food challenge data can be further analysed to assess the symptoms and doses consumed for positive food challenges. From this analysis predictive values for SPT and specific IgE on food challenge outcome at different ages can be determined.

- EAT study – sleep and maternal quality of life

We have an important data in this area that requires further analysis and publication.

- EAT – order of introduction of foods and efficacy of intervention

Randomization of the order of introduction of the four foods: peanut, egg, sesame and fish, was effective in resulting in the same mean age of introduction. We can attempt an analysis

of timing of introduction by splitting the age of introduction for these four foods by the median.

- Factors associated with outgrowing food allergy

We can explore which factors influence the likelihood of outgrowing food allergy by the three year final visit and whether the early introduction regimen, or any other factors, impacted on the likelihood of this occurring.

- EAT – adverse event data

The EAT adverse event data warrants dissemination in a paper in its own right.

- EAT – Eczema, TEWL and Filaggrin (with Dr Carsten Flohr)

A paper looking at whether eczema (yes/no and severity)/raised TEWL predict challenge-proven food allergy (follow on paper from our JID publication that focused on the 3 months follow up point).

A paper examining the relationship between FLG mutation carriage and raised TEWL at three months and whether these predict later onset eczema/challenge-proven food allergy (follow on paper from our BJD publication that focused on the 3 months follow up point).

A paper that examines the natural history of eczema up to 3 years of age, in relation to FLG carriage and raised TEWL in early life.

A follow on paper from our recently accepted JACI paper on water hardness and eczema risk/skin barrier impairment, looking at the association longitudinally, beyond the 3 month follow up point.

- EAT – skin and gut microbiome (with Dr Carsten Flohr)

Analyses looking at the association between the gut and skin microbiome in relation to eczema/FLG carriage/TEWL and food allergy risk at 3 months and 1 year.

Analyses examining the association between stool inflammatory markers with the gut microbiome data and the development of eczema and food allergy during the first year of life.

We will also examine how hygiene-related environmental exposures, such as antibiotic prescribing in early life, pet exposure and personal hygiene practices as well as water hardness, impact on the skin and gut microbiome during the first year of life.

The highly significant food-specific per-protocol effects, especially to peanut but also to egg, warrant a follow on study of the cohort to determine whether the benefits of intervention are preserved over time. It is important to ensure that any reduction through early intervention is long-lived. This has important safety and public health implications. The high retention rate of more than 91% of the original population will facilitate this follow up.

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PUBLICATIONS

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Flohr C, England K, Radulovic S, et al. Filaggrin loss-of-function mutations are associated with early-onset eczema, eczema severity and transepidermal water loss at 3 months of age. *Br J Dermatol* 2010; **163:** 1333-6.

Flohr C, Perkin M, Logan K, et al. Atopic dermatitis and disease severity are the main risk factors for food sensitization in exclusively breastfed infants. *J Invest Dermatol* 2014; **134:** 345-50.

In press

Perkin MR, Craven J, Logan K, et al. The Association between Domestic Water Hardness, Chlorine and Atopic Dermatitis Risk in Early Life: A Population-Based Cross-Sectional Study. *J Allergy Clin Immunol. Accepted for publication.*

REFERENCES

1 Nwaru BI, Hickstein L, Panesar SS, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. *Allergy* 2014; **69:** 62-75.

2 Grundy J, Matthews S, Bateman B, Dean T, Arshad SH. Rising prevalence of allergy to peanut in children: Data from 2 sequential cohorts. *J Allergy Clin Immunol* 2002; **110:** 784-9.

3 Koplin JJ, Osborne NJ, Wake M, et al. Can early introduction of egg prevent egg allergy in infants? A population-based study. *J Allergy Clin Immunol* 2010; **126:** 807-13.

4 World Health Organization. Global Strategy for Infant and Young Child Feeding. Geneva; 2003.

5 Department of Health. Infant Feeding Recommendation. 2003 (http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4097197)

6 World Health Organization. Exclusive breastfeeding for six months best for babies everywhere. 2011 Jan 15.

7 Department of Health. Weaning - starting solid food. 2008;

8 Koplin JJ, Allen KJ. Optimal timing for solids introduction - why are the guidelines always changing? *Clin Exp Allergy* 2013; **43:** 826-34.

9 Falth-Magnusson K, Kjellman NI. Development of atopic disease in babies whose mothers were receiving exclusion diet during pregnancy--a randomized study. *J Allergy Clin Immunol* 1987; **80:** 868-75.

10 Zeiger RS, Heller S. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol* 1995; **95:** 1179-90.

11 Saarinen UM, Kajosaari M. Does dietary elimination in infancy prevent or only postpone a food allergy? A study of fish and citrus allergy in 375 children. *Lancet* 1980; **1:** 166-7.

12 Katz Y, Rajuan N, Goldberg MR, et al. Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. *J Allergy Clin Immunol* 2010; **126:** 77-82.

13 Du Toit G., Katz Y, Sasieni P, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* 2008; **122:** 984-91.

14 McAndrew F, Thompson J, Fellows L, Large A, Speed M, Renfrew MJ. Infant Feeding Survey 2010. Health and Social Care Information Centre; 2012.

15 Palmer DJ, Metcalfe J, Makrides M, et al. Early regular egg exposure in infants with eczema: A randomized controlled trial. *J Allergy Clin Immunol* 2013; **132:** 387-92.

16 Du TG, Roberts G, Sayre PH, et al. Identifying infants at high risk of peanut allergy: the Learning Early About Peanut Allergy (LEAP) screening study. *J Allergy Clin Immunol* 2013; **131:** 135-43.

17 Du TG, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015; **372:** 803-13.

18 Dalal I, Binson I, Reifen R, et al. Food allergy is a matter of geography after all: sesame as a major cause of severe IgE-mediated food allergic reactions among infants and young children in Israel. *Allergy* 2002; **57:** 362-5.

19 Rona RJ, Keil T, Summers C, et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol* 2007; **120:** 638-46.

20 Perkin MR, Strachan DP. Which aspects of the farming lifestyle explain the inverse association with childhood allergy? *J Allergy Clin Immunol* 2006; **117:** 1374-81.

21 NHS choices. Food allergies in babies. 2015 (http://www.nhs.uk/Conditions/pregnancy-and-baby/pages/food-allergies-in-children.aspx#close)

22 Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. Peanut Allergy. London: Department of Health, 1998 (http://cot.food.gov.uk/cotreports/cotwgreports/cotpeanutallergy)

23 Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. Statement on the review of the 1998 COT recommendations on peanut avoidance. 2008 (http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2008/cot200807peanut)

24 American Academy of Pediatrics, Committee on Nutrition. Hypoallergenic Infant Formulas. *Pediatrics* 2000; **106:** 346-9.

25 Greer FR, Sicherer SH, Burks AW. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 2008; **121:** 183-91.

26 Australian Society of Clinical Immunology and Allergy. Infant feeding advice. 2010 (http://www.allergy.org.au/images/stories/hp/info/ASCIA_Infant_Feeding_Advice_2010.pdf)

27 Muraro A, Halken S, Arshad SH, et al. EAACI Food Allergy and Anaphylaxis Guidelines. Primary prevention of food allergy. *Allergy* 2014; **69:** 590-601.

28 Bergmann RL, Diepgen TL, Kuss O, et al. Breastfeeding duration is a risk factor for atopic eczema. *Clin Exp Allergy* 2002; **32:** 205-9.

29 Sears MR, Greene JM, Willan AR, et al. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. *Lancet* 2002; **360:** 901-7.

30 Zutavern A, von Mutius E, Harris J, et al. The introduction of solids in relation to asthma and eczema. *Arch Dis Child* 2004; **89:** 303-8.

31 Poole JA, Barriga K, Leung DY, et al. Timing of initial exposure to cereal grains and the risk of wheat allergy. *Pediatrics* 2006; **117:** 2175-82.

32 Alm B, Aberg N, Erdes L, et al. Early introduction of fish decreases the risk of eczema in infants. *Arch Dis Child* 2009; **94:** 11-5.

33 Hill DJ, Hosking CS, Zhie CY, et al. The frequency of food allergy in Australia and Asia. *Environ Toxicol Pharmacol* 1997; **4:** 101-10.

34 Obeng BB, Amoah AS, Larbi IA, et al. Food allergy in Ghanaian schoolchildren: data on sensitization and reported food allergy. *Int Arch Allergy Immunol* 2011; **155:** 63-73.

35 Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015; **372:** 803-13.

36 Bellach J, Schwarz V, Ahrens B, et al. Early introduction of hen's egg during weaning results in frequent allergic reactions: first results from a randomized placebo-controlled trial on hen's egg allergy prevention. *EAACI Online Library* 2015;

37 ICH. Harmonised Tripartitie Guideline for good clinical practice E6(R1). 1996.

38 Medical Research Council. MRC guidelines for good clinical practice in clinical trials. 1998.

39 Reilly JJ, Ashworth S, Wells JC. Metabolisable energy consumption in the exclusively breast-fed infant aged 3--6 months from the developed world: a systematic review. *Br J Nutr* 2005; **94:** 56-63.

40 Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. *Clin Exp Allergy* 2000; **30:** 1540-6.

41 Hill DJ, Heine RG, Hosking CS. The diagnostic value of skin prick testing in children with food allergy. *Pediatr Allergy Immunol* 2004; **15:** 435-41.

42 Du Toit G, Roberts G, Sayre PH, et al. Identifying infants at high risk of peanut allergy: the Learning Early About Peanut Allergy (LEAP) screening study. *J Allergy Clin Immunol* 2013; **131:** 135-43.

43 Agostoni C, Decsi T, Fewtrell M, et al. Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2008; **46:** 99-110.

44 Skevington SM, Lotfy M, O'Connell KA. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. *Qual Life Res* 2004; **13:** 299-310.

45 Kunz B, et al. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology* 1997; **195:** 10-9.

46 Farahmand S, Tien L, Hui X, Maibach HI. Measuring transepidermal water loss: a comparative in vivo study of condenser-chamber, unventilated-chamber and open-chamber systems. *Skin Res Technol* 2009; **15:** 392-8.

47 Royal College of Paediatrics and Child Health. UK-WHO growth charts, 0-18 years. 2009 (http://www.rcpch.ac.uk/growthcharts)

48 WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: Growth velocity based on weight, length and head circumference: Methods and development. Geneva: World Health Organization, 2009 (http://www.who.int/childgrowth/publications/technical_report_velocity/en/)

49 Brough HA, Santos AF, Makinson K, et al. Peanut protein in household dust is related to household peanut consumption and is biologically active. *J Allergy Clin Immunol* 2013; **132:** 630-8.

50 Hill DJ, Hosking CS, de Benedictis FM, et al. Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: an international study. *Clin Exp Allergy* 2008; **38:** 161-8.

51 Brown LD, Cai TT, DasGupta A. Interval estimations for a binomial proportion. *Statistical Science* 2011; **16:** 101-17.

52 Office for National Statistics. 2011 Census: Aggregate data (England and Wales) [computer file]. UK Data Service Census Support. Downloaded from: http://infuse.mimas.ac.uk. This information is licensed under the terms of the Open Government Licence [http://www.nationalarchives.gov.uk/doc/open-government-licence/version/2].; 2011.

53 Collin SM, Granell R, Westgarth C, et al. Pet ownership is associated with increased risk of non-atopic asthma and reduced risk of atopy in childhood: findings from a UK birth cohort. *Clin Exp Allergy* 2015; **45:** 200-10.

54 Kelleher M, Dunn-Galvin A, Hourihane JO, et al. Skin barrier dysfunction measured by transepidermal water loss at 2 days and 2 months predates and predicts atopic dermatitis at 1 year. *J Allergy Clin Immunol* 2015.

55 Johnke H, Norberg LA, Vach W, Host A, Andersen KE. Patterns of sensitization in infants and its relation to atopic dermatitis. *Pediatr Allergy Immunol* 2006; **17:** 591-600.

56 Schafer T, Bohler E, Ruhdorfer S, et al. Epidemiology of food allergy/food intolerance in adults: associations with other manifestations of atopy. *Allergy* 2001; **56:** 1172-9.

57 Marrs T, Bruce KD, Logan K, et al. Is there an association between microbial exposure and food allergy? A systematic review. *Pediatr Allergy Immunol* 2013; **24:** 311-20.

58 Ziyab AH, Karmaus W, Yousefi M, et al. Interplay of filaggrin loss-of-function variants, allergic sensitization, and eczema in a longitudinal study covering infancy to 18 years of age. *PLoS One* 2012; **7:** e32721.

59 Young E, Stoneham MD, Petruckevitch A, Barton J, Rona R. A population study of food intolerance. *Lancet* 1994; **343:** 1127-30.

60 Kramer MS, Kakuma R. Optimal duration of exclusive breastfeeding. *Cochrane Database Syst Rev* 2002; CD003517.

61 Quigley MA, Kelly YJ, Sacker A. Infant feeding, solid foods and hospitalisation in the first 8 months after birth. *Arch Dis Child* 2008.

62 Leonard SA, Sampson HA, Sicherer SH, et al. Dietary baked egg accelerates resolution of egg allergy in children. *J Allergy Clin Immunol* 2012; **130:** 473-80.

63 Nowak-Wegrzyn A, Bloom KA, Sicherer SH, et al. Tolerance to extensively heated milk in children with cow's milk allergy. *J Allergy Clin Immunol* 2008; **122:** 342-7, 347.

64 Beyer K, Morrow E, Li XM, et al. Effects of cooking methods on peanut allergenicity. *J Allergy Clin Immunol* 2001; **107:** 1077-81.

65 Perkin MR, Logan K, Marrs T, et al. Enquiring about Tolerance (EAT) Study - feasibility of an early allergenic food introduction regimen. *J Allergy Clin Immunol* 2016.

66 Obeng BB, Amoah AS, Larbi IA, et al. Food allergy in Ghanaian schoolchildren: data on sensitization and reported food allergy. *Int Arch Allergy Immunol* 2011; **155:** 63-73.

67 Du Toit G, Katz Y, Sasieni P, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* 2008; **122:** 984-91.

68 Kung SJ, Steenhoff AP, Gray C. Food allergy in Africa: myth or reality? *Clin Rev Allergy Immunol* 2014; **46:** 241-9.

69 Gray C, Kung SJ. Food allergy in South Africa: joining the food allergy epidemic?: review articles. *Current Allergy & Clinical Immunology* 2012; **25:** 24-9.

70 Hentze S. Age of introduction, frequency and quantity of peanut and peanut products consumption among 4–36 month-old black infants in the Cape Metropole Region. University of Cape Town; 2006.

71 Bolling K, Grant C, Hamlyn B, Thornton A. Infant feeding survey 2005. The Information Centre for health and social care and the UK Health Departments; 2005.

72 Verhasselt V, Milcent V, Cazareth J, et al. Breast milk-mediated transfer of an antigen induces tolerance and protection from allergic asthma. *Nat Med* 2008; **14:** 170-5.

73 Liu AH, Jaramillo R, Sicherer SH, et al. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005-2006. *J Allergy Clin Immunol* 2010; **126:** 798-806.

74 Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics* 1998; **101:** E8.

75 Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin C. Composite outcomes in randomized trials: greater precision but with greater uncertainty? *JAMA* 2003; **289:** 2554-9.

76 Osborne NJ, Koplin JJ, Martin PE, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol* 2011; **127:** 668-76.

APPENDICES

Consent forms

1. EAT recruitment leaflet
2. EAT Study enrolment consent form - mother & child (including stool and skin swab sections)
3. EAT one page summary information sheet
4. EAT maternal skin prick test addendum consent form
5. EAT paternal skin prick & blood test addendum consent form

Food challenge proformas

6. Open food challenge (<1 year)
7. Double blind placebo controlled food challenge (1 year+)
8. Double blind placebo controlled food challenge (3 years)
9. Frequent consumer challenge (3 years)
10. FPIES challenge (1 year+)

Clinical visit proformas

11. Enrolment visit (3 months)
12. One year visit
13. Three years visit

Questionnaires

14. Enrolment food frequency questionnaire
15. Enrolment general questionnaire
16. Example interim questionnaire

APPENDIX 1 - Eat Recruitment Leaflet

1 in 3 children in the UK develop allergies, such as food allergy, eczema, asthma or hay fever.

Could your child be one of them?

We need your help to find a way to tackle this problem.

EAT
Enquiring About Tolerance

EAT
Enquiring About Tolerance

Our study will look at how we introduce certain foods into children's diets. Your help can make a difference.

Please consider becoming part of our efforts to halt the rise in food allergy.

Call 0800 358 0021

Visit: www.eatstudy.co.uk

Food allergy is common in infants and can sometimes be severe and life-threatening.

We don't fully understand why food allergy develops. We would like to know whether introducing certain foods early into the diet could stop infants developing allergy to those foods, and possibly eczema, asthma and hay fever.

Our medical team at the Evelina Children's Hospital in London wants to conduct some research to see whether the early introduction of certain foods alongside regular breastfeeding can help prevent the development of food allergy, and possibly other allergies.

Is your child eligible?

If your baby is younger than 3 months of age, and if your baby is still exclusively or mainly breastfed and has had no solid foods, then he or she may be able to help us.

Please visit our website www.eatstudy.co.uk to find out more about our study. If your child is eligible please consider taking part.

Contact the EAT Study Team on **0800 358 0021**

There is also a BBC Horizon programme about allergy that you might like to see: "Allergy Planet" (username: mother, password: babies09).

EAT
Enquiring About Tolerance

APPENDIX 2 - EAT Study enrolment consent form - mother & child (including stool and skin swab sections)

EAT
Enquiring About Tolerance

Guy's and St Thomas' NHS
NHS Foundation Trust

St Thomas' Hospital
Lambeth Palace Road
London SE1 7EH
EAT Study Recruitment Line: 0800 358 0021

Post Natal Parent/Guardian Informed Consent Form – **Mother & Child**

Randomized controlled trial of early introduction of allergenic foods to induce tolerance in infants

The Enquiring About Tolerance (EAT) Study

Please make sure you have read the one page summary sheet available from the EAT Study website at http://www.eatstudy.co.uk/links (or see the contact details at the end of this form if you would like us to send you a paper copy) which explains what the study involves for you and your baby.
You and your child are being invited to take part in a research study. This information leaflet and consent form explains in detail what **you and your child's** participation in the study will involve. If you agree to participate in the study, we will ask you to sign this consent form when you attend the allergy trials unit with your baby when they are 3 months old. If you have any questions about your or your child's participation in the study please contact us.
Before you make a decision it is important for you to understand why the research is being done and what it will involve. Please take your time to read the following information carefully and discuss it with others if you wish.

What is the purpose of the study?
Food allergy now affects 6% (one in sixteen) children. Two successive studies from the Isle of Wight undertaken in 1989 and then 1994-1996 suggested that peanut allergy had doubled and peanut sensitization tripled. The purpose of this study is to test an approach for the prevention of the development of food allergy.
Food allergic reactions can range in severity from a minor reaction such as a skin rash (nettle rash or urticaria) through to the severe type of reaction called anaphylaxis, where symptoms can become life threatening. Fortunately, it is very rare for food allergy to result in death.
There is currently no available treatment for food allergies other than avoidance of the food and immediate treatment of accidental exposures with antihistamines (such as Piriton) and intramuscular adrenaline (Epi-pen). Whilst children can grow out of cow's milk and egg allergies, peanut allergy is rarely outgrown, so children and families have to be very cautious about their eating habits and always carry emergency medications for the whole of their lives.

The reasons for this study

Breast feeding is best for your baby and this study aims to encourage all participating mothers to breast feed for 6 months or more. This is in line with current UK Government advice that breastfeeding will help protect your baby from: "ear infections, asthma, eczema, chest infections, obesity, gastro-intestinal infections, childhood diabetes and urine infections."

The reason for this study is that there is uncertainty as to when is the best time to introduce solid foods, and in particular when to introduce the common allergenic foods, as the best way of preventing your child developing food allergies.

The current UK Government recommendations hope to prevent food allergy by reducing or avoiding exposure to the allergenic foods in the early weaning diet.

Numerous studies spanning several decades have attempted to achieve a reduction in food allergies, including peanut allergy, by eliminating foods such as peanut, egg and milk from the diet of infants and mothers during pregnancy and whilst breastfeeding. These studies have had little success in reducing the frequency of food allergy.

One possible explanation for the failure of these studies is that the elimination of foods was not properly achieved. An alternative reason may be that avoidance is not the best strategy and that the early introduction of peanut may actually protect against the development of peanut allergy. There are countries in the world where children eat peanut foods early in life and incidence of peanut allergy in these countries is low e.g. Asia and Africa. This is also true in Israeli children where our study findings reveal that eating a high dose of peanut protein early is associated with a low prevalence of peanut allergy.

There are also now studies suggesting that delaying the introduction of solid foods that may cause allergies for too long may also be associated with a higher risk of causing a food allergy.

Given these observations and the current uncertainty regarding when is the best time to introduce allergenic foods into the weaning diet in order to minimise risks of development of food allergies, we wish to investigate whether early introduction of peanut and other allergenic foods into your child's diet or avoidance of these foods may help to decrease their chance of developing food allergies.

The Learning Early About Peanut Allergy (LEAP) Study

Our study group is already undertaking a randomized trial introducing peanut into the diet of infants aged between 4 and 10 months of age who are at high risk of developing food allergies to see whether this decreases the chances of developing peanut allergy – the LEAP study (**www.leapstudy.co.uk**). 620 infants are taking part and half are successfully consuming a peanut snack.

Why have my baby and I been chosen?

We have contacted mothers with a baby approaching 3 months of age who live in England and Wales. In order to take part in the study you must be planning on exclusively breast-feeding your baby for at least 3 months. Your baby will not be able to enter the study at 3 months of age if he or she has not been exclusively breast fed for 3 months.

We believe the opportunity to try and reduce your child's chance of developing food allergies is best when they are young. That is why this study is seeking to test a dietary intervention during early infancy. The study will enrol 1302 infants and their mothers at 3 months of age.

Do my child and I have to take part?
It is up to you whether you and your child want to participate in the study. If you decide you would like to take part you will be given this information sheet to keep and be asked to sign the consent form when you attend the allergy trials unit. If you decide you would like to take part you are still free to withdraw at any time without giving a reason. A decision not to take part or to withdraw at any time will not affect the standard of care you will receive in the future.

What will happen to me if I decide to take part?
Before you attend our allergy trials unit with your 3 month old baby we would like you to behave just the same as you would have done if you were not taking part in the study.
If you take part we will ask you to complete two questionnaires. The first is about your diet during pregnancy and since you have been breastfeeding. The second includes a few lifestyle related questions, such as whether you keep a pet at home, and whether you use any medicated creams or emollients on your child's skin. These can be completed online (or we can post them to you if you do not have internet access).
When you attend the final 3 year assessment visit with your baby we would like to perform skin prick testing and a blood test on you (and your partner) to see if you are allergic to any common foods or airborne allergens (e.g. pollen and pets).

What will happen to my child if we decide to take part?
This type of study is known as a randomized study. Sometimes because we do not know which way of treating patients is best we need to make comparisons. All children who take part in this study will be put into one of two groups at three months of age. The groups are selected randomly by a computer which has no information about the individual – i.e. by chance. Participants in each group will then have a different treatment, and the two groups will be compared. The chance of your child being in each of the two groups is 50% (the same as if a coin was tossed).

Because we do not know the best way to prevent food allergy, we will compare different prevention methods in this study. We are comparing early introduction (with the support of dieticians) of solid foods, including foods that sometimes cause food allergy, with the usual UK Government infant feeding advice to not introduce solids until around 6 months. At 3 months of age participants will be randomised into one of two different groups:

Group 1 – Participants will be encouraged to continue to breast feed. Your baby will have a skin prick test to ensure they have not already developed a food allergy. At three months of age mothers will introduce baby rice mixed with breast milk or water. Your baby will then be started on a cow's milk yoghurt (2 small yoghurts eaten during a week). Subsequently your baby will have introduced in randomized order the other allergenic foods – egg (1 egg a week), fish (20 grams/about one tablespoon a week), peanut (3 teaspoons of peanut butter a week) and sesame (3 teaspoons of tahini – sesame paste). Wheat (2 wheat-based breakfast cereal biscuits e.g. Weetabix a week) will be introduced last and not before four months of age, The aim is for of all foods to be being ingested in the required quantities by five months of age.

Group 2 – Participants will follow the existing UK Government recommendations which recommend exclusively breast feeding for around six months and no early (before six months) introduction of allergenic foods.

How does the infant feeding method for Group 1 differ from the current UK Government recommendations?
The UK Government currently makes several recommendations with regard to how long you should breastfeed for and when and what solids your baby should be introduced to. How these compare with what we are doing for Group 1 in the EAT Study is summarised in Appendix 1 at the end of this document.

Duration of the study
Infants will be enrolled at 3 months of age. The study will continue until the child reaches 3 years of age. Participants will be closely observed at all stages of the study, but particularly during the first year of your infant's life. All children will return to the allergy trials unit at 1 year and 3 years of age for assessments including a blood test, a non-invasive test of skin barrier function and skin prick testing to see if they have developed any allergies. If your child needs to have a food challenge to clarify whether he is allergic to a food, the challenge will take approximately 5-6 hours. You will be given specific appointments for the visits at mutually convenient times.

Enrolment visit (3 months of age)

- At enrolment your child will be randomised into one of the 2 groups described above.
- If your child is in Group 1 (the early introduction group). They will have skin prick tests to peanut, cow's milk, sesame, egg, wheat and fish. This will ensure that they are not already allergic to these foods.
- If these results suggest they may be allergic to a particular food, children in Group 1 will be invited to have a challenge for that particular food on our day unit. A food challenge involves feeding your child small amounts of the food under close medical supervision in the children's allergy unit at St Thomas', gradually increasing the amount to a portion that the children in the intervention half of the study will be consuming. If they show signs of a reaction they will be advised to avoid that food but will still consume the other foods.
- Children in Group 2 (the standard introduction group), will follow the current UK Government advice of around six months exclusive breast feeding and no early introduction of allergenic foods. Children in Group 2 will not have skin prick testing done at the enrolment visit as we want their introduction to complementary foods to be the same as what would have happened if they were not participating in the study.

What happens at clinic visits at 3 months, 1 year and 3 years of age?
The following procedures will be performed during these visits:

- A blood test: at the end of the study follow-up we will process the bloods samples to look for food allergies. We will also look at additional blood characteristics which may help us to understand why some children develop food allergies and others do not. At the enrolment and one year assessment we will take not more than 10 mls of blood (approximately 2 teaspoons). At three years of age we would like to take a little bit more blood from him/her: 20 mls (4 teaspoons). These are small quantities of blood that will quickly be replenished by your child's body. At the three month visit we will encourage you to breastfeed your infant when they have their blood test as this has been shown to significantly reduce their discomfort. At the one and three year visits a local anaesthetic ('numbing cream') can be applied to minimise discomfort (this is not licensed to be used under one year of age).
- Skin prick testing (Group 1 at enrolment visit, both Groups at 1 and 3 year visits): to assess for allergies to foods and environmental factors. This involves a small

amount of the allergen being placed onto the skin and then pricked through the first couple of layers of skin with a very small (1mm) lancet (it does not draw blood). If your child is allergic to any of the allergens being tested a small bump (hive) will develop within 5-15 minutes. This disappears after about 30 minutes.

- Measurement of height and weight.
- We will assess your child for signs of eczema. This will involve asking you some questions and examining your child. This would be performed as part of a normal allergy assessment.
- Your baby's skin provides a natural barrier against water loss. There is some evidence to suggest that children who lose more water than others across their skin have a tendency to develop dry skin and eczema. We will use a simple non-invasive probe to measure the amount of water your child looses across the skin. This does not cause any discomfort and requires the non-invasive probe to be held in place for about a minute, until a stable reading is produced.
- As part of assessing your baby's skin we will take skin swabs. This does not cause any discomfort.
- At the three month and one year visits we will ask you to bring a dirty nappy with you so we can collect a stool sample. We believe the natural bacteria the baby has in their bowel may influence whether they develop conditions like eczema and perhaps food allergies as well. At the three month visit we will give you a kit to take home for you to collect a sample from a dirty nappy when your baby is five months old. We would like you to post the sample back to us in special appropriate packaging. We will provide full details of what you need to do both in the pack and with a video on our website.
- We will ask you to let us know if your child has had any reactions to any foods.
- Health checks: We will contact you, once a month for the first year and three monthly until three years of age. These consultations include a short questionnaire about which foods your child is currently eating. They will also make sure that you and your child are managing with the study and you will be able to express any concerns you may have about your child's health.
- Five day food diaries. On three occasions (when your infant is 6 months old and just before the 1 year and 3 years assessments) we will ask you to complete a food diary for five days of all the foods your child has consumed in that time. The dietician will help explain what you should fill in.
- If your child is in Group 1 (the group that weans onto solid foods early) we will ask you to give the foods on a regular basis until your child is one year of age and encourage you to continue giving the foods until 3 years of age. After that it will be left to your own choice whether you wish to continue giving the foods to your child. If your child is in Group 2 (the group that follows UK Government advice) we will ask you to ensure your child avoids the allergenic foods during the first six months of their life.
- At the one year and three years assessments a food challenge will be performed to see whether or not your child is food allergic if they have positive skin prick tests to any of the six intervention foods. Children who have a slightly greater chance of an allergic reaction during the food challenge (e.g. children with asthma) will require an intravenous cannula to be inserted during their challenge. This is a small plastic tube that sits in a vein, just underneath the skin during the challenge and allows us to give medication directly into the blood stream in the unlikely event of a severe reaction.
- If your child is diagnosed with a food allergy you will be given the appropriate advice and we will continue to monitor your child in the appropriate clinic for as long as is necessary.

- You will be given full written information about preventing, recognising and treating allergic reactions in your child. A nurse or doctor will also discuss this information with you. If you feel that you need more information then you will be able to contact a member of the study team.

Additional visits

- If your child has what you think might be a reaction to a food we will encourage you to contact us so that we can decide whether the history is suggestive of a food allergy. If so, we will invite you and your child back to the allergy unit to be investigated further with skin prick tests as described above and a food challenge if necessary to confirm or rule out a definite food allergy.

Parent responsibility

The greatest responsibility is to carry out the required study intervention - either avoidance until six months of age or introduction of the allergenic foods from 3 months of age, alongside continued breastfeeding, depending on the group to which your child is randomised. Dieticians will work closely with you to help you with this.

If your child is randomised to the group that receives the allergenic foods it is very important that no other individual (friend or family member) who is currently avoiding these foods because of an allergy eats the child's food. This is to prevent any allergic reactions in these individuals.

What are my child's alternatives?

There are currently no established strategies for the prevention of food allergy.

What are the side effects of the treatment received?

Currently approximately 6% of children in the UK will develop food allergies (approximately 1.5% peanut, 1.5% cow's milk, 1.5% egg and 1.5% other allergenic foods). There is a small theoretical possibility that either intervention – be it complete avoidance or introduction of allergenic foods – could increase the rate of food allergy. In order to guard against this possibility your child will be monitored closely and appropriate investigations or actions taken. An independent safety committee of experts will monitor the study closely to detect any such increased rates of allergy in either group. Whether or not our hypothesis is correct, children in the standard introduction group will share the same risk of developing food allergies as other children in the UK who are not enrolled in the study.

Additional although unlikely risks include worsening of eczema, excessive weight loss or gain, and/or metabolic abnormalities. We will also record whether your child has any infectious illnesses such as diarrhoea or chest infections. The study doctors, nurses and dieticians will closely monitor your child during the study in order to prevent and detect any such changes, and will advise on ways to immediately correct any possible problems that may arise.

Why do you want a blood sample from me?

The sample from you will be stored and will subsequently be used to investigate your own allergy status.

What are the possible disadvantages and risks of me taking part?

<u>Financial and time requirements</u>

We are able to reimburse your travels costs related to your participation in this study. The assessment visits at 3 months, 1 year and 3 years of age will last approximately one to two hours.

We will ask you to complete a series of questionnaires about you and your baby's diet and health. The following table summarises these and gives an indication of how long we anticipate they will take to complete. You will be able to complete all the questionnaires on line but we can send you a paper copy if you require. We will use email to inform you about appointment times for the assessment visits and for general communication with you.

Assessment point	Subject	Duration
3 months	Family health and environment	20 minutes
3 months	Maternal diet in pregnancy & whilst breast feeding	20 minutes
4-12 months - monthly	Infant health and diet	20 minutes
6 months	5 day infant food diary	1 hour
One year assessment	5 day infant food diary	1 hour
15-35 months - 3 monthly	Infant health and diet	20 minutes
Three year assessment	Infant health and diet	20 minutes
Three year assessment	5 day infant food diary	1 hour

Risk of allergic reactions

Certain study procedures are associated with a small risk of allergic reaction; the risks associated with each procedure are detailed below. Potential symptoms of an allergic reaction may include some or all of the following symptoms: nausea, vomiting, itching, urticaria (nettle rash), swelling, wheezing or difficulty in breathing, and/or a drop in blood pressure. Allergic reactions are usually mild but may occasionally be moderate or severe. The most severe type of reaction is called anaphylaxis which is where the symptoms described become life threatening. Such reactions are very rare and the study investigators will do everything possible in order to avoid causing an allergic reaction, but if a reaction were to occur, it would be promptly dealt with by experienced children's doctors and nurses.

Skin prick testing

There is a theoretical risk that you could have an allergic reaction after skin prick testing. However no allergic reactions have ever occurred following skin prick testing in the clinical experience of the study team who have performed this test in approximately 9000 children over the last 12 years. Skin prick testing will always take place in a clinic by an experienced doctor or nurse who will be able to promptly recognise and treat the signs of any reaction.

Early introduction or standard introduction of the allergenic foods

If your child is randomised to the group which will receive the allergenic foods earlyonly children who have had a negative skin prick test will have the food introduced unsupervised; otherwise the allergenic food will be introduced under strict clinical supervision so that an experienced children's nurse and doctor will be present to quickly recognise and treat any allergic reaction in the unlikely event that one was to occur.

Additionally, as mentioned above, there is a very small risk that being in the standard introduction arm or the early introduction arm of the study may result in an increased risk of food allergy. However your child will be closely monitored at regular intervals throughout the study, and additionally you can contact a member of the study team via a dedicated study telephone line. They will be able to advise or assess your child should you have concerns that he/she is developing a food allergy.

Oral food challenges

Your child may experience an allergic reaction during a food challenge. However oral food challenges are routinely carried out for clinical reasons. Over the last 12 years, the study team has performed over 2500 food challenges in children aged 3 months to 3 years without a single case of life threatening anaphylaxis. In addition these food challenges will always be carried out by experienced children's doctors and nurses who will closely monitor your child during the procedure. They will be able to recognise the symptoms of an allergic reaction as it is beginning and administer appropriate medication to reverse the reaction.

Discomfort associated with study investigations

Skin prick testing

Some people find skin prick testing slightly uncomfortable (to some children it feels like a prickle, others do not feel anything). After skin prick testing has been performed you develop a small hive (a bit like nettle rash) to any of the tests you are allergic too. This can be slightly itchy for about 10 minutes. Most people tolerate this very well but if necessary a small dose of antihistamine will be given after the testing to minimise the discomfort.

Skin examination and testing of skin barrier function (child)

An experienced doctor will examine your child for signs of eczema. The test to measure the amount of water your child looses across the skin takes only a minute and does not cause any discomfort. Taking the skin swabs causes no discomfort.

Blood Test (child)

The blood test may cause discomfort. However this can be performed using a local anaesthetic ('numbing') cream to minimise discomfort. An experienced phlebotomist or nurse will take the blood. Other side effects of the blood test include a small risk of bleeding, bruising, or infection at the site.

Cannulation (child)

Only a small number of children will require a cannula during the food challenges that take place in this study. The side effects of cannulation are similar to those of blood testing; discomfort, bleeding, bruising or infection at the site. Again the cannulation will take place after the application of a local anaesthetic cream and will be performed by an experienced doctor or nurse.

Blood sample - parents

We will obtain blood when you attend the three year assessment.

What are the possible benefits of taking part?

We will encourage all participating mothers to achieve at least 3 months exclusive breast feeding and hope that mothers in the standard introduction arm of the study will achieve the six month target. We will ensure mothers are aware of the different sources of support that are available within the hospital and the community to assist with establishing successful breast feeding.

Ultimately we hope that all the treatments in this study will help your child. However, there is no guarantee that your child will not develop food allergy if they participate in the study. The information we get from this study may help us to prevent the development of food allergy in more children in the future.

In the same way as if they did not take part in the trial, any child who develops food allergy during the trial will be offered appropriate testing to confirm or refute the diagnosis. Usual follow up care with specialist doctors, nurses and dieticians will also be offered.

What if new information becomes available?
Sometimes during the course of a research project new information becomes available about the treatment being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want your child to continue in the study. If you decide to withdraw your child, your doctor will make the appropriate arrangements for the care needed by your child to continue. If you decide your child should continue in the study you will once again be asked to sign an updated consent form. Your doctor may also decide it is in your child's best interests for them to be withdrawn from the study. If this occurs the reasons will be explained and appropriate care will be organised for your child.

What happens when the research is completed?
Once the trial is completed you will be aware of your child's allergic status. If they have no allergies then they will not need any further intervention. Those participants who may have developed food allergy or who have other allergic disorders, will be given appropriate advice and follow up appointments in an appropriate clinic (in the same way as for children who have not taken part in the study).

What if something goes wrong?
This trial is insured by Zurich as part of the 'no fault' clinical trials policy of Kings College London. If you are harmed due to someone's negligence then you may have grounds for legal action. Regardless of this, if you wish to complain, or have any concerns about the study, the normal NHS complaints mechanism is available to you via the Patient Advocacy and Liaison Service (PALS). They may be contacted by the following means:

Tel: 020 7188 8801 or 8803 Email: pals@gstt.nhs.uk

Will our participation in the study be kept confidential?
All information which is collected about you and your child during the course of the research will be kept strictly confidential. Research folders will be labelled as confidential and kept in a locked office at all times. Access to these folders will be restricted to study investigators, study statisticians, and appointed audit authorities. Any information that is stored electronically will be kept 'locked' by password access.
With your consent, your GP will be informed that your child is taking part in the study and of any diagnoses (e.g. asthma or eczema) that may be made during the study.

What will happen to the results of the study?
During the study a newsletter will be posted or emailed to all participants informing them of the study progress. Once the study is completed the information will be audited and then submitted for publication to a peer reviewed scientific journal. Once again all the study findings will be made available to participants in a lay person format.

Who is organising and funding the research?
The study is being run by Prof Gideon Lack and his team of researchers. The Food Standards Agency, a Government Department, the Medical Research Council, and the Department of Health's National Institute of Health Research (NIHR) are funding the research.

Who has reviewed the study?
St Thomas' Hospital Research Ethics Committee, the Food Standards Agency, the Medical Research Council, and the NIHR have reviewed the study.

Storage of Blood Samples
You have the option to have you and your child's samples of blood stored for use in **future** research studies. These future studies may help researchers learn more about allergy, asthma and the immune system (the body's natural defence system against infectious disease and illness).

- Researchers may also study the genetics of your child's disease and other related diseases. Future genetic tests may provide information regarding the relationship between inherited characteristics and a disease condition or treatment being studied.
- Reports on future studies using these stored samples and genetic tests will not be given to you or your doctor and they will not be put in your medical record. Future studies will not be identified with you and will not affect your routine medical care.
- The stored samples will be used for research that has been approved by scientific and ethical review groups at an institution. The samples will not be sold. However, the information obtained from the samples may in the future lead to the development of commercial products. You can change your mind at any time and ask to have your samples destroyed. If your samples have not been processed they will be destroyed from the date of your request. If your sample(s) have been processed then the information will be used as part of the overall study analysis.

Benefits of Stored Material
The benefit of research on stored samples is the information that can be learned about allergy, asthma and other related diseases. There are no direct benefits to you from the collection and storage of these samples. You will not receive any financial gain from studies done using your stored samples.

Risks of Stored Material
We will make every attempt to insure that your personal information will be confidential, but complete confidentiality cannot be guaranteed.

Contact for Further Information
If you would like to receive more information regarding the study then please contact the EAT Study Recruitment Line by telephone on 0800 358 0021.

EAT web address: www.eatstudy.co.uk
www.eatstudy.com

CONSENT FORM

Title of Project:
Randomized controlled trial of early introduction of allergenic foods to induce tolerance in infant

Name of Researcher: Professor Gideon Lack

Contact Details: 0800 358 0021

Please initial box

1. I confirm that I have read and understand the "Post Natal Parent/Guardian Informed Consent Form – Mother & Child" dated 1st August 2011 (Version 2.00) for the above study and have had the opportunity to ask questions. ☐

2. I understand that our participation is voluntary and that we are free to withdraw at any time, without giving any reason, without our medical care or legal rights being affected. ☐

3. I agree that samples of our blood may be used for the research described. I understand how the samples will be collected, that giving samples for this research is voluntary and that I am free to withdraw my approval at any time, without giving any reason, without our medical care or legal rights being affected. ☐

4. I agree to take part in the above study. ☐

Patient Identification Number:

Participant (mother) (print name)

Participant (mother) (signature)

Date

Name of person conducting informed consent discussion (print)

Signature of person conducting informed consent discussion

Date

Making a Decision for Stored Human Subject Material

Please read this section of the consent carefully and answer the questions listed below. It relates to the use of samples taken from you and your child in **future** research that may be undertaken. The samples will be completely de-identified and this will ensure that no findings from this future research can be traced back to the original research subjects. The choice is up to you. No matter what you decide it will not affect the care you receive as part of the study. You should answer both of the statements.

1. I agree to permit the collection and storage of our blood samples for future research studies to learn more about allergy, asthma and the immune system (the body's natural defence system against infectious disease and illness).

   Yes ☐ No ☐

2. In addition, I agree to permit my child's stored samples to be used in future research for genetic (i.e. DNA) testing and for other diseases related to the immune system. I understand that checking yes below gives permission to use my child's stored samples for future genetic testing and future immune system studies that may or may not be related to food allergy.

   Yes ☐ No ☐

Signature _____

Date _____

Thank you for agreeing to take part in the study.

You will be given a copy of the information sheet and a signed consent form to keep.

Appendix 1:
UK Government infant feeding recommendations in relation to the EAT Study

How long to exclusively breastfeed for:
The UK Government recommends that mothers try to breastfeed exclusively for about the first six months of their child's life. Exclusively means giving no other milk substitutes (e.g. infant formula) or any solid foods.
However, we know from the government's own UK 2005 Infant Feeding Survey that despite this recommendation currently only 13% of mothers manage to exclusively breastfeed for 3 months, 7% of mothers manage for 4 months and less than 1% achieves 6 months.

Protecting against infections and allergy:
The UK Government also recommends that "six months is the best age for introducing solids. Before this, your baby's digestive system is still developing and weaning too soon may increase the risk of infections and allergy".

Infections*:* Some studies have suggested a reduced risk of diarrhoeal or chest infections in infants exclusively breastfed for 6 months or more.
However, the recent Millennium Cohort Study which has followed up 15,980 UK infants born between 2000 and 2002 found that the age at which infants had solids introduced into their diets had no effect on the risk of being admitted to hospital for these conditions.

Allergy*:* The UK Government states that babies who have a family history atopy (this means a history of eczema, asthma or hay fever) who are more likely to develop allergies, are particularly recommended to exclusively breast feed for six months and introduce the allergenic foods one at a time, but not before six months of age.
However, a World Health Organization review in 2002 found no evidence that achieving six months exclusive breastfeeding as opposed to 3-4 months exclusive breastfeeding leads to a significant reduction in risk of atopic eczema, asthma, or other atopic outcomes.

Age to introduce solids:
The UK Government also states that "solid foods should never be introduced before four months".
However, we know that the actual age that mothers introduced solids into their infants' diet in the Millennium Cohort Study was 3.8 months. This is almost identical to the governments own figure from the UK 2005 Infant Feeding Survey in which 51% of infants had started solids by four months.

What solids to introduce:
The UK Government currently recommends avoiding introducing foods that may cause allergies before six months and includes in their list: "...wheat-based foods and other foods containing gluten (e.g. bread, rusks, some breakfast cereals), eggs, fish, shellfish, nuts *and* seeds."
However, there is growing evidence that introducing foods too late may increase the chances of an allergy developing. Wheat allergy was increased in one study if it was introduced either before 4 months of age or after 6 months of age.

Peanuts:
The government issued new guidelines with regard to peanut consumption on the 25th August 2009. There is no longer any restriction on a woman consuming peanuts during pregnancy and lactation as part of a healthy balanced diet, unless she is allergic to peanuts. The new guidance states: "If your child already has a known allergy, such as a diagnosed food allergy or diagnosed eczema, or if there is a history of allergy in your child's immediate family (if the child's parents, brothers or sisters have an allergy such as asthma, eczema, hay fever, or other types of allergy), then your child has a higher risk of developing peanut allergy. In these cases you should talk to your GP, health visitor or medical allergy specialist before you give peanuts or foods containing peanuts to your child for the first time."

APPENDIX 3 - EAT one page summary information sheet

EAT
Enquiring About Tolerance

Thank you for your interest in the EAT Study. Volunteering for a clinical research study is a personal decision that requires careful consideration of the potential benefits and risks involved. To help you make an informed choice, this booklet has been prepared by the EAT Study team as a brief introduction, to answer a few of the many questions you might have about the study and what it means to participate.

What are the goals of the EAT Study?

The EAT Study aims to find out how to best prevent food allergy in young children. Current UK Government guidelines recommend exclusive breastfeeding until about six months of age and no early introduction of the foods associated with food allergies ("allergenic foods") as a means of prevention. However, there are other countries, such as Israel, Ghana and others in Africa and Asia, where allergenic foods (peanuts) are a regular part of an infant's diet. Yet, in these countries, peanut allergy is diagnosed far less often than in the UK. So which approach - avoidance or consumption - is right? The EAT Study aims to help provide an answer to this question in order to help decrease the enormous burden that food allergy has on our children.

What about breastfeeding?

Breastfeeding is best for your baby. We are aiming for **all** the mothers who take part in our study to achieve the UK Government recommended aim of at least 6 months of breastfeeding.

How could delaying eating allergenic foods prevent food allergy?

The idea behind the current recommendations is that a baby cannot have a reaction to these foods if they are not eating them. In the EAT Study following the current UK Government infant feeding guidelines will be the first approach that will be compared for preventing food allergies.

How could eating allergenic foods prevent food allergy?

The experience of the countries mentioned above with early introduction of peanuts has also been suggested for other foods. A study has found that delaying the introduction of wheat into an infant's diet was associated with an increased chance of wheat allergy.

Taken together with laboratory evidence, this could mean that by regularly exposing a child's developing immune system to the allergenic foods early in their development, the body gradually learns to accept the presence of the food without causing an allergic reaction.

Early introduction of solids into an infant's diet is not new. A generation ago (1975), 49% of infants in the United Kingdom had been given solids by 8 weeks of age.

A diet that includes regular, measured consumption of some of the main allergenic foods (cow's milk, sesame, wheat, egg, fish and peanut) is the second approach to food allergy prevention that will be tested in the EAT Study.

Why should I be concerned about food allergies in my child?

Food allergies affect 6% of children. Whilst the severity of reactions to foods can vary, food allergies must be taken very seriously. The reaction to a food may be severe - even life-threatening. Whilst the majority of children outgrow allergies to certain foods (cow's milk and egg), for other allergenic foods, such as peanut, sesame and fish, the allergy is more likely to be lifelong. With no cure at present, people allergic to these foods must take extraordinary precautions to avoid all traces of the food.

Who can take part in the EAT Study?

Participation in the EAT Study is open to all mothers planning on exclusively breastfeeding their infant for at least 3 months. Exclusive means that your infant has no other milk (e.g. cow's milk formula) or solid foods before this stage. You must also not be planning on leaving England or Wales in the next couple of years.

If we decide to participate, what will we need to do?

Infants enrolled in the study will be randomly assigned to one of two groups, either the "early introduction" group or the "standard introduction" group. Because the EAT Study is a randomized study, assignment to one group or another is entirely left to chance, and neither parents nor doctors have any influence on the process. If your child is assigned to the "early introduction group", you will be asked to continue to breastfeed your baby until at least six months of age. You will also introduce first baby rice and then some cow's milk based yoghurts from 3 months of age. Subsequently you will introduce the other allergenic foods – peanut, sesame, fish, wheat and egg. By six months of age in addition to still being breastfed your child will be consuming these foods at least twice per week.

If your child is assigned to the "standard introduction group" you will be asked to follow the standard UK Government infant feeding guidelines: exclusive breastfeeding until around six months of age and no early introduction of the allergenic foods. After 6 months the UK Government leaves it up to your discretion when you want to introduce these allergenic foods. The study will last until your child is 3 years of age. We will see all the children at enrolment onto the study (at 3 months of age), when they are 1 year old and then at 3 years of age when they finish the study. All the assessments will take place at the Evelina Children's Hospital at St Thomas' Hospital.

Is it difficult to follow the dietary recommendations?

Mothers in the "early introduction" group will be given a personalised diary by one of the study registered dieticians giving you a timetable of which foods are to be introduced and in what order. They will be able to help with practical advice and information to assist you in introducing these foods into your child's diet. EAT Study dieticians will also be available to answer specific questions or provide advice as needed by participants.

What happens during the study visits?

Clinic visits allow EAT Study specialists to assess the health of each child and their progress in the study, as well as provide an opportunity for parents to raise any questions or concerns directly with the clinical study team. A typical study visit will entail an examination for eczema, tests to determine whether your child is allergic to the allergenic foods (early introduction arm), and the collection of a blood sample to assess your child's health and their immune system's reaction to the foods. The doctors may also ask about medical and dietary histories of your child and family.

What happens if my child is already allergic to the foods?

Children enrolled in the EAT study in the "early introduction" group will be screened for evidence of pre-existing food allergies. Any infant with a result suggesting a possible allergy to one of the foods will be given their first planned exposure to the food under the medical supervision of EAT Study specialists at Evelina Children's Hospital at St Thomas' Hospital. In this environment, any resulting allergic reaction can be diagnosed quickly and appropriate medical interventions to reverse the reaction may begin without delay.

How will you find out if my child develops a food allergy?

During the course of the study, we will contact you on a regular basis to ask if your child has had any symptoms suggestive of a food allergy. You will also be able to contact us by telephone if you think your child may have had a reaction to a food. If the symptoms are suggestive of food allergy we will arrange for your child to be assessed at the Evelina Children's' Hospital. EAT Study staff will provide individual counselling on treating and dealing with childhood allergies and continue to monitor your child's progress for the duration of the study. Referrals will be made outside the study as appropriate.

Are there any other risks to participating in the study?

While every precaution has been and will be taken to ensure the safety of all procedures and recommendations involved in the EAT Study, volunteering for a clinical research study generally carries some potential risk to its participants, both known and unknown. EAT Study staff will explain the potential risks to you in detail and answer any questions you might have before you decide to participate.

What if I still have questions?

Our doctors and nurses will be happy to answer any questions you might have about participating in the EAT Study and may be contacted on 020 7188 4877 or visit our website at www.eatstudy.co.uk or email us at EatStudy@gstt.nhs.uk. We also encourage you to discuss enrolling your child in the EAT Study with your spouse, friends and family doctor, in order to assist you in making a confident informed decision on whether to participate.

APPENDIX 4 - EAT maternal skin prick test addendum consent form

EAT
Enquiring About Tolerance

Guy's and St Thomas' NHS
NHS Foundation Trust

St Thomas' Hospital
Lambeth Palace Road
London SE1 7EH
EAT Study Recruitment Line: 0800 358 0021

Randomized controlled trial of early introduction of allergenic foods to induce tolerance in infants

The Enquiring About Tolerance (EAT) Study

Parent Informed Consent Form – **Mother**

Addendum: Maternal consent for skin prick testing

What happens to me at the 3 year clinic visit?

The original consent form that was signed at the enrolment of your child onto the EAT study included information about the parents' participation in the study. As the mother of the child enrolled on the EAT study, you were randomly allocated to either exclusively breastfeed your child for around six months (standard introduction group) or to continue breastfeeding but commence introducing the allergenic foods early (early introduction group). The consent form also specified that we would take a blood sample from you at your child's three year visit and that this sample will be stored and will subsequently be used to investigate your own allergy status and how it relates to that of your child.

We would also like to undertake skin prick testing which gives an immediate assessment of your potential allergy status. This is exactly the same procedure that your child underwent at the one year visit (and at enrolment if your child was in the early introduction group).

Discomfort associated with study investigations

Some people find skin prick testing slightly uncomfortable (to some it feels like a prickle, others do not feel anything). After skin prick testing has been performed you develop a small hive (a bit like nettle rash) to any of the tests you are potentially allergic to. This can be slightly itchy for about 10 minutes. Most people tolerate this very well but if necessary a small dose of antihistamine will be given after the testing to minimise the discomfort.

What will happen to the results of the tests?

The skin prick tests provide an immediate result. We will discuss the interpretation of these results with you at that time. The blood samples will not be analysed immediately and as they measure the same kind of allergy antibodies as the skin tests the reports on the blood samples will not be given to you or your doctor.

CONSENT FORM

Title of Project:
Randomized controlled trial of early introduction of allergenic foods to induce tolerance in infant
Addendum: Maternal consent for skin prick testing

Name of Researcher: Professor Gideon Lack Contact Details: 0800 358 0021

Please initial box

1. I confirm that I have read and understand the "Parent Informed Consent Form – Mother" dated 1st August 2012 (Version 1.00). Addendum: Maternal consent for skin prick testing" and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I agree to skin prick testing as part of the above study. ☐

_____
Participant (mother) (print name)

_____
Participant (mother) (signature)

_____
Date

_____
Name of person conducting informed consent discussion (print)

_____
Signature of person conducting informed consent discussion

_____
Date

Thank you for agreeing to have skin prick testing undertaken.

You will be given a copy of the information sheet/consent form to keep.

APPENDIX 5 - EAT paternal skin prick & blood test addendum consent form

EAT
Enquiring About Tolerance

Guy's and St Thomas' NHS
NHS Foundation Trust

St Thomas' Hospital
Lambeth Palace Road
London SE1 7EH
EAT Study Recruitment Line: 0800 358 0021

Randomized controlled trial of early introduction of allergenic foods to induce tolerance in infants

The Enquiring About Tolerance (EAT) Study

Parent Informed Consent Form – **Father**

Paternal consent for skin prick testing/blood test

What happens to me at the 3 year clinic visit?

The original consent form that was signed at the enrolment of your child onto the EAT study included information about the parents' participation in the study, specifically that we would take a blood sample from you at your child's three year visit and that this sample will be stored and will subsequently be used to investigate your own allergy status in relation to that of your child.

We would also like to undertake skin prick testing which gives an immediate assessment of your potential allergy status. This is exactly the same procedure that your child underwent at the one year visit (and at enrolment if your child was in the early introduction group).

At the enrolment visit the original consent form was signed by the mother of the EAT participant. Whether or not you also signed the original consent form, we need you to read this new consent form carefully as it specifically seeks your own consent for having both the blood test and skin prick testing undertaken.

Discomfort associated with study investigations

Skin prick testing

Some people find skin prick testing slightly uncomfortable (to some it feels like a prickle, others do not feel anything). After skin prick testing has been performed you develop a small hive (a bit like nettle rash) to any of the tests you are potentially allergic to. This can be slightly itchy for about 10 minutes. Most people tolerate this very well but if necessary a small dose of antihistamine will be given after the testing to minimise the discomfort.

Blood Test

The blood test may cause discomfort. However this can be minimised using a local anaesthetic ('numbing') cream if required. An experienced phlebotomist, nurse or doctor will take the blood. Other side effects of the blood test include a small risk of bleeding, bruising, or infection at the site.

What will happen to the results of the tests?

The skin prick tests provide an immediate result. We will discuss the interpretation of these results with you at that time. The blood samples will not be analysed immediately and as they measure the same kind of allergy antibodies as the skin tests the reports on the blood samples will not be given to you or your doctor.

CONSENT FORM

Title of Project:

Randomized controlled trial of early introduction of allergenic foods to induce tolerance in infant

Paternal consent for skin prick testing/blood test

Name of Researcher: Professor Gideon Lack Contact Details: 0800 358 0021

Please initial box

1. I confirm that I have read and understand the "Parent Informed Consent Form – Father" dated 1st August 2012 (Version 1.00). Addendum: Paternal consent for skin prick testing/blood test" and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I agree that the blood sample will be used for the research described. I understand how the sample will be collected, that giving samples for this research is voluntary and that I am free to withdraw my approval at any time, without giving any reason, without my medical care or legal rights being affected. ☐
4. I agree to skin prick and blood testing as part of the above study. ☐

_____

Participant (father) (print name)

_____

Participant (father) (signature)

_____

Date

_____

Name of person conducting informed consent discussion (print)

_____

Signature of person conducting informed consent discussion

_____

Date

Thank you for agreeing to have this testing undertaken.

You will be given a copy of this information sheet/consent form to keep.

Storage of Blood Samples

You have the option to have your sample of blood stored for use in **future** research studies. These future studies may help researchers learn more about allergy, asthma and the immune system (the body's natural defence system against infectious disease and illness).

- Reports on future studies using these stored samples will not be given to you or your doctor and they will not be put in your medical record. Future studies will not be identified with you and will not affect your routine medical care.
- The stored samples will be used for research that has been approved by scientific and ethical review groups at an institution. The samples will not be sold. However, the information obtained from the samples may in the future lead to the development of commercial products. You can change your mind at any time and ask to have your samples destroyed. If your samples have not been processed they will be destroyed from the date of your request. If your sample(s) have been processed then the information will be used as part of the overall study analysis.

Benefits of Stored Material

The benefit of research on stored samples is the information that can be learned about allergy, asthma and other related diseases. There are no direct benefits to you from the collection and storage of these samples. You will not receive any financial gain from studies done using your stored samples.

Risks of Stored Material

We will make every attempt to insure that your personal information will be confidential, but complete confidentiality cannot be guaranteed.

Contact for Further Information

If you would like to receive more information about your own involvement in the EAT study then please contact the EAT Study Team by telephone on 0800 358 0021.

Making a Decision for Stored Human Subject Material

Please read this section of the consent form carefully and answer the question listed below. It relates to the use of the blood sample taken from you in **future** research that may be undertaken. The sample will be completely de-identified and this will ensure that no findings from this future research can be traced back to the original research subjects. The choice is up to you. No matter what you decide it will not affect the medical care you receive.

1. I agree to permit the collection and storage of my blood sample for future research studies to learn more about allergy, asthma and the immune system (the body's natural defence system against infectious disease and illness).

Yes ☐ No ☐

Signature _____

Date _____

APPENDIX 6 - Open food challenge (<1 year)

EAT
Enquiring About Tolerance

Open Food Challenge (<1 year)

Wheat ☐ Sesame ☐ Peanut ☐ Cow's milk ☐ Egg ☐ Cod ☐

OFC Date: _____

Consent form

1. Benefits and risks of OFC explained to family	Yes ☐	No ☐
2. Signed by parent	Yes ☐	No ☐
3. Copy given to parents	Yes ☐	No ☐
4. Copy placed in notes	Yes ☐	No ☐

Emergency equipment

1. Anaphylaxis drug box present	Yes ☐	No ☐
2. Resuscitation trolley present	Yes ☐	No ☐
3. Medications pre-prescribed	Yes ☐	No ☐
4. Emergency medications drawn up *1:1000 adrenaline in 1ml syringe for weight <7.5kg, EpiPen Jr if 7.5kg+*	Yes ☐	No ☐
5. Bed space oxygen and suction checked	Yes ☐	No ☐
6. PICU informed (if high risk challenge)	Yes ☐	NA ☐

Challenge food

1. Brought in by family (egg, milk, fish)	Yes ☐	No ☐
2. Store in fridge until needed	Yes ☐	No ☐

*Challenge team present (write * next to lead team member for child)*

Doctor: _____

Nurse: _____

Dietician: _____

Signature of Team Member: _____ Date: _____

Previous reactions

Previous reaction/s to the challenge food: Yes ☐ No ☐

If yes: Date of most recent reaction: _____

Symptoms:_____

_____

Route: Ingestion ☐ Contact ☐ Inhalation ☐

Amount of food that caused the reaction: _____

Time from ingestion /exposure to initial symptoms: _____

Treatment received: Epinephrine ☐ Antihistamine ☐ Other ☐_____

History of anaphylaxis to the challenge food: Yes ☐ No ☐

If yes: Date of anaphylactic reaction: _____

Most recent test results

Skin prick test (date): _____

Specific IgE (date): _____

Other current food allergies: _____

Medical Examination

Past medical history (specifically history of wheeze/asthma):

_____

_____

Current medications Yes ☐ No ☐

_____

_____

Signature of Team Member: _____ Date: _____

Baseline physical examination

_____

_____

_____

Weight: _____

Cannulation

Cannulation required Yes ☐ No ☐

Due to history of persistent asthma Yes ☐ No ☐

Due to history of previous food anaphylaxis Yes ☐ No ☐

Skin Prick Tests

Required: Yes ☐ No ☐

	Left arm/Back				Right arm/Back		
	Wheal Diameter	**Wheal** Perpendicular	**Wheal** Mean		**Wheal** Diameter	**Wheal** Perpendicular	**Wheal** Mean
Positive control				**Positive control**			
Negative control				**Negative control**			

Signature of Team Member: _____ Date: _____

Open food challenge – observations*

Dose of food protein (grams)	Obs time	Time dose started	Time dose completed	Pulse	Resps	02 sats	Temp	Other eg BP, Cap refill
0.01g†								
0.05g†								
0.1g								
0.2g								
0.5g								
1.2g								
OR 2g cumulative dose								
+30 minutes								
+60 minutes								
+90 minutes								
+120 minutes								

*observations to be recorded pre dose † at investigator's discretion

Challenge comments:

_____

_____

Signature of Team Member: _____ Date: _____

Open food challenge - symptoms and signs

	Major criteria						Minor criteria				
Dose of food protein (grams)	**Itchy rash**	**Resp signs***	**≥3 urticarial lesions**	**Angio-edema**	**Hypo-tension for age**	**Severe abdo pain†**	**Vomiting**	**Diarrhoea**	**Nose or eyes rubbing ≥3 mins**	**Rhino--rhoea ≥3 mins**	**Scratch-ing ≥3 mins**
0.01g*											
0.05g*											
0.1g											
0.2g											
0.5g											
1.2g											
OR 2g cumulative dose											
+30 minutes											
+60 minutes											
+90 minutes											
+120 minutes											

* At least one of: Wheezing; Inability to speak; Stridor; Dysphonia; Aphonia
† Such as abnormal stillness or doubling over that persists for ≥3 minutes

Challenge outcome: Positive **(1+ major and/or 2+ minor criteria)** ☐ Negative ☐ Indeterminate ☐

Time stopped: _____ Total dose ingested (g food protein): _____

Signature of Team Member: _____ Date: _____

Treatment given

_____

_____

_____

_____

_____

Post challenge care

Emergency care plan (B)	Yes ☐	No ☐
Delayed reaction letter (B)	Yes ☐	No ☐
GP letter (B)	Yes ☐	No ☐
Allergy reaction training (+)	Yes ☐	No ☐
AE form updated (SNAP) (B)	Yes ☐	No ☐
Possible food allergy database (B)	Yes ☐	No ☐
Local allergy referral (+)	Yes ☐	No ☐
Prescription (B)	Yes ☐	No ☐

EpiPen (for use when wt>7.5) ☐ Antihistamine ☐ Other: _____

Dietician education

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Revised order of introduction of key foods *(if applicable)*: __ __ __ __ __

Signature of Team Member: _____ Date: _____

Discharge decision

Decision made by: _____

Time discharged: _____

Follow up

24hr post challenge phone call: Yes ☐ No ☐

_____

_____

_____

_____

_____

_____

Signature of Team Member: _____ Date: _____

APPENDIX 7 - Double blind placebo controlled food challenge (1 year+)

DBPCFC (≥1 year)

Date: _____

Wheat ☐ Sesame ☐ Peanut ☐ Cow's milk ☐ Egg ☐ Cod ☐

Low dose pair of 0.025g required*? Yes ☐ No ☐

***Infrequent/never consumer of <u>peanut/sesame</u>, no previous challenge, SPT ≥5mm**

Consent form

1. Benefits and risks of DBPCFC explained to family	Yes ☐	No ☐
2. Signed by parent	Yes ☐	No ☐
3. Copy given to parents	Yes ☐	No ☐
4. Copy placed in notes	Yes ☐	No ☐

Emergency equipment

1. Anaphylaxis drug box present	Yes ☐	No ☐
2. Resuscitation trolley present	Yes ☐	No ☐
3. Medications pre-prescribed	Yes ☐	No ☐
4. Emergency medications drawn up	Yes ☐	No ☐
5. Bed space oxygen and suction checked	Yes ☐	No ☐

Challenge food

1. Brought in by family (egg, milk, fish)	Yes ☐	No ☐
2. Store in fridge until needed	Yes ☐	No ☐

*Challenge team present (please place a * next to lead team member)*

Doctor: _____ Nurse: _____ Dietician: _____

Signature of Team Member: _____ Date: _____

Previous reactions

Previous reaction/s to the challenge food: Yes ☐ No ☐

If yes, date of most recent reaction: _____

Symptoms:_____

_____

Route: Ingestion ☐ Contact ☐ Inhalation ☐

Amount of food that caused the reaction: _____

Time from ingestion /exposure to initial symptoms: _____

Treatment received: Epinephrine ☐ Antihistamine ☐ Other ☐_____

History of anaphylaxis to the challenge food: Yes ☐ No ☐

If yes: Date of anaphylactic reaction: _____

Most recent test results

Skin prick test (date): _____

Medical Examination

Past medical history (specifically history of wheeze/asthma):

_____

_____

Current medications Yes ☐ No ☐

_____

_____

NB: Ineligible for challenge if child has received:

- short-acting beta-2 agonists in last 12 hours *e.g. salbutamol (Ventolin or terbutaline (Bricanyl)*
- long-acting beta-2 agonists in last 24 hours *e.g. salmeterol (Serevent) or formoterol (Oxis)*
- short-acting antihistamines in the last 48 hours *e.g. chlorphenamine (Piriton)*
- long-acting antihistamines in the last 7 days *e.g. cetirizine (Zertec) or loratadine (Clarityn*

Remember: some cough and cold medicines and anti-itch medicines contain antihistamines

Baseline physical examination **Weight**: _____

_____

_____

Cannulation

Cannulation required	Yes ☐	No ☐
Due to history of persistent asthma:	Yes ☐	
Due to history of previous food anaphylaxis	Yes ☐	
Low starting dose challenge	Yes ☐	

Signature of Team Member: _____ Date: _____

DBPCFC – observations* Baseline measurements: BP:_____ Temp:_____

Food dose	Obs time	Time dose started	Time dose completed	Pulse	Resps	02 sats	Other eg, BP, Cap refill
Low dose A‡							
Low dose B‡							
Dose 1							
Dose 2							
Dose 3							
Dose 4							
Dose 5							
Repeated dose† ___							
Open dose							
+30 minutes							
+60 minutes							
+90minutes							
+120 minutes							

*observations to be recorded pre dose † at investigator's discretion

‡ Infrequent/never consumer of <u>peanut/sesame at three year visit</u>, no previous challenge, SPT ≥5mm (start with low dose pair of 0.025g)

Challenge comments **Acute reaction sheet completed: Yes ☐**

_____

_____

_____

Signature of Team Member: _____ Date: _____

DBPCFC - symptoms and signs

	Major criteria						Minor criteria					Other symptoms and/or signs
Dose of food protein (grams)	**Itchy rash**	**Resp signs***	**≥3 urticarial lesions**	**Angio-edema**	**Hypo-tension for age**	**Severe abdo pain†**	**Vomiting**	**Diarrhoea**	**Nose or eyes rubbing ≥3 mins**	**Rhino--rhoea ≥3 mins**	**Scratch-ing ≥3 mins**	
Low dose A												
Low dose B												
Dose 1												
Dose 2												
Dose 3												
Dose 4												
Dose 5												
Repeated dose												
Open dose												
+30 minutes												
+60 minutes												
+90 minutes												
+120 minutes												

* At least one of: Wheezing; Inability to speak; Stridor; Dysphonia; Aphonia † Such as abnormal stillness or doubling over that persists for ≥3 minutes

Challenge outcome: Positive **(1+ major and/or 2+ minor criteria)** ☐ Negative ☐ Indeterminate ☐ Incomplete ☐
(If indeterminate or incomplete: returning for repeat DBPCFC ☐ or cumulative open dose ☐)

Time stopped: _____ Total dose ingested (g food protein): _____

Signature of Team Member: _____ Date: _____

Treatment given

_____

_____

_____

_____

_____

Post challenge care

Emergency care plan & training (B)	Yes ☐	No ☐
Delayed reaction letter (B)	Yes ☐	No ☐
GP letter (B)	Yes ☐	No ☐
Possible food allergy database done/updated (B)	Yes ☐	No ☐
Prescription (B)	Yes ☐	No ☐

EpiPen ☐ Antihistamine ☐ Other: _____

Dietitian education

_____

_____

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_____

_____

Signature of Team Member: _____ Date: _____

Discharge decision

Decision made by: _____ Time discharged: _____

Follow up

Best follow up phone number _____

Best follow up time _____

24hr post challenge phone call made: Yes ☐ No ☐

Comments _____
_____
_____
_____
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_____

Signature of Team Member: _____ Date: _____

APPENDIX 8 - Double blind placebo controlled food challenge (3 years)

EAT
Enquiring About Tolerance

DBPCFC (≥3 year)

Date: _____

Wheat ☐ Sesame ☐ Peanut ☐ Cow's milk ☐ Egg ☐ Cod ☐

Low dose pair of 0.025g required*? Yes ☐ No ☐

***Infrequent/never consumer of <u>peanut/sesame</u>, no previous challenge, SPT ≥5mm**

Consent form

1. Benefits and risks of DBPCFC explained to family	Yes ☐	No ☐
2. Signed by parent	Yes ☐	No ☐
3. Copy given to parents	Yes ☐	No ☐
4. Copy placed in notes	Yes ☐	No ☐

Emergency equipment

1. Anaphylaxis drug box present	Yes ☐	No ☐
2. Resuscitation trolley present	Yes ☐	No ☐
3. Medications pre-prescribed	Yes ☐	No ☐
4. Emergency medications drawn up *(EpiPen Jr)*	Yes ☐	No ☐
5. Bed space oxygen and suction checked	Yes ☐	No ☐

Challenge food

1. Brought in by family (egg, milk, fish)	Yes ☐	No ☐
2. Store in fridge until needed	Yes ☐	No ☐

*Challenge team present (please place a * next to lead team member)*

Doctor: _____ Nurse: _____ Dietician: _____

Signature of Team Member: _____ Date: _____

Previous reactions

Previous reaction/s to the challenge food: Yes ☐ No ☐

If yes, date of most recent reaction: _____

Symptoms:_____

_____

Route: Ingestion ☐ Contact ☐ Inhalation ☐

Amount of food that caused the reaction: _____

Time from ingestion /exposure to initial symptoms: _____

Treatment received: Epinephrine ☐ Antihistamine ☐ Other ☐_____

History of anaphylaxis to the challenge food: Yes ☐ No ☐

If yes: Date of anaphylactic reaction: _____

Most recent test results

Skin prick test (date): _____

Medical Examination

Past medical history (specifically history of wheeze/asthma):

_____

_____

Current medications Yes ☐ No ☐

_____

_____

NB: Ineligible for challenge if child has received:

- short-acting beta-2 agonists in last 12 hours *e.g. salbutamol (Ventolin or terbutaline (Bricanyl)*
- long-acting beta-2 agonists in last 24 hours *e.g. salmeterol (Serevent) or formoterol (Oxis)*
- short-acting antihistamines in the last 48 hours *e.g. chlorphenamine (Piriton)*
- long-acting antihistamines in the last 7 days *e.g. cetirizine (Zertec) or loratadine (Clarityn*

Remember: some cough and cold medicines and anti-itch medicines contain antihistamines

Baseline physical examination **Weight**: _____

_____

_____

Cannulation

Cannulation required Yes ☐ No ☐

Due to history of persistent asthma: Yes ☐

Due to history of previous food anaphylaxis Yes ☐

Low starting dose challenge Yes ☐

Signature of Team Member: _____ Date: _____

DBPCFC – observations* Baseline measurements: BP:_____ Temp:_____

Food dose	Obs time	Time dose started	Time dose completed	Pulse	Resps	02 sats	Temp	Other eg, Cap refill
Low dose A‡								
Low dose B‡								
Dose 1								
Dose 2								
Dose 3								
Dose 4								
Dose 5								
Repeated dose† ___								
Open dose								
+30 minutes								
+60 minutes								
+90minutes								
+120 minutes								

*observations to be recorded pre dose † at investigator's discretion

‡ Infrequent/never consumer of <u>peanut/sesame at three year visit</u>, no previous challenge, SPT ≥5mm (start with low dose pair of 0.025g)

Challenge comments **Acute reaction sheet completed: Yes ☐**

_____

_____

_____

Signature of Team Member: _____ Date: _____

DBPCFC - symptoms and signs

	Major criteria						Minor criteria					Other symptoms and/or signs
Dose of food protein (grams)	**Itchy rash**	**Resp signs***	**≥3 urticarial lesions**	**Angio-edema**	**Hypo-tension for age**	**Severe abdo pain†**	**Vomiting**	**Diarrhoea**	**Nose or eyes rubbing ≥3 mins**	**Rhino--rhoea ≥3 mins**	**Scratch-ing ≥3 mins**	
Low dose A												
Low dose B												
Dose 1												
Dose 2												
Dose 3												
Dose 4												
Dose 5												
Repeated dose												
Open dose												
+30 minutes												
+60 minutes												
+90 minutes												
+120 minutes												

* At least one of: Wheezing; Inability to speak; Stridor; Dysphonia; Aphonia † Such as abnormal stillness or doubling over that persists for ≥3 minutes

Challenge outcome: Positive **(1+ major and/or 2+ minor criteria)** ☐ Negative ☐ Indeterminate ☐ Incomplete ☐
(If indeterminate or incomplete: returning for repeat DBPCFC ☐ or cumulative open dose ☐)

Time stopped: _____ Total dose ingested (g food protein): _____

Signature of Team Member: _____ Date: _____

Treatment given

_____

_____

_____

_____

_____

Post challenge care

Emergency care plan & training (B)	Yes ☐	No ☐
Delayed reaction letter (B)	Yes ☐	No ☐
GP letter (B)	Yes ☐	No ☐
Possible food allergy database done/updated (B)	Yes ☐	No ☐
Prescription (B)	Yes ☐	No ☐

EpiPen ☐ Antihistamine ☐ Other: _____

Dietitian education

_____

_____

_____

_____

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_____

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_____

_____

_____

_____

_____

_____

_____

_____

_____

Signature of Team Member: _____ Date: _____

Discharge decision

Decision made by: _____ Time discharged: _____

Follow up

Best follow up phone number _____

Best follow up time _____

24hr post challenge phone call made: Yes ☐ No ☐

Comments _____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Signature of Team Member: _____ Date: _____

APPENDIX 9 - Frequent consumer challenge (3 years)

EAT
Enquiring About Tolerance

FREQUENT CONSUMER CHALLENGE (≥3 year)

Date: _____

Wheat ☐ Sesame ☐ Peanut ☐ Cow's milk ☐ Egg ☐ Cod ☐

Consent form

1. Benefits and risks of OPEN FC explained to family	Yes ☐	No ☐
2. Signed by parent	Yes ☐	No ☐
3. Copy given to parents	Yes ☐	No ☐
4. Copy placed in notes	Yes ☐	No ☐

Emergency equipment

1. Anaphylaxis drug box present	Yes ☐	No ☐
2. Resuscitation trolley present	Yes ☐	No ☐
3. Bed space oxygen and suction checked	Yes ☐	No ☐

Challenge food

1. Brought in by family (egg, milk, fish)	Yes ☐	No ☐
2. Store in fridge until needed	Yes ☐	No ☐

*Challenge team present (please place a * next to lead team member)*

Doctor: _____ Nurse: _____ Dietician: _____

Signature of Team Member: _____ Date: _____

Previous reactions

Previous reaction/s to the challenge food: Yes ☐ No ☐

If yes, date of most recent reaction: _____

Symptoms:_____

_____

Route: Ingestion ☐ Contact ☐ Inhalation ☐

Amount of food that caused the reaction: _____

Time from ingestion /exposure to initial symptoms: _____

Treatment received: Epinephrine ☐ Antihistamine ☐ Other ☐_____

History of anaphylaxis to the challenge food: Yes ☐ No ☐

If yes: Date of anaphylactic reaction: _____

Most recent test results

Skin prick test (date): _____

Other current food allergies: _____

Medical Examination

Past medical history (specifically history of wheeze/asthma):

_____

_____

Current medications Yes ☐ No ☐

_____

_____

Baseline physical examination **Weight**: _____

_____

_____

_____

Signature of Team Member: _____ Date: _____

OPEN FC – observations Baseline observations: Temp:_____ BP:_____

Food dose	Obs time	Time dose started	Time dose completed	Pulse	Resps	02 sats	Other eg BP, Cap refill
Open dose							
*Split dose**							
+30 minutes							
+60 minutes							

* If required

OPEN FC - symptoms and signs

	Major criteria						Minor criteria					Other symptoms and/or signs
Dose of food protein (grams)	Itchy rash	Resp signs*	≥3 urticarial lesions	Angio-edema	Hypo-tension for age	Severe abdo pain†	Vomiting	Diarrhoea	Nose or eyes rubbing ≥3 mins	Rhino--rhoea ≥3 mins	Scratch-ing ≥3 mins	
Open dose												
Split dose¶												
+30 minutes												
+60 minutes												

* At least one of: Wheezing; Inability to speak; Stridor; Dysphonia; Aphonia ¶ If required
† Such as abnormal stillness or doubling over that persists for ≥3 minutes

Challenge outcome: Positive **(1+ major and/or 2+ minor criteria)** ☐ Negative ☐ Indeterminate ☐

Time stopped: _____ Total dose ingested (g food protein): _____

Signature of Team Member: _____ Date: _____

Treatment given

Post challenge care

Possible food allergy database done/updated (B) Yes ☐ No ☐

Dietitian education ONLY IF POSTIVE CHALLENGE

Signature of Team Member: _____ Date: _____

APPENDIX 10 - FPIES challenge (1 year+)

EAT
Enquiring About Tolerance

ID sticker

FPIES CHALLENGES (≥1 year) Date: _____

Wheat ☐ Sesame ☐ Peanut ☐ Cow's milk ☐ Egg ☐ Cod ☐

Consent form

1. Benefits and risks of FPIES challenge explained to family	Yes ☐	No ☐
2. Signed by parent	Yes ☐	No ☐
3. Copy given to parents	Yes ☐	No ☐
4. Copy placed in notes	Yes ☐	No ☐

Emergency equipment

1. Anaphylaxis drug box present	Yes ☐	No ☐
2. Resuscitation trolley present	Yes ☐	No ☐
3. Medications (including volume 20ml/kg) pre-prescribed	Yes ☐	No ☐
4. Bed space oxygen and suction checked	Yes ☐	No ☐
5. Cannula inserted	Yes ☐	

Carrier/Challenge foods

1. Brought in by family	Yes ☐	No ☐
2. Store in fridge until needed	Yes ☐	No ☐

*Challenge team present (please place a * next to lead team member)*

Doctor: _____ Nurse: _____ Dietician: _____

Signature of Team Member: _____ Date: _____

Previous reactions

Severity of reaction?

Fluid support required (IV, NG, ORT) ☐

Admitted to hospital ☐

Systemic compromise (listless, unresponsive, colour change) ☐

Severe (any of above) ☐ ***Not severe*** ☐

Date of most recent FPIES reaction: _____

Amount of food that caused the reaction: _____

Time from ingestion /exposure to initial symptoms: _____

Treatment received: _____

Most recent test results

Skin prick test (date): _____

Other current food allergies: _____

Medical Examination

Past medical history (specifically history of wheeze/asthma):

_____

_____

Current medications Yes ☐ No ☐

_____

_____

Baseline physical examination **Current Weight**: _____

_____

_____

_____

Signature of Team Member: _____ Date: _____

FPIES CHALLENGE PROCEDURE

(Dietitians to complete calculations)

1) No history of severe FPIES reaction

Initial challenge dose

0.3g/kg x weight_____= _____g food protein (max 3g)?

Give this amount in 2-3 portions within 45 minutes

Time total challenge dose completed: _____

2) History of severe FPIES reaction

Initial challenge dose

0.06g/kg x weight_____= _____g food protein?

Time initial challenge dose completed: _____

1 & 2) Both groups

Age appropriate portion
Observe for four hours. Then give a **2 g** protein portion of the challenge food (an age appropriate single portion – i.e. an EAT portion).

Time second dose 2 completed: _____

Observe for a further 2 hours after ingestion of the second dose.

FPIES CHALLENGE - symptoms and signs

Vomiting	☐	*Number of episodes:* _____
Diarrhoea	☐	*Number of episodes:* _____
Colour change (pallor/cyanosis)	☐	
Blood passed PR	☐	
Neutrophil count raised	☐	
Faecal eosinophils present	☐	

Acute challenge outcome:

Positive	☐
Negative	☐
Indeterminate*	☐

*Indeterminate if vomiting = 1 episode AND/OR diarrhoea = 1 episode

Time stopped: _____

Total dose ingested (g food protein): _____

Signature of Team Member: _____ Date: _____

Treatment given

_____

_____

_____

_____

Signature of Team Member: _____ Date: _____

FPIES CHALLENGE – observations* Baseline observations: Temp:_____ BP:_____

Food dose	Obs time	Pulse	Resps	02 sats	Other eg BP, Cap refill	Other observations
Baseline						
Initial symptoms						
+ 15 minutes						
+ 30 minutes						
+ 45minutes						
+ 60 minutes						
+ 90 minutes						
+120 minutes						
+150 minutes						
+180 minutes						
+240 minutes						

Challenge Comments

_____

_____

_____

_____

Signature of Team Member: _____ Date: _____

Post Challenge Care

Emergency care plan (B)	Yes ☐	No ☐
GP letter (B)	Yes ☐	No ☐
Possible food allergy database done/updated (B)	Yes ☐	No ☐

Post Challenge Consumption Plan

Consume EAT portion (2g protein) daily for next 7 days

Discharge decision

Decision made by: _____ Time discharged: _____

Follow up

1 WEEK post challenge phone call: Yes ☐ No ☐

Delayed challenge outcome:

Positive ☐

Negative ☐

Indeterminate* ☐

*Indeterminate if vomiting = 1 episode AND/OR diarrhoea = 1 episode

Visit comments

_____

_____

_____

_____

_____

Dietitian Comments/Education

_____

_____

_____

_____

_____

_____

_____

_____

_____

Signature of Team Member: _____ Date: _____

APPENDIX 11 - Enrolment visit (3 months) proforma

EAT
Enquiring About Tolerance

Time of arrival: ___:___

Pre-screening Questionnaires.

Mother's diet completed: Yes ☐ No ☐

3/12 Questionnaire completed: Yes ☐ No ☐

Comment: _____

Screening Questions.

1. **Age** between 13^{+0} and 17^{+0} weeks Yes ☐ No ☐
2. **Exclusively** breast fed (breast milk) until 3/12 visit Yes ☐ No ☐
3. Singleton pregnancy Yes ☐ No ☐
4. Term delivery Yes ☐ No ☐
5. Previous significant health concerns Yes ☐ No ☐
6. Planning to move abroad in the next 3 years Yes ☐ No ☐
7. Family currently excluding any one of the study foods from the household Yes ☐ No ☐
8. Informed consent taken Yes ☐ No ☐
9. Both parents aware of child's participation in study Yes ☐ No ☐

   If no, please give details……..
10. Any previous blood test? Yes ☐ No ☐

    If yes, give details if any issues……..

Signature of Team Member: _____ Date: _____

Current Health Questions.

Is your child currently fit and well? Yes ☐ No ☐

If no, please give details:

_____

_____

_____

Please list any regular or recently taken medications/vitamins/supplements:

Name	Dose	Frequency	Start Date	Stop Date

Randomisation.

Has the participant been randomised? Yes ☐ No ☐

If no, please give details:

_____

_____

_____

Into which group has the participant been randomised (please circle)?

INTERVENTION (Early Weaning)	CONTROL (Standard Weaning)
Food 1:	
Food 2:	
Food 3:	
Food 4:	

Signature of Team Member: _____ Date: _____

Birth History. *(from Red Book)*

Mode of delivery: Vaginal delivery ☐ C-Section ☐
Gestational birth age: _____ Birth weight (kg): _____

SKIN SWABS TAKEN: Yes ☐ No ☐

Label swabs on packaging, sterile gloves, 2 drops of normal saline on each swab, one from each direction. Swab is taken from a 2x2cm area. **Ensure that sterile gloves holding the swab does not touch anything apart from the child's skin.**

Left antecubital fossa (elbow crease, abbreviation: EC) Yes ☐ No ☐
Eczema present Yes ☐ No ☐

Left outer forearm (1/3 between wrist and elbow, FA) Yes ☐ No ☐
Eczema present Yes ☐ No ☐

Control swab taken (open & close in mid air, CS) Yes ☐ No ☐

Each swab needs to be labelled with child's bar code & ID, date of today, and site swabbed as well as whether eczema was present or not (Y/N). All samples need to go into rack in -80C freezer in Well Child lab as soon as possible. Rack posititions need to be logged on Excel spreadsheet.

TEWL.

Any moisturiser (including bath oils) used on baby's skin in the last 24 hours? Yes ☐ No ☐

If yes, give details (what, where and when?):

_____

Measurement	**1st**	**2nd**	**3rd**
Flux			
Room temperature (°C) [target 20+/-2°C]			
Room humidity (%) [target 38-50%]			
Time of TEWL measurement	_____:_____		
Child calm throughout	Yes ☐ No ☐		
Decent measurement curves	Yes ☐ No ☐		

Signature of Team Member: _____ Date: _____

Anthropometry.

Measurement	1st	2nd	3rd
LEFT triceps skin fold (mm)			
LEFT subscapular skin fold (mm)			
LEFT Mid Upper Arm Circumference (cm)			
Length (cm)			
Head circumference (cm)			
Weight (kg)			

Photocopy child's measurement page from Red Book Done ☐
EAT length and weight plotted on growth charts in child's Red Book. Done ☐

Skin examination and severity assessment.

1. Has the baby got signs of visible eczema (poorly demarcated redness with surface change, i.e. fine scaling, vesicles, oozing, crusting or lichenification) in any of the following places?

Body area	Eczema present?	
	Yes	No
Around the eyes (skin crease)		
Around the ears (skin crease)		
Around the neck (skin crease)		
Fronts of the elbows (skin crease)		
Behind the knees (skin crease)		
Front of the ankles (skin crease)		
Cheeks (any patch involving one or both cheeks, non flexural)		
Forearms (elbow to wrist), at least one patch on EACH forearm (non flexural)		
Lower legs (knee to ankle), at least one patch on EACH leg (non flexural)		
Any other place. Please specify:		

NB: Individual patches have to be larger than 1cm to be scored positive for skin creases and greater than 2cm to be scored positive for non-flexural skin. Please still record smaller areas and other locations under 'Any other place'.

Signature of Team Member: _____ Date: _____

Beware of black skin. Redness may be difficult to see and is not an essential criterion in black skin, but there must be surface change (ie scaling, vesicles, oozing, crusting and/or lichenification).

2. Does the child's skin feel dry (xerosis)? Yes ☐ No ☐

3. <u>If yes</u>, how dry? (Please refer to laminated pictures) Mild ☐ Moderate ☐ Severe ☐

4. Is there evidence of fine scale (ichthyosis)? Yes ☐ No ☐

5. <u>If yes</u>, is this predominantly affecting the extensor surfaces of the limbs? Yes ☐ No ☐

6. Is there keratosis pilaris (thickening around the base of hair follicles on outer upper arms, outer thighs, or cheeks)? Yes ☐ No ☐

7. If yes, which area(s) is/are affected? Upper arms ☐ Outer thighs ☐ Cheeks ☐

8. Is there palmar hyperlinearity (higher number of skin creases)? Not sure ☐ Yes ☐ No ☐

Additional comments:

_____

_____

_____

SCORAD (use ScoradCard programme): _____

Signature of Team Member: _____ Date: _____

Skin Prick Tests.

- Read after 15 minutes.
- Positive control: Both positives should be >0mm. If one or both negative, repeat immediately. If repeat negative, reschedule for 7 days.
- Negative control: If ≥1mm, substract mean negative reading from mean positive reading. The negative control must be smaller than the positive control for the test results to be valid. If negative control ≥ positive control, repeat all tests.
- Allergens: (1) If both results ≥1mm and ≥2mm difference between results a third SPT to be performed, the mean of two closest results to be recorded. (2) If one result <1mm and one ≥1mm, a third SPT to be performed. (2a) If two of these results <1mm, then 0mm to be recorded. (2b) If two of these results ≥1mm, the mean of those two results to be recorded.
- Always test the allergens in the order listed on the proforma.

Additional test done	**Wheal** Diameter	**Wheal** Perpendicular	**Wheal** Mean	**Flare** Diameter	**Flare** Perpendicular	**Flare** Mean

RIGHT arm (please always test allergens in this order) – Wheal measurements

	Wheal Diameter	**Wheal** Perpendicular	**Wheal** Mean		**Wheal** Diameter	**Wheal** Perpendicular	**Wheal** Mean
Positive control				**Milk**			
Wheat				**Cod**			
Sesame				**Egg**			
Peanut				**Negative control**			

LEFT arm – Wheal measurements

	Wheal Diameter	**Wheal** Perpendicular	**Wheal** Mean		**Wheal** Diameter	**Wheal** Perpendicular	**Wheal** Mean
Positive control				**Milk**			
Wheat				**Cod**			
Sesame				**Egg**			
Peanut				**Negative control**			

Signature of Team Member: _____ Date: _____

Dietary Education.

Early Introduction (Intervention Arm):

- ☐ Food introduction EAT Star chart
- ☐ 'Baby's First' booklet (3-5 months of age)
- ☐ EAT Weekly Diary (3 copies)
- ☐ Breastfeeding and Nutrition Handout
- ☐ Returning to Work Handout

Standard Weaning (Control Arm):

- ☐ 'Best for Baby' Guidance booklet
- ☐ Breastfeeding and Nutrition Handout
- ☐ Returning to Work Handout

☐ Reminded of online infant questionnaires
☐ Reminded of 5 day food records (at 6 months, 1 year, 3 years of age)
☐ Provided wheat, egg & milk containing commercial baby foods lists

Further Resources:
☐ Breastfeeding and Work NHS booklet
☐ Other: _____

Method of Dietetic Education:
☐ EAT Video & Brief Verbal ☐ Full Verbal

Additional details:

_____
_____
_____
_____
_____

Mother suspected any adverse reaction to breast milk in baby? Yes ☐ No ☐

Details:_____
_____
_____
_____

Signature of Team Member: _____ Date: _____

Blood samples.

Total volume taken from child _____

PBMC (blue top bottle for Victor's lab) sample taken: Yes ☐ No ☐

Samples sent to : GSTT ☐ Victor ☐

Additional details:

_____

_____

Blood Results.

Blood results normal (see values below) Yes ☐ No ☐

Parents spoken to **directly** about results: Yes ☐ No ☐

Comment: _____

Signature of Team Member: _____ Date: _____

Closing check list.

Informed consent given to parent. ☐
EAT Contact information added to Red Book. ☐
GP letter given to parent. ☐
Travel expenses form/envelope given to parents ☐
AE form updated (SNAP) (SPT+ve infants) ☐
Possible food allergy database (SPT+ve infants) ☐
Dust pack given ☐
Stool sample collected ☐
If not, stool sample collection pack given ☐

Additional visit comments.

_____

_____

_____

Signature of Team Member: _____ Date: _____

APPENDIX 12 - One year visit proforma

EAT
Enquiring About Tolerance

Age at visit: _____

Time of arrival: ___:___ **Skin swabs taken:** Yes ☐ No ☐

Time of EMLA application: ___:___

Arm of study: Control ☐ Intervention ☐

1 year visit category: Low risk ☐ Medium risk ☐ High risk ☐

Previous food allergy history:

	3/12 visit		Post 3/12 visit			
	SPT +ve	Challenge +ve	Acute food reaction	Challenge +ve	Chronic food reaction	Home DBPCFC +ve
Wheat						
Sesame						
Peanut						
Milk						
Cod						
Egg						

Eczema history at 3/12 visit: Yes ☐ No ☐ **Scorad at 3/12 visit:** _____

Introduction food consumption history:

	Wheat	Sesame	Peanut	Milk	Cod	Egg
≥2 g every week in last month						
≥2 g in last month						
Eaten ≥2 g >3 times ever						
Frequent/**I**nfrequent/**N**ever						

NB Frequent if ≥2 g in last month AND eaten≥2 g >3 times ever
2g food protein:1 small pot of cow's milk yoghurt (about 40-60 grams per pot); ½ small egg; 1fishfinger or 1/8 fish fillet (25 grams); 1 ½ rounded teaspoons peanut butter; 1 ½ teaspoons tahini (sesame paste); 1 wheat based biscuit cereal (e.g. Weetabix)_____

_____

Signature of Team Member: _____ Date: _____

Original consent checked: Yes ☐ No ☐

Stool & skin supplementary consent page signed and filed (and copy to parents): Yes ☐ No ☐

12 month questionnaire completed: Yes ☐ No ☐

Interim questionnaires up to date: Yes ☐ No ☐

Food diary completed Yes ☐ No ☐

5 day food diary ☐ **14 day food diary** ☐

Health Questions:

Has your child been admitted (overnight) to hospital? Yes ☐ No ☐

If yes, please give details:

_____

_____

_____

Is your child currently fit and well? Yes ☐ No ☐

If no, please give details:

_____

_____

_____

Please list any regular or recently taken antihistamines/asthma treatments:

Name	Dose	Frequency	Start Date	Stop Date

NB: Ineligible for challenge if child has received:

- short-acting beta-2 agonists in last 12 hours *e.g. salbutamol (Ventolin or terbutaline (Bricanyl)*
- long-acting beta-2 agonists in last 24 hours *e.g. salmeterol (Serevent) or formoterol (Oxis)*
- short-acting antihistamines in the last 48 hours *e.g. chlorphenamine (Piriton)*
- long-acting antihistamines in the last 7 days *e.g. cetirizine (Zertec) or loratadine (Claritynn*

Remember: some cough and cold medicines and anti-itch medicines contain antihistamines

Signature of Team Member: _____ Date: _____

EAT
Enquiring About Tolerance

TEWL.

Any moisturiser (including bath oils) or other topical treatments used on baby's skin in the last 24 hours?

Yes ☐ No ☐

If Yes, Please give details:

_____

_____

Measurement	**1st**	**2nd**	**3rd**
Flux			
Room temperature (°C) [target 20+/-2°C]			
Room humidity (%) [target 38-50%]			
Time of TEWL measurement			
Child calm throughout	Yes ☐ No ☐		
Decent measurement curves	Yes ☐ No ☐		

Anthropometry.

Measurement	**1st**	**2nd**	**3rd**
LEFT triceps skin fold (mm)			
LEFT subscapular skin fold (mm)			
Length (cm)			
Head circumference (cm)			
Arm circumference (cm)			
Weight (kg)			

EAT length and weight plotted on growth charts in child's Red Book. Done ☐

Photocopy measurement table and immunisation chart from Red Book Done ☐

Signature of Team Member: _____ Date: _____

EAT
Enquiring About Tolerance

Skin examination and severity assessment.

1. Has the child got signs of visible eczema (poorly demarcated redness with surface change, i.e. fine scaling, vesicles, oozing, crusting or lichenification) in any of the following places?

Body area	**Eczema present?**	
	Yes	**No**
Around the eyes (skin crease)		
Around the ears (skin crease)		
Around the neck (skin crease)		
Fronts of the elbows (skin crease)		
Behind the knees (skin crease)		
Front of the ankles (skin crease)		
Cheeks (any patch involving one or both cheeks, non flexural)		
Forearms (elbow to wrist), at least one patch on EACH forearm (non flexural)		
Lower legs (knee to ankle), at least one patch on EACH leg (non flexural)		
Any other place. Please specify:		

NB: Individual patches have to be larger than 1cm to be scored positive for skin creases and greater than 2cm to be scored positive for non-flexural skin. Please still record smaller areas and other locations under 'Any other place'.

Beware of black skin. Redness may be difficult to see and is not an essential criterion in black skin, but there must be surface change (ie scaling, vesicles, oozing, crusting and/or lichenification).

2. Does the child's skin feel dry (xerosis)? Yes ☐ No ☐

3. If yes, how dry? (Please refer to laminated pictures)
Mild ☐
Moderate ☐
Severe ☐

4. Is there evidence of fine scale (ichthyosis)? Yes ☐ No ☐

5. If yes, is this predominantly affecting the extensor surfaces of the limbs? Yes ☐ No ☐

Signature of Team Member: _____ Date: _____

EAT
Enquiring About Tolerance

6. Is there keratosis pilaris (thickening around the base of hair follicles on outer upper arms, outer thighs, or cheeks)? Yes ☐ No ☐

7. If yes, which area(s) is/are affected?
Upper arms ☐
Outer thighs ☐
Cheeks ☐

8. Is there palmar hyperlinearity (higher number of skin creases)?
Not sure ☐
Yes ☐
No ☐

Additional comments, if needed:

_____
_____
_____
_____

SCORAD (use ScoradCard programme): _____

Skin swabs taken: Yes ☐ No ☐

Label swabs on packaging, sterile gloves, 2 drops of normal saline on each swab, one from each direction. Swab is taken from a 2x2cm area. **Ensure that sterile gloves holding the swab <u>does not</u> touch anything apart from the child's skin.**

Left antecubital fossa (elbow crease, abbreviation: EC) Yes ☐ No ☐
Eczema present Yes ☐ No ☐

Left outer forearm (1/3 between wrist and elbow, OF) Yes ☐ No ☐
Eczema present Yes ☐ No ☐

Control swab taken (open & close in mid air, CS) Yes ☐ No ☐

Each swab needs to be labelled with child's bar code & ID, date of today, and site swabbed as well as whether eczema was present or not (Y/N). All samples need to go into rack in -80C freezer in Well Child lab <u>as soon as possible</u>. Rack posititions need to be logged on Excel spreadsheet.

Additional comments:

_____
_____
_____

Signature of Team Member: _____ Date: _____

EAT
Enquiring About Tolerance

Skin Prick Tests.

- Read after 15 minutes.
- Use commercial solutions for all tests.
- Positive control: If the histamine positive control is ≤ 3 mm, then it should be repeated immediately. If the repeat test remains ≤ 3 mm, then the testing should be rescheduled for approximately 7 days' time.
- Negative control: If the saline negative control test is ≥ 3 mm, then it should be repeated immediately. If the repeat test remains ≥ 3 mm, the testing should be rescheduled for approximately 7 days' time. If ≥1mm, subtract negative reading from positive reading. The negative control must be smaller than the positive control for the test results to be valid. If negative control ≥ positive control, repeat all tests.
- Always test the allergens in the order listed on the proforma.

Left arm

	Wheal Diameter	**Wheal** Perpendicular	**Wheal** Mean		**Wheal** Diameter	**Wheal** Perpendicular	**Wheal** Mean
Positive control				**Milk**			
Wheat				**Cod**			
Sesame				**Egg**			
Peanut				**Negative control**			

Right arm

	Wheal Diameter	**Wheal** Perpendicular	**Wheal** Mean		**Wheal** Diameter	**Wheal** Perpendicular	**Wheal** Mean
Cat				**3 Tree**			
Dog				**Soya**			
H.D.M				**Kiwi**			
5 Grasses				**Other**			

Frequent consumer challenge required:

Milk ☐ Egg ☐ Wheat ☐ Cod ☐ Peanut ☐ Sesame ☐

DBPCFC required:

Milk ☐ Egg ☐ Wheat ☐ Cod ☐ Peanut ☐ Sesame ☐

Order: ___ ___ ___ ___ ___ ___

(NB 1. Milk 2. Egg 3. Wheat 4. Fish is recommended order)

Signature of Team Member: _____ Date: _____

Dietary Education

Early Introduction (Intervention Arm):

- ☐ 'EATing Well & Snack Ideas' Handouts (1-5 years of age)
- ☐ EAT Monthly Diaries (x 2 copies)
- ☐ EAT Options Sheet

Standard Weaning (Control Arm):

- ☐ 'EATing Well & Snack Ideas' Handouts (1-5 years of age)

☐ Reviewed dietary history of 6 EAT Study key foods, soya and kiwi intake (if needed)

☐ Reviewed and clarified received food diaries (6 month, 1 year)

☐ Reviewed upcoming online questionnaires every 3 months, and of 5 day food diary at 3 years of age

Further Resources (if applicable):

☐ Kiwi Avoidance Handout (EAT Study)

☐ Soya Avoidance Handout (AllergyUK)

☐ Nut-free: Guide to Managing Nut Allergy (SNDRi/NDR-UK)

☐ Sesame Avoidance Information Handout (Anaphylaxis Campaign)

☐ Other: _____

Is the child currently on any Multivitamin Supplements? ☐ Yes ☐ No

If yes (when started, type of supplementation and amount given each time):

_____

Additional details:

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Signature of Team Member: _____ Date: _____

EAT
Enquiring About Tolerance

Blood samples.

Total volume taken from child _____

PBMC (blue top bottle for Victor's lab) sample taken: Yes ☐ No ☐

Samples sent to : GSTT ☐ Victor ☐

Additional details,

_____

_____

_____

Closing checklist

Travel expenses / envelope given to parents ☐

Possible food allergy database completed/updated ☐

Stool sample obtained ☐

If no, stool sample pack given ☐

Dust pack given ☐

Additional visit comments, if needed:

_____

_____

_____

_____

_____

_____

_____

_____

_____

Signature of Team Member: _____ Date: _____

APPENDIX 13 - Three years visit proforma

EAT
Enquiring About Tolerance

3 YEAR VISIT PROFORMA

Age at visit: _____ **Time of arrival:** ___:___

Time of EMLA application: ___:___ (child)
___:___ (parent(s))

Arm of study: Control ☐ Intervention ☐

3 year visit category: Low risk ☐ High risk ☐

Attach STICKER or write NAME and DATE OF BIRTH here.

What time did the child last have a drink (other than water) ___:___
What time did the child last eat anything (finished eating) ___:___

Previous food allergy history:

	1 year visit		Post 1 year visit			
	SPT +ve	**DBPCFC +ve** (include date)	**Acute food reaction**	**DBPCFC +ve** (include date)	**Chronic food reaction**	**Home DBPCFC +ve**
Wheat						
Sesame						
Peanut						
Milk						
Cod						
Egg						

Eczema history at 1 year visit: Yes ☐ No ☐ Scorad at 1 year visit: _____

Intervention food consumption history:

	Wheat	Sesame	Peanut	Milk	Cod	Egg
≥2 g every week in last month						
≥2 g in last month						
Eaten ≥2 g >3 times ever						
Frequent/**I**nfrequent/**N**ever						
Wheat consumed at least daily for last 6 weeks? (Y/N)						

NB Frequent if ≥2 g in last month AND eaten≥2 g >3 times ever
2g food protein:1 small pot of cow's milk yoghurt (about 40-60 grams per pot); ½ small egg; 1fishfinger or 1/8 fish fillet (25 grams); 1 ½ rounded teaspoons peanut butter; 1 ½ teaspoons tahini (sesame paste); 1 wheat based biscuit cereal (e.g. Weetabix)

_____

_____

Signature of Team Member: _____ Date: _____

3 YEAR VISIT PROFORMA

Visit Checklist:

	Yes	No	N/A
Original consent checked including stool and skin addendum if applicable (i.e. original consent before version 2 AND 1 yr visit date after 30/09/2011)			
Mother & child opted out of storage for future research on original consent (Q1)			
Child opted out of storage for future genetic testing on original consent (Q2)			
MOTHER:- SPT supplementary consent page signed and filed (and copy to mother)			
FATHER:- SPT & blood test consent page signed and filed (and copy to father)			
Father opted out of storage for future research (if paternal consent signed)			
36 month Q completed? (if No, complete before departure)			
3 month General Q completed?			
If No, 3 month Short General Q completed? (if No, complete before departure)			
3 yr food diary completed online			
3 yr food diary completed on paper			
Contact details checked and additional numbers (dad/grandparent) recorded on front sheet of notes			
Parents specifically asked not to be contacted in the future			

Health Questions:

Has your child been admitted (overnight) to hospital since their 1 year EAT visit? Yes ☐ No ☐

If yes, please check SAE database (*S:\PaediatricAllergy\EAT Study\GCP\Adverse Events\SAEs\SAE Database\SAE Database*) and give **details if not recorded**:

_____

_____

Is your child currently fit and well? Yes ☐ No ☐

If no, please give details:_____

_____

Please list any regular or recently taken **antihistamines/asthma treatments**:

Name	Dose	Frequency	Start Date	Stop Date

NB: Ineligible for challenge if child has received:

- short-acting beta-2 agonists in last 12 hours *e.g. salbutamol (Ventolin or terbutaline (Bricanyl)*
- long-acting beta-2 agonists in last 24 hours *e.g. salmeterol (Serevent) or formoterol (Oxis)*
- short-acting antihistamines in the last 48 hours *e.g. chlorphenamine (Piriton)*
- long-acting antihistamines in the last 7 days *e.g. cetirizine (Zertec) or loratadine (Clarityn*

Remember: some cough and cold medicines and anti-itch medicines contain antihistamines

Signature of Team Member: _____ Date: _____

EAT
Enquiring About Tolerance

3 YEAR VISIT PROFORMA

Child's Skin Prick Tests.

- Read after 15 minutes.
- Positive control: If the histamine positive control is negative, then it should be repeated immediately. If the repeat test remains negative, then the testing should be rescheduled for approximately 7 days' time.
- Negative control: If the saline negative control test is ≥ 3 mm, then it should be repeated immediately. If the repeat test remains ≥ 3 mm, the testing should be rescheduled for approximately 7 days' time. If ≥1mm, subtract negative reading from positive reading. The negative control must be smaller than the positive control for the test results to be valid. If negative control ≥ positive control, repeat all tests.
- Always test the allergens in the order listed on the proforma.

Left arm

	Wheal Diameter	**Wheal** Perpendicular	**Wheal** Mean		**Wheal** Diameter	**Wheal** Perpendicular	**Wheal** Mean
Positive control				**Egg**			
Wheat				**Kiwi**			
Sesame				**Soya**			
Peanut				**Raw egg white**			
Milk				**Negative control**			
Cod				**Other:**			

Right arm

	Wheal Diameter	**Wheal** Perpendicular	**Wheal** Mean		**Wheal** Diameter	**Wheal** Perpendicular	**Wheal** Mean
Cat				**Brazil nut**			
Dog				**Hazelnut**			
H.D.M				**Cashew**			
5 Grasses				**Almond**			
3 Tree				**Walnut**			

Signature of Team Member: _____ Date: _____

EAT Enquiring About Tolerance

3 YEAR VISIT PROFORMA

Skin examination and severity assessment.

1. Has the child got signs of visible eczema (poorly demarcated redness with surface change, i.e. fine scaling, vesicles, oozing, crusting or lichenification) in any of the following places?

Body area	Eczema present?	
	Yes	No
Around the eyes (skin crease)		
Around the ears (skin crease)		
Around the neck (skin crease)		
Fronts of the elbows (skin crease)		
Behind the knees (skin crease)		
Front of the ankles (skin crease)		
Cheeks (any patch involving one or both cheeks, non flexural)		
Forearms (elbow to wrist), at least one patch on EACH forearm (non flexural)		
Lower legs (knee to ankle), at least one patch on EACH leg (non flexural)		
Any other place. Please specify:		

NB: Individual patches have to be larger than 1cm to be scored positive for skin creases and greater than 2cm to be scored positive for non-flexural skin. Please still record smaller areas and other locations under 'Any other place'. Beware of black skin. Redness may be difficult to see and is not an essential criterion in black skin, but there must be surface change (ie scaling, vesicles, oozing, crusting and/or lichenification).

Skin Examination			
	Yes	No	Not sure
Does the child's skin feel dry (xerosis)?			
If yes, how dry? (Please refer to laminated pictures) Mild ☐ Moderate ☐ Severe ☐			
Is there evidence of fine scale (ichthyosis)?			
If yes, is this predominantly affecting the extensor surfaces of the limbs?			
Is there keratosis pilaris (thickening around the base of hair follicles on outer upper arms, outer thighs, or cheeks)?			
If yes, which area(s) is/are affected? Upper arms ☐ Outer thighs ☐ Cheeks ☐			
Is there palmar hyperlinearity (higher number of skin creases)?			

Signature of Team Member: _____ Date: _____

3 YEAR VISIT PROFORMA

Additional skin comments, if needed:

_____
_____
_____
_____

SCORAD (use ScoradCard programme): _____

Anthropometry

Measurement	1st	2nd	3rd
LEFT triceps skin fold (mm)			
LEFT subscapular skin fold (mm)			
Height (cm)			
Head circumference (cm)			
Arm circumference (cm)			
Blood Pressure			
Weight (kg)			

EAT height and weight plotted on growth charts in child's Red Book & photocopied. Done ☐

Photocopy measurement table from Red Book if new measurements since 1 yr visit Done ☐

Photocopy immunisation chart from Red Book if missing in notes/updated Done ☐

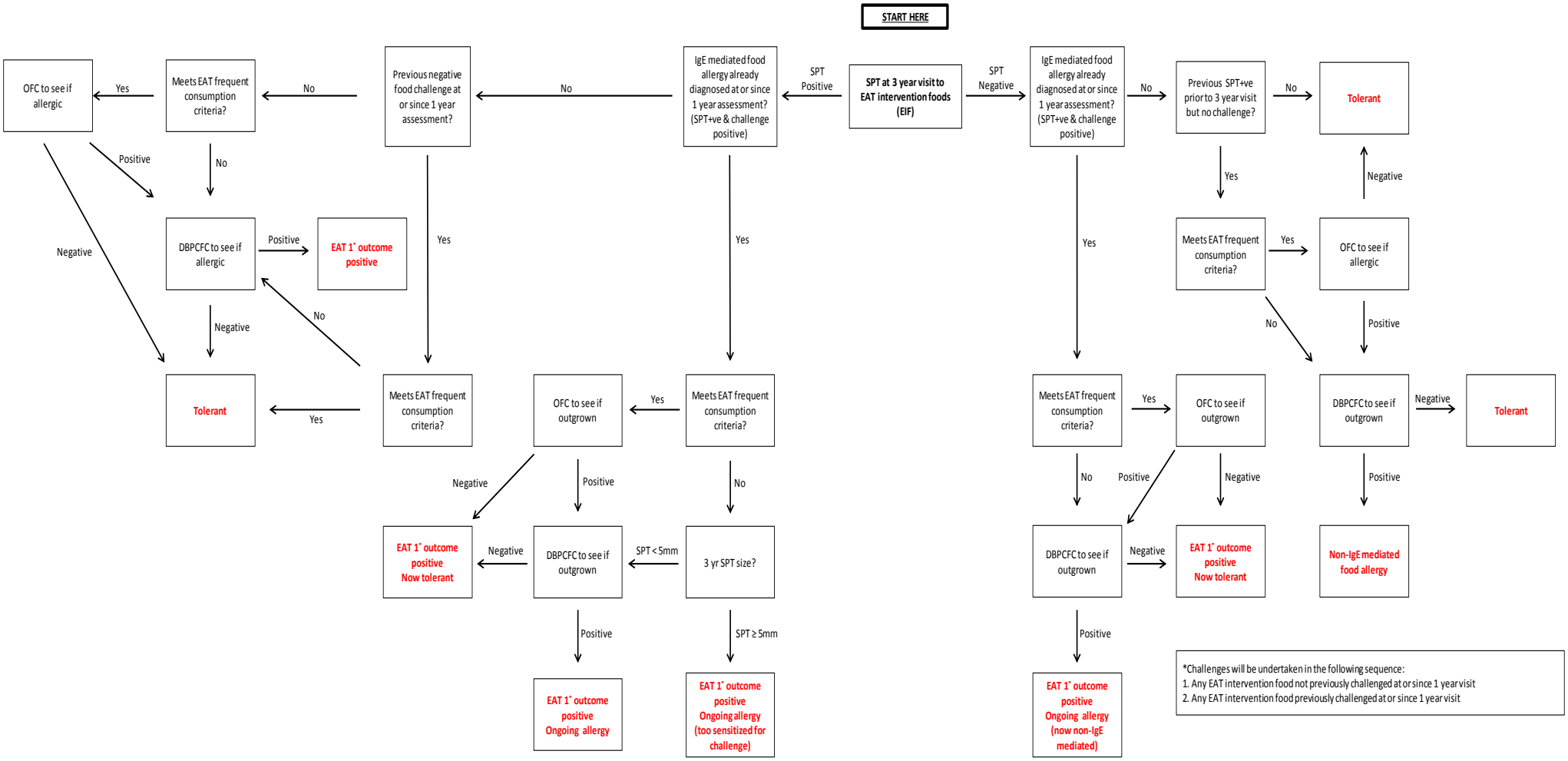
Signature of Team Member: _____ Date: _____

3 Year Visit

3 YEAR VISIT PROFORMA

FOLLOW EAT 3 YEAR ON THE ALGORITHM:

ALGORITHM MARKING THE OUTCOME FOR EAT STUDY FOOD (M,E,W,C,P,S)



Frequent consumer challenge required: Milk ☐ Egg ☐ Wheat ☐ Cod ☐ Peanut ☐ Sesame ☐

DBPCFC required: Milk ☐ Egg ☐ Wheat ☐ Cod ☐ Peanut ☐ Sesame ☐

Signature of Team Member: _____ Date: _____

EAT
Enquiring About Tolerance

3 YEAR VISIT PROFORMA

Parental Skin Prick Tests.

Enquire about history of food allergy symptoms.
Note **any** symptoms but **only SPT for IgE–mediated symptoms** – e.g urticaria, angiodema, wheeze or anaphylaxis:

MOTHER	**Wheal** diameter	**Wheal** perp	**Wheal** mean		**Food name***	**Food symptoms****	**SPT (Y/N?)**	**Wheal** diameter	**Wheal** perp	**Wheal** mean
Positive control				**Food 1**						
Cat				**Food 2**						
Dog				**Food 3**						
HDM D.PTE				**Food 4**						
HDM 2 D.FAM				**Food 5**						
Birch				**Food 6**						
Timothy grass				**Food 7**						
Hazelnut				**Food 8**						
Negative control				**Other**						

FATHER	**Wheal** diameter	**Wheal** perp	**Wheal** mean		**Food name***	**Food symptoms****	**SPT (Y/N?)**	**Wheal** diameter	**Wheal** perp	**Wheal** mean
Positive control				**Food 1**						
Cat				**Food 2**						
Dog				**Food 3**						
HDM D.PTE				**Food 4**						
HDM 2 D.FAM				**Food 5**						
Birch				**Food 6**						
Timothy grass				**Food 7**						
Hazelnut				**Food 8**						
Negative control				**Other**						

*SPT where applicable to fish (cod, salmon†, tuna†), seafood (prawn, scallop†, squid†), tree nuts (brazil nut, cashew, almond, walnut, pine nut†, pecan†, pistachio†, macadamia†), peanut and sesame. †SPT solution will need to be borrowed from NHS outpatients if necessary.
Note food symptom from the following list: **U urticaria, **ANG** angiodema, **W** wheeze, **ANA** anaphylaxis, **OAS** oral allergy syndrome, **V** vomiting or **D** diarrhoea

Signature of Team Member: _____ Date: _____

EAT
Enquiring About Tolerance

3 YEAR VISIT PROFORMA

Parental allergen consumption history

Have any of the allergenic foods below NEVER been consumed?

Mother

Yes, one or more allergenic foods has never been consumed (complete table) ☐
No, all the allergenic foods listed below have been consumed ☐

Food	**Never consumed** (please tick)
Peanut	
Hazelnut	
Brazil nut	
Cashew	
Almond	
Walnut	
Pinenut	
Sesame	
Cod	
Salmon	
Tuna	
Prawn	
Scallop	
Squid	

Father

Yes, one or more allergenic foods has never been consumed (complete table) ☐
No, all the allergenic foods listed below have been consumed ☐

Food	**Never consumed** (please tick)
Peanut	
Hazelnut	
Brazil nut	
Cashew	
Almond	
Walnut	
Pinenut	
Sesame	
Cod	
Salmon	
Tuna	
Prawn	
Scallop	
Squid	

Signature of Team Member: _____ Date: _____

EAT Enquiring About Tolerance

3 YEAR VISIT PROFORMA

Dietary Education

Both Groups

☐ Review 3 year paper and online food diaries

Resources for Participants who are EAT 1° outcome positive (no challenge) or SPT positive to kiwi, soya, raw egg white or tree-nut(s):

☐ Kiwi Avoidance Handout (EAT Study)
☐ Soya Avoidance Handout (AllergyUK)
☐ Nut-free: Guide to Managing Nut Allergy (SNDRi/NDR-UK)
☐ Introduction of Tree-nuts Handout (EAT study)
☐ Peanut and Tree-nut Advice Handout (EAT study)
☐ Sesame Avoidance Information Handout (Anaphylaxis Campaign)
☐ Raw Egg White Allergy Handout (EAT Study)
☐ Other: _____

Is the child currently on any Multivitamin Supplements? ☐ Yes ☐ No

If yes (when started, type of supplementation and amount given each time):

_____

Additional details:

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Signature of Team Member: _____ Date: _____

EAT
Enquiring About Tolerance

3 YEAR VISIT PROFORMA

Blood samples.

Time blood sample taken ___:___

Total volume taken from child _____

PBMC (blue top bottle for Victor's lab) sample taken: Yes ☐ No ☐

Samples sent to : GSTT ☐ Victor ☐

Additional details,

_____

_____

_____

Blood sample taken from Mother: Yes ☐ No ☐

Blood sample taken from Father: Yes ☐ No ☐

Closing checklist

Travel expenses / envelope given to parents ☐

Possible food allergy database completed/updated if required ☐

"EAT- on"/"What happens next?" newsletter ☐

Management plan if required ☐

Prescription if required ☐

GP referral/feedback letter if required ☐

Mother GP referral/feedback letter if required ☐

Father GP referral/feedback letter if required ☐

Additional visit comments, if needed:

_____

_____

_____

_____

_____

_____

Signature of Team Member: _____ Date: _____

APPENDIX 14 - Enrolment food frequency questionnaire

Maternal Diet Questionnaire Pregnancy and Breastfeeding

The following questions ask how often you consumed different foods, firstly during pregnancy and secondly during breastfeeding.

The questionnaire takes about 15 minutes to complete.
If you need to break off midway - click the save button and when you return by clicking the link in your email you will resume from the saved position.

EAT
Enquiring About Tolerance

Q.1. **Baby's mother's first name**

Q.2. **Baby's mother's surname**

General Diet

	not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	every day
Q.4. **Milk and milk products** (e.g. custard, yoghurt, ice cream, chocolate, butter, margarines, cheese-pizza, cheese sauces, lasagne, cheesy biscuits)										
Milk - During Pregnancy	○	○	○	○	○	○	○	○	○	○
Milk - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.5. **Wheat** (e.g. bread, cereals, pasta, pizza, cakes, pies and pastry)										
Wheat - During Pregnancy	○	○	○	○	○	○	○	○	○	○
Wheat - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.6. **White Fish** (e.g. tuna, fish cakes, battered fish and fish fingers)										
White Fish - During Pregnancy	○	○	○	○	○	○	○	○	○	○
White Fish - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.7. **Shell Fish** (e.g. crab, prawns, shrimps, lobster and crayfish)										
Shell Fish - During Pregnancy	○	○	○	○	○	○	○	○	○	○
Shell Fish - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.8. **Oily Fish** (e.g. mackerel, salmon, sardines, pilchards, herring, kipper, white bait, trout, crab, FRESH tuna)										
Oily Fish - During Pregnancy	○	○	○	○	○	○	○	○	○	○
Oily Fish - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.9. **Peanuts** (e.g. Bombay Mix, peanut butter, peanut brittle, peanut cookies, satay, some vegetarian meals)										
Peanuts - During Pregnancy	○	○	○	○	○	○	○	○	○	○
Peanuts - During Breastfeeding	○	○	○	○	○	○	○	○	○	○

Breads

	not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	every day
Q.11. **Brioche**										
Brioche - During Pregnancy	○	○	○	○	○	○	○	○	○	○
Brioche - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.12. **Bagels**										
Bagels - During Pregnancy	○	○	○	○	○	○	○	○	○	○
Bagels - During Breastfeeding	○	○	○	○	○	○	○	○	○	○

		not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	every day
Q.13.	**Croissant, Pain au chocolate**										
	Croissant - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Croissant - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.14.	**Danish pastries**										
	Danish pastries - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Danish pastries - During Breastfeeding	○	○	○	○	○	○	○	○	○	○

Breakfast Cereals

		not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	every day
Q.16.	**Special K**										
	Special K - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Special K - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.17.	Peanut containing breakfast cereals **(e.g. Crunchy Nut Cornflakes, Honey Nut loops, Honey and Nut Branflakes, Weetabix honey and nut minis, nut containing muesli)**										
	Peanut Cereal - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Peanut Cereal - During Breastfeeding	○	○	○	○	○	○	○	○	○	○

Meat Dishes

		not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	every day
Q.19.	**Casserole/Stew - milk/cream based (including those with a ready made sauce)**										
	Casserole - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Casserole - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.20.	**Curry - milk/cream based (including those with a ready made sauce)**										
	Curry - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Curry - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.21.	**Lasagne/Mousaka**										
	Lasagne - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Lasagne - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.22.	**Chicken Kiev/Chicken Cordon Bleu**										
	Chicken Kiev - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Chicken Kiev - During Breastfeeding	○	○	○	○	○	○	○	○	○	○

Fish

		not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	every day
Q.24.	**Fish in Breadcrumbs (including fish fingers)**										
	Breadcrumbed Fish - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Breadcrumbed Fish - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.25.	**Fish in Batter**										
	Battered Fish - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Battered Fish - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.26.	**Fish in sauce** (including cook in a bag)										
	Fish in Sauce - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Fish in Sauce - During Breastfeeding	○	○	○	○	○	○	○	○	○	○

Savoury Dishes

		not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	every day
Q.28.	**Quiche/ Savoury flan**										
	Quiche - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Quiche - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.29.	**Eggs** (boiled, poached, fried, scrambled, omelette)										
	Eggs - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Eggs - During Breastfeeding	○	○	○	○	○	○	○	○	○	○

Q.30.	**Cheese** (any type)										
	Cheese - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Cheese - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.31.	**Pizza**										
	Pizza - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Pizza - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.32.	**Crispy Pancakes** (frozen)										
	Crispy Pancakes - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Crispy Pancakes - During Breastfeeding	○	○	○	○	○	○	○	○	○	○

Savoury Dishes (continued)

		not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	every day
Q.34.	**Savoury Pancakes**										
	Savoury Pancakes - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Savoury Pancakes - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.35.	**Scotch Egg/ Snack Egg**										
	Scotch Egg - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Scotch Egg - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.36.	**Creamy pasta dish** (e.g. Carbonara, macaroni cheese)										
	Creamy Pasta - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Creamy Pasta - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.37.	**Toad in the Hole**										
	Toad in the Hole - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Toad in the Hole - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.38.	**Yorkshire Pudding**										
	Yorkshire Pudding - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Yorkshire Pudding - During Breastfeeding	○	○	○	○	○	○	○	○	○	○

Vegetable Dishes

		not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	every day
Q.40.	**Egg Pasta** (fresh or dried) **/ Egg Noodles**										
	Egg Pasta - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Egg Pasta - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.41.	**Egg Fied Rice**										
	Egg Fried Rice - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Egg Fried Rice - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.42.	**Vegetable in cheese sauce** (e.g. cauliflower cheese)										
	Cheese Sauce Vegetables - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Cheese Sauce Vegetables - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.43.	**Prepared Salad** (e.g. coleslaw, potato salad)										
	Prepared Salad - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Prepared Salad - During Breastfeeding	○	○	○	○	○	○	○	○	○	○

Soups, Accompanying Sauces, Dressings, Dips and Sandwich Fillings

		not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	every day
Q.45.	**Hollandaise sauce, Béarnaise sauce**										
	Hollandaise - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Hollandaise - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.46.	**Tartare sauce, Mayonnaise, Salad Cream, Seafood dressing, Blue Cheese dressing**										
	Other Dressings - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Other Dressings - During Breastfeeding	○	○	○	○	○	○	○	○	○	○

		not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	every day
Q.47.	**Soured Cream based dips**										
	Soured Cream - During Pregnancy										
	Soured Cream - During Breastfeeding										
Q.48.	**Sandwich fillings** (e.g. Coronation chicken, Chicken Tikka, etc.)										
	Sandwich Fillings - During Pregnancy										
	Sandwich Fillings - During Breastfeeding										
Q.49.	**Sandwich spread**										
	Sandwich Spread - During Pregnancy										
	Sandwich Spread - During Breastfeeding										

Sesame

		not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	every day
Q.51.	**Humus/tahini**										
	Humus - During Pregnancy										
	Humus -During Breastfeeding										
Q.52.	**Bread with sesame seeds / bread buns with sesame seeds**										
	Sesame Bread - During Pregnancy										
	Sesame Bread - During Breastfeeding										
Q.53.	**Sesame crackers / sesame breadsticks**										
	Sesame Crackers - During Pregnancy										
	Sesame Crackers - During Breastfeeding										
Q.54.	**Sesame snaps**										
	Sesame Snaps - During Pregnancy										
	Sesame Snaps - During Breastfeeding										

Biscuits/Cereal Bars

		not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	every day
Q.56.	**Full and half covered chocolate biscuits (e.g. chocolate hobnob, Jaffa cake, Kitkat, Classic etc.)**										
	Chocolate Biscuits - During Pregnancy										
	Chocolate Biscuits - During Breastfeeding										
Q.57.	**Snickers flap jack**										
	Snickers Flap Jack - During Pregnancy										
	Snickers Flap Jack - During Breastfeeding										
Q.58.	**Tracker roasted nut bar**										
	Tracker Nut Bar - During Pregnancy										
	Tracker Nut Bar - During Breastfeeding										
Q.59.	**Eat Natural - fruit and nut bar**										
	Eat Fruit & Nut Bar - During Pregnancy										
	Eat Fruit & Nut Bar - During Breastfeeding										
Q.60.	**Breakfast cereal bar (e.g. Special K bar)**										
	Breakfast Cereal Bar - During Pregnancy										
	Breakfast Cereal Bar - During Breastfeeding										

Cakes

		not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	every day
Q.62.	**Sponge cakes (e.g. Madeira, fruit, Victoria, etc.)**										
	Sponge Cakes - During Pregnancy										
	Sponge Cakes - During Breastfeeding										
Q.63.	**Sponge cake bar (e.g. mini rolls, Jamaica ginger cake)**										
	Sponge Cake Bar - During Pregnancy										
	Sponge Cake Bar - During Breastfeeding										

Q.64.	**Doughnut / yum-yums**										
	Dougnut - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Dougnut - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.65.	**Custard tart**										
	Custard Tart - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Custard Tart - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.66.	**Scone/Cheese scone**										
	Scone - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Scone - During Breastfeeding	○	○	○	○	○	○	○	○	○	○

Jams or Spreads

		not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	every day
Q.68.	**Lemon curd**										
	Lemon Curd - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Lemon Curd - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.69.	**Peanut butter**										
	Peanut Butter - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Peanut Butter - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.70.	**Snickers spread**										
	Snickers Spread - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Snickers Spread - During Breastfeeding	○	○	○	○	○	○	○	○	○	○

Puddings/Desserts

		not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	every day
Q.72.	**Sponge Puddings (e.g. treacle, chocolate, etc)**										
	Sponge Puddings -During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Sponge Puddings - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.73.	**Bread puddings (e.g. bread and butter, queen of puddings)**										
	Bread Puddings - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Bread Puddings - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.74.	**Cheesecake type dessert**										
	Cheesecake - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Cheesecake - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.75.	**Lemon meringue pie**										
	Lemon Meringue Pie - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Lemon Meringue Pie - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.76.	**Crème caramel (homemade)/ Luxury mousse (i.e. made with eggs)**										
	Crème caramel - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Crème caramel - During Breastfeeding	○	○	○	○	○	○	○	○	○	○

Puddings/Desserts (continued)

		not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	every day
Q.78.	**Ice cream (including choc ices)**										
	Ice Cream - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Ice Cream - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.79.	**Traditional trifle** (i.e. made with sponge)										
	Trifle - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Trifle - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.80.	**Waffle/pancakes**										
	Waffles - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Waffles - During Breastfeeding	○	○	○	○	○	○	○	○	○	○

		not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	every day
Q.81.	**Yoghurt/yoghurt style desserts**										
	Yoghurt - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Yoghurt - During Breastfeeding	○	○	○	○	○	○	○	○	○	○

Confectionary/Snacks

		not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	every day
Q.83.	**Bamba peanut snack**										
	Bamba - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Bamba - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.84.	**Peanuts (e.g. dry roasted/monkey nuts)**										
	Peanuts - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Peanuts - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.85.	**Milk chocolate bar (e.g. Dairy Milk, Yorkie)**										
	Milk Chocolate Bar - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Milk Chocolate Bar - During Breastfeeding	○	○	○	○	○	○	○	○	○	○

Confectionary/Snacks (continued)

		not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	every day
Q.87.	**Peanut containing chocolate bar (e.g. Snickers, Star Bar, Fuse, Picnic)**										
	Peanut Chocolate Bar - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Peanut Chocolate Bar - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.88.	**Peanut M and M's/Revels**										
	Peanut M and M's - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Peanut M and M's - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.89.	**Reeses Peanut Butter Cups**										
	Reeses Peanut Butter Cups - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Reeses Peanut Butter Cups - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.90.	**Reeses Nutrageous Bar**										
	Reeses Nutrageous Bar - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Reeses Nutrageous Bar - During Breastfeeding	○	○	○	○	○	○	○	○	○	○

Miscellaneous

		not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	every day
Q.92.	**Satay sauce**										
	Satay - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Satay - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.93.	Snickers Ice Cream										
	Snickers Ice Cream - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Snickers Ice Cream - During Breastfeeding	○	○	○	○	○	○	○	○	○	○
Q.94.	Peanut Soup										
	Peanut Soup - During Pregnancy	○	○	○	○	○	○	○	○	○	○
	Peanut Soup - During Breastfeeding	○	○	○	○	○	○	○	○	○	○

Household Consumption

Q.95. **Please place a tick against all the individuals who live in the baby's home:**

- ☐ *Mother*
- ☐ *Father/Partner*
- ☐ *Other children*
- ☐ *Other relatives*

Father/Partner: How often does this family member take the following?

	not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	everyd ay
Father/Partner: Milk and milk products (e.g. custard, yoghurt, ice cream, chocolate, butter, margarines, cheese-pizza, cheese sauces, lasagne, cheesy biscuits)										
Father/Partner: Wheat (e.g. bread, cereals, pasta, pizza, cakes, pies and pastry)										
Father/Partner: White Fish (e.g. tuna, fish cakes, battered fish and fish fingers)										
Father/Partner: Shell Fish (e.g. crab, prawns, shrimps, lobster and crayfish)										
Father/Partner: Oily Fish (e.g. mackerel, salmon, sardines, pilchards, herring, kipper, white bait, trout, crab, FRESH tuna)										
Father/Partner: Peanuts (e.g. Bombay Mix, peanut butter, peanut brittle, peanut cookies, satay, some vegetarian meals)										
Father/Partner: Sesame (e.g. humus, tahini, bread or buns with sesame seeds, sesame crackers, sesame breadsticks or sesame snaps)										
Father/Partner: Eggs and egg products (e.g. omelette/frittata, egg fried rice, fresh pasta, egg)										

Q.97. How many other children live in the baby's home

- *One*
- *Two*
- *Three*
- *Four or more*

Q.98. Eldest child: How often does this family member take the following?

	not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	everyd ay
Eldest child: Milk and milk products (e.g. custard, yoghurt, ice cream, chocolate, butter, margarines, cheese-pizza, cheese sauces, lasagne, cheesy biscuits)										
Eldest child: Wheat (e.g. bread, cereals, pasta, pizza, cakes, pies and pastry)										
Eldest child: White Fish (e.g. tuna, fish cakes, battered fish and fish fingers)										
Eldest child: Shell Fish (e.g. crab, prawns, shrimps, lobster and crayfish)										
Eldest child: Oily Fish (e.g. mackerel, salmon, sardines, pilchards, herring, kipper, white bait, trout, crab, FRESH tuna)										
Eldest child: Peanuts (e.g. Bombay Mix, peanut butter, peanut brittle, peanut cookies, satay, some vegetarian meals)										
Eldest child: Sesame (e.g. humus, tahini, bread or buns with sesame seeds, sesame crackers, sesame breadsticks or sesame snaps)										
Eldest child: Eggs and egg products (e.g. omelette/frittata, egg fried rice, fresh pasta, egg)										

Q.99. Second eldest child: How often does this family member take the following?

	not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	everyd ay
Second eldest child: Milk and milk products (e.g. custard, yoghurt, ice cream, chocolate, butter, margarines, cheese-pizza, cheese sauces, lasagne, cheesy biscuits)										
Second eldest child: Wheat (e.g. bread, cereals, pasta, pizza, cakes, pies and pastry)										
Second eldest child: White Fish (e.g. tuna, fish cakes, battered fish and fish fingers)										
Second eldest child: Shell Fish (e.g. crab, prawns, shrimps, lobster and crayfish)										
Second eldest child: Oily Fish (e.g. mackerel, salmon, sardines, pilchards, herring, kipper, white bait, trout, crab, FRESH tuna)										
Second eldest child: Peanuts (e.g. Bombay Mix, peanut butter, peanut brittle, peanut cookies, satay, some vegetarian meals)										
Second eldest child: Sesame (e.g. humus, tahini, bread or buns with sesame seeds, sesame crackers, sesame breadsticks or sesame snaps)										
Second eldest child: Eggs and egg products (e.g. omelette/frittata, egg fried rice, fresh pasta, egg)										

Q.100. Third eldest child: How often does this family member take the following?

	not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	everyd ay
Third eldest child: Milk and milk products (e.g. custard, yoghurt, ice cream, chocolate, butter, margarines, cheese-pizza, cheese sauces, lasagne, cheesy biscuits)	○	○	○	○	○	○	○	○	○	○
Third eldest child: Wheat (e.g. bread, cereals, pasta, pizza, cakes, pies and pastry)	○	○	○	○	○	○	○	○	○	○
Third eldest child: White Fish (e.g. tuna, fish cakes, battered fish and fish fingers)	○	○	○	○	○	○	○	○	○	○
Third eldest child: Shell Fish (e.g. crab, prawns, shrimps, lobster and crayfish)	○	○	○	○	○	○	○	○	○	○
Third eldest child: Oily Fish (e.g. mackerel, salmon, sardines, pilchards, herring, kipper, white bait, trout, crab, FRESH tuna)	○	○	○	○	○	○	○	○	○	○
Third eldest child: Peanuts (e.g. Bombay Mix, peanut butter, peanut brittle, peanut cookies, satay, some vegetarian meals)	○	○	○	○	○	○	○	○	○	○
Third eldest child: Sesame (e.g. humus, tahini, bread or buns with sesame seeds, sesame crackers, sesame breadsticks or sesame snaps)	○	○	○	○	○	○	○	○	○	○
Third eldest child: Eggs and egg products (e.g. omelette/frittata, egg fried rice, fresh pasta, egg)	○	○	○	○	○	○	○	○	○	○

Q.101. Fourth eldest child: How often does this family member take the following?

	not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	everyd ay
Fourth eldest child: Milk and milk products (e.g. custard, yoghurt, ice cream, chocolate, butter, margarines, cheese-pizza, cheese sauces, lasagne, cheesy biscuits)	○	○	○	○	○	○	○	○	○	○
Fourth eldest child: Wheat (e.g. bread, cereals, pasta, pizza, cakes, pies and pastry)	○	○	○	○	○	○	○	○	○	○
Fourth eldest child: White Fish (e.g. tuna, fish cakes, battered fish and fish fingers)	○	○	○	○	○	○	○	○	○	○
Fourth eldest child: Shell Fish (e.g. crab, prawns, shrimps, lobster and crayfish)	○	○	○	○	○	○	○	○	○	○
Fourth eldest child: Oily Fish (e.g. mackerel, salmon, sardines, pilchards, herring, kipper, white bait, trout, crab, FRESH tuna)	○	○	○	○	○	○	○	○	○	○
Fourth eldest child: Peanuts (e.g. Bombay Mix, peanut butter, peanut brittle, peanut cookies, satay, some vegetarian meals)	○	○	○	○	○	○	○	○	○	○
Fourth eldest child: Sesame (e.g. humus, tahini, bread or buns with sesame seeds, sesame crackers, sesame breadsticks or sesame snaps)	○	○	○	○	○	○	○	○	○	○
Fourth eldest child: Eggs and egg products (e.g. omelette/frittata, egg fried rice, fresh pasta, egg)	○	○	○	○	○	○	○	○	○	○

Q.102. How many other relatives live in the baby's home

- ○ *One*
- ○ *Two*
- ○ *Three*
- ○ *Four or more*

Q.103. Eldest other relative living in baby's home: How often does this family member take the following?

	not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	everyd ay
Eldest other relative: Milk and milk products (e.g. custard, yoghurt, ice cream, chocolate, butter, margarines, cheese-pizza, cheese sauces, lasagne, cheesy biscuits)	○	○	○	○	○	○	○	○	○	○
Eldest other relative: Wheat (e.g. bread, cereals, pasta, pizza, cakes, pies and pastry)	○	○	○	○	○	○	○	○	○	○
Eldest other relative: White Fish (e.g. tuna, fish cakes, battered fish and fish fingers)	○	○	○	○	○	○	○	○	○	○
Eldest other relative: Shell Fish (e.g. crab, prawns, shrimps, lobster and crayfish)	○	○	○	○	○	○	○	○	○	○
Eldest other relative: Oily Fish (e.g. mackerel, salmon, sardines, pilchards, herring, kipper, white bait, trout, crab, FRESH tuna)	○	○	○	○	○	○	○	○	○	○
Eldest other relative: Peanuts (e.g. Bombay Mix, peanut butter, peanut brittle, peanut cookies, satay, some vegetarian meals)	○	○	○	○	○	○	○	○	○	○
Eldest other relative: Sesame (e.g. humus, tahini, bread or buns with sesame seeds, sesame crackers, sesame breadsticks or sesame snaps)	○	○	○	○	○	○	○	○	○	○
Eldest other relative: Eggs and egg products (e.g. omelette/frittata, egg fried rice, fresh pasta, egg)	○	○	○	○	○	○	○	○	○	○

Q.104. **Second eldest other relative living in baby's home: How often does this family member take the following?**

	not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	everyd ay
Second eldest other relative: Milk and milk products (e.g. custard, yoghurt, ice cream, chocolate, butter, margarines, cheese-pizza, cheese sauces, lasagne, cheesy biscuits)										
Second eldest other relative: Wheat (e.g. bread, cereals, pasta, pizza, cakes, pies and pastry)										
Second eldest other relative: White Fish (e.g. tuna, fish cakes, battered fish and fish fingers)										
Second eldest other relative: Shell Fish (e.g. crab, prawns, shrimps, lobster and crayfish)										
Second eldest other relative: Oily Fish (e.g. mackerel, salmon, sardines, pilchards, herring, kipper, white bait, trout, crab, FRESH tuna)										
Second eldest other relative: Peanuts (e.g. Bombay Mix, peanut butter, peanut brittle, peanut cookies, satay, some vegetarian meals)										
Second eldest other relative: Sesame (e.g. humus, tahini, bread or buns with sesame seeds, sesame crackers, sesame breadsticks or sesame snaps)										
Second eldest other relative: Eggs and egg products (e.g. omelette/frittata, egg fried rice, fresh pasta, egg)										

Q.105. **Third eldest other relative living in baby's home: How often does this family member take the following?**

	not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	everyd ay
Third eldest other relative: Milk and milk products (e.g. custard, yoghurt, ice cream, chocolate, butter, margarines, cheese-pizza, cheese sauces, lasagne, cheesy biscuits)										
Third eldest other relative: Wheat (e.g. bread, cereals, pasta, pizza, cakes, pies and pastry)										
Third eldest other relative: White Fish (e.g. tuna, fish cakes, battered fish and fish fingers)										
Third eldest other relative: Shell Fish (e.g. crab, prawns, shrimps, lobster and crayfish)										
Third eldest other relative: Oily Fish (e.g. mackerel, salmon, sardines, pilchards, herring, kipper, white bait, trout, crab, FRESH tuna)										
Third eldest other relative: Peanuts (e.g. Bombay Mix, peanut butter, peanut brittle, peanut cookies, satay, some vegetarian meals)										
Third eldest other relative: Sesame (e.g. humus, tahini, bread or buns with sesame seeds, sesame crackers, sesame breadsticks or sesame snaps)										
Third eldest other relative: Eggs and egg products (e.g. omelette/frittata, egg fried rice, fresh pasta, egg)										

Q.106. **Fourth eldest other relative living in baby's home: How often does this family member take the following?**

	not eaten	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	everyd ay
Fourth eldest other relative: Milk and milk products (e.g. custard, yoghurt, ice cream, chocolate, butter, margarines, cheese-pizza, cheese sauces, lasagne, cheesy biscuits)										
Fourth eldest other relative: Wheat (e.g. bread, cereals, pasta, pizza, cakes, pies and pastry)										
Fourth eldest other relative: White Fish (e.g. tuna, fish cakes, battered fish and fish fingers)										
Fourth eldest other relative: Shell Fish (e.g. crab, prawns, shrimps, lobster and crayfish)										
Fourth eldest other relative: Oily Fish (e.g. mackerel, salmon, sardines, pilchards, herring, kipper, white bait, trout, crab, FRESH tuna)										
Fourth eldest other relative: Peanuts (e.g. Bombay Mix, peanut butter, peanut brittle, peanut cookies, satay, some vegetarian meals)										
Fourth eldest other relative: Sesame (e.g. humus, tahini, bread or buns with sesame seeds, sesame crackers, sesame breadsticks or sesame snaps)										
Fourth eldest other relative: Eggs and egg products (e.g. omelette/frittata, egg fried rice, fresh pasta, egg)										

Mother's Health

Q.107. How often have you taken the following during your pregnancy?

	never	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	every day
Pregnancy: Vitamin/mineral/folic acid supplement (e.g. Pregnacare or Sanatogen Mother To Be)	○	○	○	○	○	○	○	○	○	○
Pregnancy: Paracetamol	○	○	○	○	○	○	○	○	○	○
Pregnancy: Heartburn/reflux medication (e.g. Gaviscon)	○	○	○	○	○	○	○	○	○	○

Q.108. Have you taken Folic Acid during this pregnancy?

- ○ *No*
- ○ *Yes - started pre conception*
- ○ *Yes - started after conception (0 to 5 weeks)*
- ○ *Yes - started after conception (6 to 12 weeks)*
- ○ *Yes - started after conception (after 12 weeks)*

Q.109. How often have you taken the following during breast feeding?

	never	once a mth or less	once every 2 wks	once a week	twice a week	3 times a week	4 times a week	5 times a week	6 times a week	every day
Breast feeding: Vitamin/mineral/folic acid supplement (e.g. Pregnacare Breast-feeding or Sanatogen New Mother)	○	○	○	○	○	○	○	○	○	○
Breast feeding: Vitamin D supplements alone (400 IU or 10 ug)	○	○	○	○	○	○	○	○	○	○

Many thanks for completing the questionnaire.
Please click the submit button.
Do please contact us if you have any queries about the questions.
eatstudy@gstt.nhs.uk OR 0800 358 0021
We look forward to seeing you and your baby shortly at St Thomas'

The EAT Study Team

APPENDIX 15 - Enrolment general questionnaire

ID.name **Name, login or ID of respondent**

EAT 3 Month General Questionnaire

This questionnaire asks about your baby and family.
It includes questions about your family's health and environment.

The questionnaire takes about 20 minutes to complete.
If you need to break off midway - click the save button
and when you return by clicking the link in your email
you will resume from the saved position.

Q1. **Baby's mother's first name**

Q2. **Baby's mother's surname**

Q3. **What ethnic group does your baby belong to?**

- *White*
- *Mixed*
- *Asian or Asian British*
- *Black or Black British*
- *Chinese or other ethnic group*

Q4. **White: Please tick the appropriate box to indicate your cultural background**

- *British*
- *Irish*
- *Any other White background*

If "Any other White background". Please describe.

Q5. **Mixed: Please tick the appropriate box to indicate your cultural background**

- *White and Black Caribbean*
- *White and Black African*
- *White and Asian*
- *Any other Mixed background*

If "Any other Mixed background". Please describe.

Q6. **Asian or Asian British. Please tick the appropriate box to indicate your cultural background**

- *Indian*
- *Pakistani*
- *Bangladeshi*
- *Any other Asian background*

If "Any other Asian background". Please describe.

Q7. **Black or Black British. Please tick the appropriate box to indicate your cultural background**

- *Caribbean*
- *African*
- *Any other Black background*

If "Any other Black background". Please describe.

Q8. **Chinese or other ethnic group. Please tick the appropriate box to indicate your cultural background**

- *Chinese*
- *Any other*

If "Any other". Please describe.

Family size

Q9. **Does your child have any brothers or sisters?**

- *Yes*
- *No*

Q10. **If "yes", How many brothers and sisters?**

Number of brothers

Number of sisters

Family background

Q11. **Mother's age in years**

Q12. **Father's age in years**

Q13. **How old was the baby's mother when she left full-time education?**

- *16 years or less*
- *17 or 18 years*
- *19 years or over*
- *Still studying*

Q14. **What is or was the baby's mother's paid occupation?**

Q15. **How old was the baby's father when he left full-time education?**

- *16 years or less*
- *17 or 18 years*
- *19 years or over*
- *Still studying*

Q16. **What is or was the baby's father's paid occupation?**

Family history of allergy

Q17. **Which relative(s) have ever suffered from asthma?**
Tick as many boxes as apply

- [ ] *None*
- [ ] *Mother of the baby*
- [ ] *Father of the baby*
- [ ] *Grandparents of the baby*
- [ ] *Siblings (brothers or sisters of the baby)*

Number of affected siblings

Q18. **Which relative(s) have ever suffered from eczema**
Tick as many boxes as apply

- [ ] *None*
- [ ] *Mother of the baby*
- [ ] *Father of the baby*
- [ ] *Grandparents of the baby*
- [ ] *Siblings (brothers or sisters of the baby)*

Number of affected siblings

Q19. **Which relative(s) have ever suffered from hay fever**
Tick as many boxes as apply

- [ ] *None*
- [ ] *Mother of the baby*
- [ ] *Father of the baby*
- [ ] *Grandparents of the baby*
- [ ] *Siblings (brothers or sisters of the baby)*

Number of affected siblings

Q20. **Which relative(s) have ever suffered from food allergies?**
Tick as many boxes as apply

- [ ] *None*
- [ ] *Mother of the baby*
- [ ] *Father of the baby*
- [ ] *Grandparents of the baby*
- [ ] *Siblings (brothers or sisters of the baby)*

Number of affected siblings

Q21. **Please list the foods to which the family member(s) have an allergy to**

Mother's food allergies

Father's food allergies

Grandparent's food allergies

Sibling's food allergies

Home environment

Q22. **What type of fuel is <u>mainly</u> used for heating your baby's home?**

- ○ *Gas*
- ○ *Oil*
- ○ *Electricity*
- ○ *Wood*
- ○ *Coal*
- ○ *Other*

Q23. **Does your house have a water softener fitted?**

- *Yes*
- *No*

Q24. **In what type of area do you live?**

- *Urban*
- *Rural - non-farm*
- *Rural - farm*

Q25. **What is the postcode of the baby's home?**

Q26. **How would you describe the location of your house?**

- *In a street with very dense traffic (main road)*
- *In a street with moderate traffic (residential road)*
- *In a quiet street/road with little or no traffic*

Q27. **Are there any areas of mould in your flat or house?**

- *Yes*
- *No*

Smoking

Q28. **Does any household member currently smoke?**

- *Yes*
- *No*

Q29. **Which household member(s) smoke?**

	In the house	*Outside only*	*Non-smoker*
Mother smoking location			
Father smoking location			
Other household member smoking location			

If "Other household member". Who?

Q30. **Did the mother smoke during pregnancy?**

- *Yes*
- *No*

Child care

Q31. **Does your baby attend a childminder or day care (nursery or crèche)?**

- *No*
- *Childminder*
- *Nursery/crèche*

Q32. **How many hours per week does your child spend at a childminder or day care?**

Q33. **How old (in weeks) was your baby when he/she first started to attend a childminder or day care?**

Q34. **Approximately how many other children are cared for?**

Childminder number of children cared for

Nursery/crèche number of children cared for

Q35. **Are there pets present at the childminders or day care?**

	Yes	*No*
Pets at childminder		
Pets at nursery or crèche		

Direct pet contact

Q36. **Do you currently own any pets?**

- ☐ *None*
- ☐ *Dog*
- ☐ *Cat*
- ☐ *Horse or pony*
- ☐ *Other*

If "Other". Please describe.

Q37. **How many pets do you own?**

Number of dogs owned	☐
Number of cats owned	☐
Number of horses or ponies owned	☐
Number of other pets owned	☐

Q38. **Where are the pets allowed?**

	Outside only	*Inside*	*In baby's bedroom*
Dog location in house	☐	☐	☐
Cat location in house	☐	☐	☐
Other pet location in house	☐	☐	☐

Q39. **On average, how many hours per week does your baby spend visiting places with pets?**
This is asking about contact with pets in places other than the baby's home

☐

Indirect pet contact

Q40. **Does your baby have regular contact (once a week or more) with pet owning friends and/or family?**
This is asking about contact with the people who own the pets rather than the pets themselves

- ○ *Yes*
- ○ *No*

Q41. **On average, how many hours per week does your baby spend in contact with pet owning friends and/or family?**
This is asking about contact with the people who own the pets rather than the pets themselves

☐

Pet avoidance behaviour

Q42. **Have you chosen not to have any pets or a particular type of pet because of allergies within the family?**

- ○ *Yes*
- ○ *No*

Q43. **Have you disposed of a pet since your baby was born?**

- ○ *Yes*
- ○ *No*

If yes, what type of pet/s and why were they removed from the home?

Infant Health

Questions on chest problems

Q44. **Has your baby ever had wheezing or whistling in the chest at any time point in the past?**
(By "wheezing" we mean breathing that makes a high-pitched whistling or squeaking sound from the chest, not the throat)

- ○ *Yes*
- ○ *No*

Q45. How old (in weeks) was your baby when he/she first began to wheeze?

Q46. Has your baby had wheezing or whistling in the chest during or soon after a cold or flu?

- *Yes*
- *No*

Q47. Has your baby had wheezing or whistling in the chest even without having a cold or flu?

- *Yes*
- *No*

Q48. How many episodes of wheezing has your child had?

- *1 to 3*
- *4 to 12*
- *More than 12*

Q49. Do these episodes cause him/her to be short of breath?

- *Yes, always*
- *Yes, occasionally*
- *No, never*

Questions on skin problems

Q50. Has your child ever had swelling of the skin?

- *Yes*
- *No*

Q51. Which part of the body has been affected? (tick as many as apply)

- *Lips and/or face*
- *Elsewhere on the body*

Q52. At what age (in weeks) did this swelling first occur?

Q53. Has your child ever had hives (medical name: urticaria)?

- *Yes*
- *No*

Q54. At what age (in weeks) did the hives (urticaria) first appear?

Q55. Has your baby had an itchy skin condition? (By "itchy" we mean scratching or rubbing the skin)

- *Yes*
- *No*

Q56. Has your baby had this itchy skin condition in the last week?

- *Yes*
- *No*

Q57. Has this itchy skin condition affected the skin creases? (By "skin creases" we mean the fronts of the elbows, behind the knees, the front of the ankles, under the buttocks, around the neck, around the eyes or the ears)

- *Yes*
- *No*

Q58. Has this skin condition affected the skin away from the creases; e.g. the cheeks, forearms or the lower legs?

- *Yes*
- *No*

Q59. **Does your baby suffer from generally dry skin?**

- *Yes*
- *No*

Q60. **Does your child have eczema?**

- *Yes*
- *No*

Q61. **Was this confirmed by a doctor?**

- *Yes*
- *No*

Patient-Orientated Eczema Measure (POEM)

Q62. **Over the last week, on how many days has your baby's....**

	No days	*1-2 days*	*3-4 days*	*5-6 days*	*Every day*
....skin been itchy because of the eczema?					
....sleep been disturbed because of the eczema?					
...skin been bleeding because of the eczema?					
....skin been weeping or oozing clear fluid because of the eczema?					
....skin been cracked because of the eczema?					
....skin been flaking off because of the eczema?					
....skin felt dry or rough because of the eczema?					

Hygiene Practices

Q63. **How often in a normal day is your baby's face washed or wiped?**

- *Not at all*
- *1-2 times*
- *3-4 times*
- *5 or more times*

Q64. **Do you normally use baby wipes/wet wipes for this?**

- *Yes*
- *No*

Q65. **How often in a normal day are your baby's hands washed or wiped?**

- *Not at all*
- *1-2 times*
- *3-4 times*
- *5 or more times*

Q66. **Do you normally use baby wipes/wet wipes for this?**

- *Yes*
- *No*

Q67. **How often do you bathe your baby?**

- *Hardly ever*
- *Once a week*
- *2-4 times a week*
- *5-6 times a week*
- *Daily*
- *More than daily*

Skin treatments

Q68. **Do you use any products in the bath? (*Tick as many as apply)***

- ☐ *None*
- ☐ *Bubble bath*
- ☐ *Bath emollient (e.g. Aveeno Bath Oil, Oilatum Bath Emollient, Balneum Bath Oil)*
- ☐ *Shampoo*
- ☐ *Soap*
- ☐ *Other*

If "Other". Please describe.

Q69. **Do you use any moisturising cream/lotion/oil on your baby?**

- ○ *Never*
- ○ *Once a week or less*
- ○ *2-4 times a week*
- ○ *5-6 times a week*
- ○ *Daily*
- ○ *More than daily*

Q70. **What is the name of the moisturising cream/lotion/oil that you use most frequently?**

Q71. **How old (in weeks) was your baby when you started using moisturising cream/lotion/oil on their skin?**

Q72. **Do you use any steroid cream(s) on your baby?**

- ○ *Never*
- ○ *Once a week or less*
- ○ *2-4 times a week*
- ○ *5-6 times a week*
- ○ *Daily*
- ○ *More than daily*

Q73. **Please name the steroid cream(s) that you use?**

Q74. **How old (in weeks) was your baby when you started using steroid cream on their skin?**

Q75. **Have you used either Protopic (tacrolimus) or Elidel (pimecrolimus) on your baby's skin?**

	Yes	*No*
Protopic	○	○
Elidel	○	○

Tummy complaints

Q76. **Has your baby been affected by the following conditions?**

	Never	*Monthly or less*	*Weekly*	*2-4 times a week*	*5-6 times a week*	*Daily*	*More than once daily*
Posseting (bringing back up small amounts of milk, often with swallowed air or 'wind')	○	○	○	○	○	○	○
Vomiting (without a temperature)	○	○	○	○	○	○	○
Colic (sudden continuous crying, bloated stomach, steadily passing wind, cramping and pulling up legs)	○	○	○	○	○	○	○

Q77. **What age (in weeks) did the condition first occur?**

Posseting age at first occurence ☐

Vomiting age at first occurence ☐

Colic age at first occurence ☐

Q78. **How many <u>days</u> has your baby been affected by the following conditions (Write "0" if none)**

Diarrhoea - days affected ☐

Constipation - days affected ☐

Q79. **At what age (in weeks) was your baby first affected?**

Diarrhoea age when first affected ☐

Constipation age when first affected ☐

Q80. **<u>On average</u>, how often does your baby have a bowel movement?**

- ○ *Once a day or more*
- ○ *Less than once a day*

Q81. **On average, how many times <u>per day</u> does your baby have a bowel movement**

☐

Q82. **On average, how many times <u>per week</u> does your baby have a bowel movement**

☐

Illnesses

Q83. **Has your baby had any of the following illnesses?**

	Never	*Once*	*Twice*	*Three times*	*Four times*	*Five or more times*
Upper respiratory tract infection (a cold) episodes	○	○	○	○	○	○
Lower respiratory tract infection (chest infection) episodes	○	○	○	○	○	○
Bronchiolitis episodes	○	○	○	○	○	○
Other infections episodes	○	○	○	○	○	○

If "Other infections", please list

Medications and supplements

Q84. **Approximately how many <u>courses</u> of antibiotics has your baby received since birth?**

- ○ *None*
- ○ *One*
- ○ *Two*
- ○ *Three*
- ○ *Four*
- ○ *Five or more*

Q85. **How old was your baby when they received their first course of antibiotics?**

☐

Q86. **Have you given your child any of the following?**

	Never	*Once*	*Twice*	*Three times*	*Four times*	*Five or more times*
Paracetamol (Calpol) frequency	○	○	○	○	○	○
Ibuprofen (Neurofen) frequency	○	○	○	○	○	○

Q87. **Have you given your child any vitamins or other supplements?**

- ☐ *Vitamin preparations (e.g. Abidec, Dalivit or Healthy Start)*
- ☐ *Iron containing preparations (e.g. Sytron, Ferrous sulphate)*
- ☐ *Mineral preparations*
- ☐ *Fish Oil supplements*
- ☐ *None*

Breast feeding

Q88. **Has your baby had any of the following to drink?**

- ☐ *Oral Rehydration Solution (e.g. Dioralyte)*
- ☐ *Water*
- ☐ *Formula milk*
- ☐ *None of the above*

Q89. **If yes, at what age (in weeks) did you baby start drinking the following:**

Oral Rehydration Solution (e.g. Dioralyte) age first drank ☐

Water - age first drank ☐

Formula milk - age first drank ☐

Q90. **How many times does your baby breast feed in a 24 hour period?**

☐

Q91. **On average, how long does each breast feed last (in minutes)?**

☐

Q92. **How much formula milk has your baby had in total?**

- ☐ *One bottle or less*
- ☐ *Two bottles*
- ☐ *3-5 bottles*
- ☐ *More than five bottles*

Quality of Life

We are measuring the baby's mother's Quality of Life. We will repeat this measure at the 1 year and 3 year assessments. We are using a widely used measure of Quality of Life produced by the World Health Organization.

The following questions ask how the baby's mother feels about her quality of life, health or other areas of life. Please choose the answer that appears most appropriate. If you are unsure which response to give to a question, the first response you think of is often the best one. We ask that you think about your life in the last four weeks.

In this section on Quality of Life please skip any questions you are not comfortable with answering.

Q93. ***How would you rate your quality of life?***

	Very poor	*Poor*	*Neither poor nor good*	*Good*	*Very good*
How would you rate your quality of life?	○	○	○	○	○

Q94.

	Very dissatisfied	*Dissatisfied*	*Neither satisfied or dissatisfied*	*Satisfied*	*Very satisfied*
How satisfied are you with your health?	○	○	○	○	○

The following questions ask how much you have experienced certain things in the last four weeks.

Q95.

	Not at all	*A little*	*A moderate amount*	*Very much*	*An extreme amount*
To what extent do you feel that physical pain prevents you from doing what you need to do?	○	○	○	○	○
How much do you need any medical treatment to function in your daily life?	○	○	○	○	○
How much do you enjoy life?	○	○	○	○	○
To what extent do you feel your life to be meaningful?	○	○	○	○	○

Q96.

	Not at all	*A little*	*A moderate amount*	*Very much*	*Extremely*
How well are you able to concentrate?	○	○	○	○	○
How safe do you feel in your daily life?	○	○	○	○	○
How healthy is your physical environment?	○	○	○	○	○

The following questions ask about how completely you experience or were able to do certain things in the last four weeks.

Q97.

	Not at all	*A little*	*Moderately*	*Mostly*	*Completely*
Do you have enough energy for everyday life?	○	○	○	○	○
Are you able to accept your bodily appearance?	○	○	○	○	○
Have you enough money to meet your needs?	○	○	○	○	○
How available to you is information that you need in your day-to-day life?	○	○	○	○	○
To what extent do you have the opportunity for leisure activities?	○	○	○	○	○

Q98.

	Very poor	*Poor*	*Neither good nor poor*	*Good*	*Very good*
How well are you able to get around?	○	○	○	○	○

Q99.

	Very dissatisfied	*Dissatisfied*	*Neither satisfied or dissatisfied*	*Satisfied*	*Very satisfied*
How satisfied are you with your sleep?	○	○	○	○	○
How satisfied are you with your ability to perform your daily living activities?	○	○	○	○	○
How satisfied are you with your capacity to work?	○	○	○	○	○
How satisfied are you with yourself?	○	○	○	○	○
How satisfied are your with your personal relationships?	○	○	○	○	○
How satisfied are you with your sex life?	○	○	○	○	○
How satisfied are you with the support you get from your friends?	○	○	○	○	○
How satisfied are you with the conditions of your living place?	○	○	○	○	○
How satisfied are you with your access to health services?	○	○	○	○	○
How satisfied are you with your transport?	○	○	○	○	○

The following question refers to how often you have felt or experienced certain things in the last four weeks.

Q100.

	Never	*Seldom*	*Quite often*	*Very often*	*Always*
How often do you have negative feelings such as blue mood, despair, anxiety, depression?	○	○	○	○	○

Baby's sleep pattern

These questions refer to your baby's sleep on average during the last week

Q101.

Where does your baby sleep?

- ○ *Infant cot/Moses basket in a separate room alone*
- ○ *Infant cot/Moses basket in the parent(s) bedroom*
- ○ *In parent(s) bed*
- ○ *Infant cot/Moses basket in room with a sibling (brother or sister)*

Other (please specify)

Q102.

How much time does your baby spend in sleep during the NIGHT (between 7 in the evening and 7 in the morning)?
Please enter time as hours.minutes e.g. Five hours would be 5.00

Q103.

How much time does your baby spend in sleep during the DAY (between 7 in the morning and 7 in the evening)?
Please enter time as hours.minutes e.g. Two and a half hours would be 2.30

Q104.

Average number of night wakings per night?

Q105.

How much time does your baby spend in wakefulness (from 10 in the evening to 6 in the morning)?
Please enter time as hours.minutes e.g. Two and a half hours would be 2.30

Q106. **How long does it take to put your baby to sleep in the evening?**
Please enter time as hours.minutes e.g. Thirty minutes would be 0.30

Q107. **How does your baby fall asleep?**

- *While feeding*
- *Being rocked*
- *Being held*
- *In bed alone*
- *In bed near parent*

Q108. **At what time does your baby usually fall asleep for the night?**
***Please enter time as e.g.* 7.30 pm**

Q109. **Do you consider your baby's sleep as a problem?**

- *Not a problem at all*
- *A small problem*
- *A very serious problem*

Many thanks for completing the questionnaire.
Please click the submit button.
Do please contact us if you have any queries about the questions.
eatstudy@gstt.nhs.uk OR 0800 358 0021
We look forward to seeing you and your baby shortly at St Thomas'

The EAT Study Team

APPENDIX 16 - Example interim questionnaire

12 Month Questionnaire

This is the twelve month questionnaire.
It asks about your baby's health and diet.

The questionnaire takes about 30 minutes to complete.
If you need to break off midway - click the save button
and when you return by clicking the link in your email
you will resume from the saved position.

Several questions recur throughout these monthly questionnaires.
These are usually of the format *"at what age in weeks did you....".*
We repeat these to ensure that we have answers to key questions
(particularly important if a mother has skipped earlier questionnaires).
Don't worry if you are no longer sure what the exact age was for these questions.
Where a mother has answered the question on multiple occasions
we will take the earliest response as the most accurate.

EAT
Enquiring About Tolerance

2. **Baby's mother's first name**

3. **Baby's mother's surname**

Infant Food Frequency Questionnaire

We are asking you to complete this short food frequency questionnaire.
It is specifically asking about foods that contain the six intervention foods.

There is a "Never" category if your infant has not eaten a particular food.

Try to remember as precisely as you can how often your infant has consumed the food during the last month.
It might help to think of your infant's consumption in terms of the standard portion of each food that they usually eat.

Example 1: If your infant eats two standard portions of a food on two days of the week
and one standard portion on another day, the infant would have had five portions in a week.
On the food frequency questionnaire you would tick the "4-6 times a week" box.

Example 2: If your infant eats a total of eight standard portions or more of a food each week,
on the food frequency questionnaire you would tick the "More than once daily" box.

The first question asks about commercial baby foods/products that contain milk, wheat or egg.
The dietician may have given you a list of examples of these that
you can refer to when completing this question.
If you do not have this list or have mislaid it you can download it from our website at:
www.eatstudy.co.uk/documents/Commercialbabyfoods.pdf

4. **In the last month how often has your infant eaten: Commercial baby foods/products**

	More than once daily	*Daily*	*4-6 times a week*	*2-3 times a week*	*Once a week*	*Once a fortnight*	*Once a month*	*Never*
Commercial baby food containing **milk** (see list)	○	○	○	○	○	○	○	○
Commercial baby food containing **wheat** (see list)	○	○	○	○	○	○	○	○
Commercial baby foods containing **egg** (see list)	○	○	○	○	○	○	○	○

5. **In the last month how often has your infant eaten: Wheat containing foods**

	More than once daily	*Daily*	*4-6 times a week*	*2-3 times a week*	*Once a week*	*Once a fortnight*	*Once a month*	*Never*
Wheat-containing breakfast cereals (e.g. Weetabix, Shreddies, Cheerios)	○	○	○	○	○	○	○	○
Bread/Toast/Breadsticks	○	○	○	○	○	○	○	○
Cooked dried pasta/Couscous/Semolina	○	○	○	○	○	○	○	○
Fresh pasta/Noodles (i.e. containing egg)	○	○	○	○	○	○	○	○
Pastry/Pie	○	○	○	○	○	○	○	○
Tortilla wraps/Fajitas/Pizza	○	○	○	○	○	○	○	○

6. **In the last month how often has your infant eaten: Egg containing foods**

	More than once daily	*Daily*	*4-6 times a week*	*2-3 times a week*	*Once a week*	*Once a fortnight*	*Once a month*	*Never*
Eggs (boiled, poached, fried, scrambled, omelette)	○	○	○	○	○	○	○	○
Croissant/Brioche	○	○	○	○	○	○	○	○
Scones including cheese scones	○	○	○	○	○	○	○	○
Cake/Sponge pudding	○	○	○	○	○	○	○	○
Pancakes/Crumpet	○	○	○	○	○	○	○	○
Jaffa Cakes	○	○	○	○	○	○	○	○
Quiche	○	○	○	○	○	○	○	○
Mayonnaise/Salad cream	○	○	○	○	○	○	○	○

7. **In the last month how often has your infant eaten: Milk containing foods**

	More than once daily	*Daily*	*4-6 times a week*	*2-3 times a week*	*Once a week*	*Once a fortnight*	*Once a month*	*Never*
Fromage frais/Yoghurt/Ice cream/Milk puddings (e.g. Rice pudding / Semolina /Tapioca/Macaroni pudding)	○	○	○	○	○	○	○	○
Custard/Triffle/Dairy desserts (e.g. Milky Bar Dessert, Rolo Dessert, Chocolate Mousse, Angel Delight)	○	○	○	○	○	○	○	○
Cream of any type (e.g. double cream)	○	○	○	○	○	○	○	○
Soft cheese/Spreadable cheese/Cream cheese	○	○	○	○	○	○	○	○
Cheese sauce (e.g. Cauliflower cheese)	○	○	○	○	○	○	○	○
Hard cheese	○	○	○	○	○	○	○	○

8. **In the last month how often has your infant eaten: Fish containing foods**

	More than once daily	*Daily*	*4-6 times a week*	*2-3 times a week*	*Once a week*	*Once a fortnight*	*Once a month*	*Never*
Fish fingers	○	○	○	○	○	○	○	○
Fish cakes	○	○	○	○	○	○	○	○
Fish (including tuna)/Fish pie	○	○	○	○	○	○	○	○
Commercial baby food containing fish (e.g. Tuna and Tomato with Rice, Cheesy Vegetables with Fish)	○	○	○	○	○	○	○	○

9. **In the last month how often has your infant eaten: Nut containing foods**

	More than once daily	*Daily*	*4-6 times a week*	*2-3 times a week*	*Once a week*	*Once a fortnight*	*Once a month*	*Never*
Peanut butter	○	○	○	○	○	○	○	○
Peanut containing cereal (including Crunchy Nut Cornflakes, Honey Nut Loops)	○	○	○	○	○	○	○	○
Peanut containing chocolates (including Snickers /Topic/Celebrations)	○	○	○	○	○	○	○	○

10. **In the last month how often has your infant eaten: Sesame containing foods**

	More than once daily	*Daily*	*4-6 times a week*	*2-3 times a week*	*Once a week*	*Once a fortnight*	*Once a month*	*Never*
Hummus	○	○	○	○	○	○	○	○
Tahini	○	○	○	○	○	○	○	○
Sesame crackers/Sesame breadsticks	○	○	○	○	○	○	○	○
Sesame snaps	○	○	○	○	○	○	○	○
Bread or Burger buns with sesame seeds	○	○	○	○	○	○	○	○

11. **In the last month how often has your infant eaten other food known to contain egg, wheat, milk, fish, sesame or peanuts as a significant ingredient (Please list food and frequency eaten)**

12. **Please list any (up to five) other specific foods that don't contain any of the six intervention foods (i.e. not containing wheat, egg, milk, fish, peanut or sesame) that your infant has eaten most frequently in the last month**

Feeding issues

13. **Most babies' first foods are a puree. Have you started giving your baby foods with lumps in?**

- ○ *Yes*
- ○ *No*

If yes, at what age did you start giving your baby foods with lumps in (weeks)?

14. **Have you started giving your baby finger foods (solid foods that they can hold in their hand and chew/suck)?**

- ○ *Yes*
- ○ *No*

If yes, at what age did you start giving your baby finger foods (weeks)?

15. **In the past two weeks, have you had any difficulties getting your baby to eat what you want them?**

- ○ *Great difficulty*
- ○ *Some difficulty*
- ○ *Occasional difficulty*
- ○ *No difficulty*

16. **The following questions are about your baby's usual feeding behaviour (not during illness, where feeding worsens for a short period of time).**

	Strongly agree	*Agree*	*Neither agree nor disagree*	*Disagree*	*Strongly disagree*	*Not applicable*
My child's diet consists of only a few foods	○	○	○	○	○	○
My child is unwilling to eat many of the foods that our family eats at mealtimes	○	○	○	○	○	○
My child is fussy/picky about what foods s/he eats	○	○	○	○	○	○
My child does not trust new foods	○	○	○	○	○	○
My child is afraid to eat things s/he has never had before	○	○	○	○	○	○
My child is constantly sampling new and different foods	○	○	○	○	○	○
If my child doesn't know what's in a new food, then s/he won't try it	○	○	○	○	○	○

17. **Is your infant in the early introduction group or the standard weaning group?**

○ *Early introduction*

○ *Standard weaning*

If in Standard Weaning group, please go to Q23

Early Introduction Group Children

In this section we ask how much of the six intervention foods your infant has been eating.

The dietician will have given you a weekly diary to help you keep track of this and you should use this to help you complete our diary below. If you have mislaid this you can download it from our website at: www.eatstudy.co.uk/documents/EATWeeklyDiary_000.pdf

We have divided the month up into four weeks. Use the last four completed weeks before your baby turned 12 months old from your weekly diary.

Each row has an option for "Not tried yet" and you should select this where appropriate.

The following table is to help remind you what the weekly guideline amounts (100%) are for some examples of the key foods and what 25%, 50% and 75% of these amounts would look like.

	25% or less	50%	75%	100%
Cow's milk (Yoghurt)	½ pot	1 pot	1½ pots	2 pots
Egg	¼ egg	½ egg	¾ egg	1 egg
Fish	½ fish finger	1 fish finger	1½ fish fingers	2 fish fingers
Peanut	¾ teaspoon peanut butter	1½ teaspoons peanut butter	2¼ teaspoons peanut butter	3 teaspoons peanut butter
Sesame	¾ teaspoon tahini	1½ teaspoons tahini	2¼ teaspoons tahini	3 teaspoons tahini
Wheat	½ Weetabix biscuit	1 Weetabix biscuit	1½ Weetabix biscuits	2 Weetabix biscuits

Frequency of consumption of the six intervention foods

18. **Week 1**

	Not tried yet	*25% or less*	*50%*	*75%*	*100%*
Cow's milk (yoghurt) Week 1	○	○	○	○	○
Egg Week 1	○	○	○	○	○
Fish Week 1	○	○	○	○	○
Peanut (butter) Week 1	○	○	○	○	○
Sesame (tahini) Week 1	○	○	○	○	○
Wheat Week 1	○	○	○	○	○

19. **Week 2**

	Not tried yet	*25% or less*	*50%*	*75%*	*100%*
Cow's milk (yoghurt) Week 2	○	○	○	○	○
Egg Week 2	○	○	○	○	○
Fish Week 2	○	○	○	○	○
Peanut (butter) Week 2	○	○	○	○	○
Sesame (tahini) Week 2	○	○	○	○	○
Wheat Week 2	○	○	○	○	○

20. **Week 3**

	Not tried yet	*25% or less*	*50%*	*75%*	*100%*
Cow's milk (yoghurt) Week 3	○	○	○	○	○
Egg Week 3	○	○	○	○	○
Fish Week 3	○	○	○	○	○
Peanut (butter) Week 3	○	○	○	○	○
Sesame (tahini) Week 3	○	○	○	○	○
Wheat Week 3	○	○	○	○	○

21. **Week 4**

	Not tried yet	*25% or less*	*50%*	*75%*	*100%*
Cow's milk (yoghurt) Week 4	○	○	○	○	○
Egg Week 4	○	○	○	○	○
Fish Week 4	○	○	○	○	○
Peanut (butter) Week 4	○	○	○	○	○
Sesame (tahini) Week 4	○	○	○	○	○
Wheat Week 4	○	○	○	○	○

Alert!

Your baby has eaten 50% or less of:

Cow's milk on {V2} weeks

Egg on {V3} weeks

Fish on {V4} weeks

Peanut on {V5} weeks

Sesame on {V6} weeks

Your baby may have been avoiding a food because of an allergy or a feeding problem that we are aware of.

In all other circumstances we think it is important that in order to protect your baby from developing a food allergy that they be eating the full weekly guideline amounts of the intervention foods.

Please contact us if you are having difficulties feeding the foods to your baby or you suspect your baby is having a problem with a food that you have not told us about.

Otherwise, we encourage you to try to feed your baby the required weekly guideline amounts.

22. **If you have had a particular problem with your baby consuming the foods over the past month please provide brief details in the following box**

Breastfeeding

23. **Is your baby still being breastfed?**

- *Yes*
- *No*

24. **How many times does your baby breastfeed in a 24 hour period?**

25. **On average, how long does each breastfeed last (in minutes)?**

26. **If no longer breast feeding, at what age did you stop breastfeeding your baby (in weeks)?**

Formula milk

27. **Has your baby ever had formula milk to drink?**

- *Yes*
- *No*

28. **At what age (in weeks), did your baby first have formula milk?**

29. **Is your baby currently having formula milk to drink**

- *Yes*
- *No*

30. **Which formula milk does your baby mainly have?**

- *Cow's milk based infant formula (e.g. Aptamil, Cow & Gate, SMA)*
- *Soya based infant formula (e.g. Wysoy, Infasoy)*
- *Rice based infant formula*
- *Oat based infant formula*
- *Goat's milk based infant formula*
- *Hydrolysed milk (e.g. Nutramigen, Pregestimil)*
- *Elemental milk (e.g. Neocate, Nutramigen AA)*

31. **How frequently does your baby have formula milk to drink on average?**

- *Less than daily*
- *Once a day or more*

32. **On average, how many bottles of formula milk does your baby drink?**

Number of bottles of formula milk per week (*If less than daily*)

Number of bottles of formula milk per day (*If once a day or more*)

33. **How much milk does your baby drink in each bottle on average?**
Answer in millilitres or ounces - whichever you prefer

Millilitres (mls) drank in each bottle

Ounces drank in each bottle

Health

Questions on chest problems

34. **Since you completed the eleven month questionnaire has your baby had wheezing or whistling in the chest?**
(By "wheezing" we mean breathing that makes a high-pitched whistling or squeaking sound from the chest, not the throat)

- *Yes*
- *No*

35. **Since you completed the eleven month questionnaire has your baby had wheezing or whistling in the chest during or soon after a cold or flu?**

- *Yes*
- *No*

36. **Since you completed the eleven month questionnaire has your baby had wheezing or whistling in the chest even without having a cold or flu?**

- *Yes*
- *No*

37. **Since you completed the eleven month questionnaire how many episodes of wheezing has your child had?**

- *1 to 3*
- *4 to 12*
- *More than 12*

38. **Since you completed the eleven month questionnaire over how many days have the wheezing episodes been occuring?**

39. **Since you completed the eleven month questionnaire have these episodes caused him/her to be short of breath?**

- *Yes, always*
- *Yes, occasionally*
- *No, never*

40. **Since you completed the eleven month questionnaire what is the outcome of the wheezing episodes?**

- *Unresolved*
- *Resolved completely*
- *Resolved but having caused other problems*

Please describe these other problems?

41. **Since you completed the eleven month questionnaire was any treatment required for the wheezing episode/s?**

	None	*Medications*	*Non-drug therapies*	*Medications and non-drug therapies*
Wheezing treatment				

The following questions refer to the last 12 months

42. **Has your child ever had wheezing or whistling in the chest at any time in the past?**

- *Yes*
- *No*

43. **Which of these two descriptions fits best your child's wheeze?**

- *My child has only short attacks of wheeze, for example with colds. In between these attacks, he/she does not normally wheeze*
- *My child wheezes always or a lot of the time. With colds he/she has attacks with more severe wheeze*

44. **In the last 12 months, how often, on average, has your child's sleep been disturbed due to wheezing?**

- *Never woken with wheezing*
- *Less than one night per week*
- *One or more nights per week*

45. **In the last 12 months, how much did wheezing interfere with your child's daily activities?**

- *Not at all*
- *A little*
- *A moderate amount*
- *A lot*

46. **In the last 12 months, did the following things cause wheezing in your child?**

	Yes	*No*	*Don't know*
Exercise (very active play)	○	○	○
Laughing, crying or excitement	○	○	○
Contact with pets or other animals	○	○	○
Food or drinks	○	○	○

47. **Looking back on the last 12 months, do you think your child has asthma?**

- ○ *Yes*
- ○ *No*

48. **In the last 12 months, did your child suffer from rattly breathing (ruttles)?**

- ○ *Never*
- ○ *Only with a cold*
- ○ *Sometimes even without a cold*
- ○ *Almost always*

Questions on ears, nose and throat problems

49. **In the past 12 months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she did NOT have a cold or the flu?**

- ○ *Yes*
- ○ *No*

50. **In the past 12 months, how much did this nose problem interfere with your child's daily activities?**

- ○ *Not at all*
- ○ *A little*
- ○ *A moderate amount*
- ○ *A lot*

51. **In the past 12 months, has your child snored at night?**

- ○ *Yes*
- ○ *No*

52. **If yes, how often?**

- ○ *Only with a cold*
- ○ *Sometimes even without a cold*
- ○ *Almost always*

53. **Did the snoring disturb your child's sleep?**

- ○ *Not at all*
- ○ *A little*
- ○ *A moderate amount*
- ○ *A lot*

54. **In the past 12 months, has your child had ear infections?**

- ○ *No, never*
- ○ *Yes, once*
- ○ *Yes, more than once*

Questions on coughing

55. **Does your child usually have a cough with colds?**

- ○ *Yes*
- ○ *No*

56. **Does your child have a cough even without having a cold?**

- ○ *No, never*
- ○ *Yes, sometimes*
- ○ *Yes, always*

57. **Do you think your child coughs more than other children?**

- *Yes*
- *No*

58. **In the last 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or a chest infection?**

- *Yes*
- *No*

59. **In the last 12 months, did the following things cause coughing in your child?**

	Yes	*No*	*Don't know*
Exercise (very active play)			
Laughing, crying or excitement			
Contact with pets or other animals			
Food or drinks			

Questions on skin problems

60. **Since you completed the eleven month questionnaire has you baby had swelling of the skin?**

- *Yes*
- *No*

61. **Which part of the body has been affected? (tick as many as apply)**

- *Lips and/or face*
- *Elsewhere on the body*

62. **Do you think this swelling was associated with your baby eating food?**

- *Yes*
- *No*

If yes, which food?

63. **Since you completed the eleven month questionnaire has your baby had hives (medical name: urticaria)?**

- *Yes*
- *No*

64. **Do you think this hives (urticaria) was associated with your baby eating food?**

- *Yes*
- *No*

If yes, which food?

Eczema

65. **Did your baby have eczema when we saw you at the Evelina Children's Hospital for the 3 month assessment?**

- *Yes*
- *No*

66. **Has you child developed eczema since we say you at the Evelina Children's Hospital for the 3 month assessment?**

- *Yes*
- *No*

67. **Was this confirmed by a doctor?**

- *Yes*
- *No*

68. **Is the eczema still present?**

- *Yes*
- *No*

69. **Has your baby's eczema flared/got worse, since you completed the eleven month questionnaire?**

- *Yes*
- *No*

70. **Did this flare result in you using any of your eczema treatments more frequently?**

- *Yes*
- *No*

71. **Did this flare result in you consulting a doctor or nurse?**

- *Yes* Please go to Q55
- *No* Please go to Q55

72. **Since you completed the eleven month questionnaire, has your baby had an itchy skin condition? (By "itchy" we mean scratching or rubbing the skin)**

- *Yes*
- *No*

73. **Has this itchy skin condition affected the skin creases? (By "skin creases" we mean the fronts of the elbows, behind the knees, the front of the ankles, under the buttocks, around the neck, around the eyes or the ears)**

- *Yes*
- *No*

74. **Has this skin condition affected the skin away from the creases; e.g. the cheeks, forearms or the lower legs?**

- *Yes*
- *No*

75. **Does your baby suffer from generally dry skin?**

- *Yes*
- *No*

76. **Since you completed the eleven month questionnaire would you say your baby has developed eczema?**

- *Yes*
- *No* If No, please go to Q56

77. **Was this confirmed by a doctor?**

- *Yes*
- *No*

Patient-Orientated Eczema Measure (POEM)

78. **Over the last week, on how many days has your baby's....**

	No days	*1-2 days*	*3-4 days*	*5-6 days*	*Every day*
....skin been itchy because of the eczema?	○	○	○	○	○
....sleep been disturbed because of the eczema?	○	○	○	○	○
...skin been bleeding because of the eczema?	○	○	○	○	○
....skin been weeping or oozing clear fluid because of the eczema?	○	○	○	○	○
....skin been cracked because of the eczema?	○	○	○	○	○
....skin been flaking off because of the eczema?	○	○	○	○	○
....skin felt dry or rough because of the eczema?	○	○	○	○	○

Hygiene Practices

79. **How often in a normal day is your baby's face washed or wiped?**

- ○ *Not at all*
- ○ *1-2 times*
- ○ *3-4 times*
- ○ *5 or more times*

80. **Do you normally use baby wipes/wet wipes for this?**

- ○ *Yes*
- ○ *No*

81. **How often in a normal day are your baby's hands washed or wiped?**

- ○ *Not at all*
- ○ *1-2 times*
- ○ *3-4 times*
- ○ *5 or more times*

82. **Do you normally use baby wipes/wet wipes for this?**

- ○ *Yes*
- ○ *No*

83. **How often do you bathe your baby?**

- ○ *Hardly ever*
- ○ *Once a week*
- ○ *2-4 times a week*
- ○ *5-6 times a week*
- ○ *Daily*
- ○ *More than daily*

Skin treatments

84. **Do you use any products in the bath? (*Tick as many as apply)***

- ☐ *None*
- ☐ *Bubble bath*
- ☐ *Bath emollient (e.g. Aveeno Bath Oil, Oilatum Bath Emollient, Balneum Bath Oil)*
- ☐ *Shampoo*
- ☐ *Soap*
- ☐ *Other*

85. **Since you completed the eleven month questionnaire have you been using any moisturising cream/lotion/oil on your baby?**

- ○ *Never*
- ○ *Once a week or less*
- ○ *2-4 times a week*
- ○ *5-6 times a week*
- ○ *Daily*
- ○ *More than daily*

What is the name of the moisturising cream/lotion/oil that you have been using most frequently?

86. **Since you completed the eleven month questionnaire have you been using any steroid cream(s) or Protopic (tracrolimus) or Elidel (pimecrolimus) on your baby?**

- ○ *Never*
- ○ *Once a week or less*
- ○ *2-4 times a week*
- ○ *5-6 times a week*
- ○ *Daily*
- ○ *More than daily*

Please name the cream(s) that you have been using? Steroid cream or Protopic (tracrolimus) or Elidel (pimecrolimus)

Tummy complaints

87. **Since you completed the eleven month questionnaire has your baby been affected by the following conditions?**

	Never	Monthly or less	Weekly	2-4 times a week	5-6 times a week	Daily	More than once daily
Posseting (bringing back up small amounts of milk, often with swallowed air or 'wind')	○	○	○	○	○	○	○
Vomiting (without a temperature)	○	○	○	○	○	○	○
Colic (sudden continuous crying, bloated stomach, steadily passing wind, cramping and pulling up legs)	○	○	○	○	○	○	○

88. **Since you completed the eleven month questionnaire on how many days has your baby been affected by the following conditions? (Write "0" if none)**

Diarrhoea - days affected ☐

Constipation - days affected ☐

89. **What is the outcome of the diarrhoea?**

- ○ *Unresolved*
- ○ *Resolved completely*
- ○ *Resolved but having caused other problems*

Please describe these other problems?

90. **What is the outcome of the constipation**

- ○ *Unresolved*
- ○ *Resolved completely*
- ○ *Resolved but having caused other problems*

Please describe these other problems?

91. **Was any treatment required for these conditions?**

	None	Medications	Non-drug therapies	Medications and non-drug therapies
Diarrhoea treatment	○	○	○	○
Constipation treatment	○	○	○	○

92. **On average, how often does your baby have a bowel movement?**

- ○ *Once a day or more*
- ○ *Less than once a day*

93. **On average, how many times per day does your baby have a bowel movement**

☐

94. **On average, how many times per week does your baby have a bowel movement**

☐

Illnesses

95. **Since you completed the eleven month questionnaire has your baby had any of the following illnesses?**

	Never	Once	Twice	Three times	Four times	Five or more times
Upper respiratory tract infection (a cold) episodes	○	○	○	○	○	○
Lower respiratory tract infection (chest infection) episodes	○	○	○	○	○	○
Bronchiolitis episodes	○	○	○	○	○	○
Other infections episodes (e.g. skin infections)	○	○	○	○	○	○

If "Other infections", please list

96. **Since you completed the eleven month questionnaire over how many days have these illness episode/s been occuring?**

Cold/s duration ☐

Chest infection/s duration ☐

Bronchiolitis duration ☐

Other infections duration ☐

97. **What is the outcome of the upper respiratory tract infection (cold) episode/s?**

- ○ *Unresolved*
- ○ *Resolved completely*
- ○ *Resolved but having caused other problems*

Please describe these other problems?

98. **What is the outcome of the lower respiratory tract infection (chest infection) episode/s?**

- ○ *Unresolved*
- ○ *Resolved completely*
- ○ *Resolved but having caused other problems*

Please describe these other problems?

99. **What is the outcome of the bronchiolitis episode/s?**

- ○ *Unresolved*
- ○ *Resolved completely*
- ○ *Resolved but having caused other problems*

Please describe these other problems?

100. **What is the outcome of the other infection episode/s?**

- ○ *Unresolved*
- ○ *Resolved completely*
- ○ *Resolved but having caused other problems*

Please describe these other problems?

101. **Was any treatment required for these episode/s?**

	None	*Medications*	*Non-drug therapies*	*Medications and non-drug therapies*
Cold treatment	○	○	○	○
Chest infection treatment	○	○	○	○
Bronchiolitis treatment	○	○	○	○
Other infections treatment	○	○	○	○

102. **Since you completed the eleven month questionnaire has your child had any adverse reaction to a food, such as eczema, breathing problems or gastrointestinal problems?**

- ○ *Yes*
- ○ *No*

103. **If yes, please give the following details:**

Food(s) suspected of causing the reaction: ☐

What problem did the food cause? ☐

104. **Since you completed the eleven month questionnaire has your baby been to a hospital Accident & Emergency department?**

- ○ *Yes*
- ○ *No*

105. **Was your baby admitted to the hospital overnight?**

- *Yes*
- *No*

106. **How long did your baby stay in hospital for (nights)?**

107. **What did the hospital staff say was wrong with your baby?**

108. **How long was your baby ill for with this problem (days)?**

109. **What is the outcome of this illness?**

- *Unresolved*
- *Resolved completely*
- *Resolved but having caused other problems*

Please describe these other problems?

110. **Was any treatment required for the illness that led to you going to A&E?**

	None	*Medications*	*Non-drug therapies*	*Medications and non-drug therapies*
A&E illness treatment				

Medications and supplements

111. **<u>Since you completed the eleven month questionnaire</u> approximately how many <u>courses</u> of antibiotics has your baby received?**

- *None*
- *One*
- *Two*
- *Three*
- *Four*
- *Five or more*

112. **<u>Since you completed the eleven month questionnaire</u> have you given your child any of the following?**

	Never	*Once*	*Twice*	*Three times*	*Four times*	*Five or more times*
Paracetamol (Calpol) frequency						
Ibuprofen (Nurofen) frequency						

113. **<u>Since you completed the eleven month questionnaire</u> have you given your child any vitamins or other supplements?**

- *Vitamin preparations (e.g. Abidec, Dalivit or Healthy Start)*
- *Iron containing preparations (e.g. Sytron, Ferrous sulphate)*
- *Mineral preparations*
- *Fish Oil supplements*
- *None*

114. **Did your child take any of the following drugs <u>during the last 12 months</u>**

	Yes	*No*	*Don't know*
Salbutamol, Ventolin, Bricanyl or other **<u>blue</u>** inhaler			
Pulmicort, Flixotide, Becotide, Beclovent or other **<u>brown</u>** inhaler			
Steroid tablets (prednisolone) **for breathing problems**			

Pet ownership

115. **Have you gained or lost any pets since you completed the 3 month questionnaire?**

- *Yes*
- *No*

Direct pet contact

116. **Do you currently own any pets?**

- ☐ *None*
- ☐ *Dog*
- ☐ *Cat*
- ☐ *Horse or pony*
- ☐ *Other*

If "Other". Please describe.

117. **How many pets do you own?**

Number of dogs owned	☐
Number of cats owned	☐
Number of horses or ponies owned	☐
Number of other pets owned	☐

118. **Where are the pets allowed?**

	Outside only	*Inside*	*In baby's bedroom*
Dog location in house	☐	☐	☐
Cat location in house	☐	☐	☐
Other pet location in house	☐	☐	☐

119. **On average, how many hours per week does your baby spend visiting places with pets?**
This is asking about contact with pets in places other than the baby's home

☐

Indirect pet contact

120. **Does your baby have regular contact (once a week or more) with pet owning friends and/or family?**
This is asking about contact with the people who own the pets rather than the pets themselves

- ○ *Yes*
- ○ *No*

121. **On average, how many hours per week does your baby spend in contact with pet owning friends and/or family?**
This is asking about contact with the people who own the pets rather than the pets themselves

☐

Child care

122. **Does your child attend a childminder or day care (nursery or crèche)?**

- ☐ *No*
- ☐ *Childminder*
- ☐ *Nursery/crèche*

123. **How many hours per week does your child spend at a childminder or day care?**

☐

124. **How old (in weeks) was your baby when he/she first started to attend a childminder or day care?**

☐

125. **Approximately how many other children are cared for?**

Childminder number of children cared for	☐
Nursery/crèche number of children cared for	☐

126. **Are there pets present at the childminders or day care?**

	Yes	*No*
Pets at childminder	○	○
Pets at nursery or crèche	○	○

Baby's sleep pattern

These questions refer to your baby's sleep on average during the last week

127. **Where does your baby sleep?**

- ○ *Infant cot/Moses basket in a separate room alone*
- ○ *Infant cot/Moses basket in the parent(s) bedroom*
- ○ *In parent(s) bed*
- ○ *Infant cot/Moses basket in room with a sibling (brother or sister)*

Other (please specify)

128. **How much time does your baby spend in sleep during the NIGHT (between 7 in the evening and 7 in the morning)?**
Please enter time as hours.minutes e.g. Five hours would be 5.00

129. **How much time does your baby spend in sleep during the DAY (between 7 in the morning and 7 in the evening)?**
Please enter time as hours.minutes e.g. Two and a half hours would be 2.30

130. **Average number of night wakings per night?**

131. **How much time does your baby spend in wakefulness (from 10 in the evening to 6 in the morning)?**
Please enter time as hours.minutes e.g. Two and a half hours would be 2.30

132. **How long does it take to put your baby to sleep in the evening?**
Please enter time as hours.minutes e.g. Thirty minutes would be 0.30

133. **How does your baby fall asleep?**

- ○ *While feeding*
- ○ *Being rocked*
- ○ *Being held*
- ○ *In bed alone*
- ○ *In bed near parent*

134. **At what time does your baby usually fall asleep for the night?**
Please enter time as e.g. 7.30 pm

135. **Do you consider your baby's sleep as a problem?**

- ○ *Not a problem at all*
- ○ *A small problem*
- ○ *A very serious problem*

Quality of Life

We are measuring the baby's mother's Quality of Life. You completed this questionnaire when your baby was 3 months old. We will repeat this measure at the 3 year assessment. We are using a widely used measure of Quality of Life produced by the World Health Organization.

The following questions ask how the baby's mother feels about her quality of life, health or other areas of life. Please choose the answer that appears most appropriate. If you are unsure which response to give to a question, the first response you think of is often the best one. We ask that you think about your life in the last four weeks.

In this section on Quality of Life please skip any questions you are not comfortable with answering.

136. **How would you rate your quality of life?**

	Very poor	*Poor*	*Neither poor nor good*	*Good*	*Very good*
How would you rate your quality of life?					

137.

	Very dissatisfied	*Dissatisfied*	*Neither satisfied or dissatisfied*	*Satisfied*	*Very satisfied*
How satisfied are you with your health?					

The following questions ask how much you have experienced certain things in the last four weeks.

138.

	Not at all	*A little*	*A moderate amount*	*Very much*	*An extreme amount*
To what extent do you feel that physical pain prevents you from doing what you need to do?					
How much do you need any medical treatment to function in your daily life?					
How much do you enjoy life?					
To what extent do you feel your life to be meaningful?					

139.

	Not at all	*A little*	*A moderate amount*	*Very much*	*Extremely*
How well are you able to concentrate?					
How safe do you feel in your daily life?					
How healthy is your physical environment?					

The following questions ask about how completely you experience or were able to do certain things in the last four weeks.

140.

	Not at all	*A little*	*Moderately*	*Mostly*	*Completely*
Do you have enough energy for everyday life?					
Are you able to accept your bodily appearance?					
Have you enough money to meet your needs?					
How available to you is information that you need in your day-to-day life?					
To what extent do you have the opportunity for leisure activities?					

141.

	Very poor	*Poor*	*Neither good nor poor*	*Good*	*Very good*
How well are you able to get around?					

142.

	Very dissatisfied	*Dissatisfied*	*Neither satisfied or dissatisfied*	*Satisfied*	*Very satisfied*
How satisfied are you with your sleep?	○	○	○	○	○
How satisfied are you with your ability to perform your daily living activities?	○	○	○	○	○
How satisfied are you with your capacity to work?	○	○	○	○	○
How satisfied are you with yourself?	○	○	○	○	○
How satisfied are your with your personal relationships?	○	○	○	○	○
How satisfied are you with your sex life?	○	○	○	○	○
How satisfied are you with the support you get from your friends?	○	○	○	○	○
How satisfied are you with the conditions of your living place?	○	○	○	○	○
How satisfied are you with your access to health services?	○	○	○	○	○
How satisfied are you with your transport?	○	○	○	○	○

The following question refers to how often you have felt or experienced certain things in the last four weeks.

143.

	Never	*Seldom*	*Quite often*	*Very often*	*Always*
How often do you have negative feelings such as blue mood, despair, anxiety, depression?	○	○	○	○	○

EAT Study 5 Day Food Diary (12 Months)

Thank you for completing the questionnaire!

When you click the submit button you will be directed automatically to our EAT Study website where
you will be able to download a diary template for the 5 day food diary (12 months).

You previously completed a food diary when your baby was 6 months old.
We will ask you to do one final 5 day diary at 3 years of age.
Please aim to complete this 5 day food diary (12 months) within 2 weeks of your child turning 12 months.
Further details are provided in the diary.

Once you have completed your food diary please bring it with you to the 12 month visit at St Thomas' Hospital.

Do please contact us if you have any queries about the questions.
eatstudy@gstt.nhs.uk OR 0800 358 0021
The EAT Study Team