# Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Perkin MR, Logan K, Tseng A, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. N Engl J Med 2016;374:1733-43. DOI: 10.1056/NEJMoa1514210

**Supplementary Appendix**

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# 1. Supplement to the Introduction

The UK Government infant feeding recommendation adopts a more pragmatic target of ***around*** six months exclusive breastfeeding compared to the World Health Organizations recommendation of six months.[1] With regards to the specific age of introduction of allergenic foods the United Kingdom government stresses avoidance of allergenic food consumption before six months and when they are introduced that this be done one food at a time to detect reactions.[2] Between 1998[3] and 2009[4] 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[5] to 2008[6] 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.[5] However the evidence basis for both the instigation and the revocation of these guidelines was limited,[7] and 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.[8] Contemporaneous with the Australian publication, the latest United Kingdom Infant Feeding Survey undertaken in the same year observed that by 8 to 10 months of age only 8% of infants had ever been given peanut, with frequencies of consumption of less than once weekly or never being reported for nuts 98%, eggs 73% and fish 44%.[9]

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.[10]

# 2. Supplement to the Methods

## EAT eligibility criteria

The eligibility criteria for enrollment onto the EAT study were: Exclusively breastfed at enrollment, 37+ weeks gestation, singleton birth, no 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 the United Kingdom for the duration of the study. A family member having a pre-existing food allergy was not an enrollment exclusion criterion for the study.

## Early introduction food order

Cow's milk (as yogurt) was always introduced first; it being a food that families would be familiar with offering young infants. The order of peanut, sesame, fish and cooked egg introduction was randomised amongst early introduction participants to avoid any preferential bias through one of these foods being introduced earlier than any of the others. Wheat was always introduced last, and not before four months of age, reflecting the guidance on optimal timing of wheat introduction.[11]

## Early introduction food portions

The full weekly amount for the allergenic foods consisted of three rounded teaspoons of smooth peanut butter, one small (less than 53g) hard-boiled egg, two small 40-60g portions of cow's milk yogurt, three teaspoons of sesame paste, 25g of white fish and two wheat-based cereal biscuits (e.g. Weetabix). Alternative forms of each allergenic food were offered by the study dietitians for participants not keen on these vehicles or to increase diversity of the infant diet, as the infants matured.

## Study assessments - skin-prick testing

At baseline, skin-prick testing was undertaken in duplicate in the early-introduction group to whole foods for raw egg white, fresh cow's milk and tahini; and to cod, wheat and peanut using commercial solutions (Stallergenes, Didcot, United Kingdom). 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.[12-15] At

one and three years of age skin-prick testing was undertaken for the whole cohort with commercial solutions to the six foods. At three years of age skin-prick testing to raw egg white was also undertaken.

## Scheduled assessments - enrollment (3 months), one and three years

All participants underwent a comprehensive assessment of their allergy status at the three scheduled assessments (Table S1). This included an examination for visible eczema using the United Kingdom diagnostic criteria-based photographic protocol of the International Study of Asthma and Allergies in Childhood Phase Two.[16] Disease severity was determined by the Scoring Atopic Dermatitis (SCORAD) index.[17] SCORAD was categorized as mild (<15), moderate (15-40), and severe (>40).[17] Quality of life was assessed using the World Health Organization's WHOQOL-BREF quality of life assessment.[18] This is a 26 item version of the WHOQOL-100 and assesses four domains of quality of life: physical, psychological, social and environment.

## 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* (Figs. S2 & S3) 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 S2 (scheduled challenges) and Fig. S2 (one year assessment) & Fig. S3 (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 S2. 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 S2. 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 Fig. S4 and Table S3. 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 S2 and S3).

## 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.

## Primary outcome - levels of evidence for food allergy

A diagnosis of food allergy was determined according to the following levels of evidence:

**Category 1A:** A positive double-blind, placebo-controlled food challenge at one year or three years of age in a child skin-prick test positive to one of the six intervention foods.

**Category 1B:** A positive double-blind, placebo-controlled food challenge between one year and three years in a child attending an unscheduled clinic visit in a child skin-prick test positive 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-label or double-blind, placebo-controlled) at between six months and one year of age that occurs in a child who was skin-prick test positive to one of the six intervention foods who subsequently refused a double-blind, placebo-controlled food challenge at one year and three years of age

The rationale for this category being that below six months only early introduction infants had challenges so this category was restricted to those infants who were six months old or more.

**Category 3:** A food allergic history in a child with a skin-prick test response of 5 or more millimetres.

The rationale for this category was that there were likely to be a small number of children who had an immediate type allergic reaction and had significant skin-prick test responses whose parents refused to allow them to undergo any further challenge.

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).

## Consumption monitoring

Within the online questionnaire, both groups completed a food frequency questionnaire section assessing how frequently foods containing the six study allergens were being consumed.[19] Early introduction group families 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 4 g of each allergenic food protein per week. For each of the last four complete weeks preceding the child's monthly birthday and for each of the allergenic foods, parents recorded the percentage of the recommended amount of food their child was consuming (100%, 75%, 50%, 25% or less, not tried yet) with guidance provided on the amount of each food constituting those percentages. This diary data was then entered into the online questionnaires.

## Measuring adherence

The key introduction period for defining adherence was considered to be between three months and six months of age. For adherence to be evaluable, early-introduction group participants needed to have completed all three of the four, five and six month interim questionnaires.[19]

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.[19]

## Anthropometry

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[20] 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.[21]

## Safety

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.

***Non-IgE mediated allergy symptoms***: A free text question allowed parents to report any adverse reaction to food and to state the food suspected of causing the problem and what the symptoms were. These were coded with regards to symptoms, triggering food and whether the symptoms were suggestive of a non-IgE or an IgE food allergy. Reports of proctocolitis and food protein induced enterocolitis syndrome like symptoms were also recorded and investigated by food challenge where possible.

## Statistical analysis

Ad hoc analyses that are presented in this manuscript but were not in the original statistical analysis plan are listed below:

1. Logistic modelling and dominance analysis of factors influencing the primary outcome (see Table S5)
2. Logistic modelling and dominance analysis of factors influencing standard-introduction group non-adherence and early-introduction group non-adherence (see Tables S13 and S14)
3. Adjusted per-protocol analysis (see Fig. 1 and Fig. S5)

4. Does response analysis (Figs.3, S8). 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 standard-introduction group food allergy prevalence by subtracting the number of baseline early-introduction group participants who were challenge positive at enrollment and completed the study with a confirmed food allergy from both the numerator (the number of allergic standard-introduction group participants) and the denominator (the number of standard-introduction group per-protocol adherent participants). This conservative analysis is presented as early-introduction group 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 standard-introduction group redresses this balance.

A number of the adverse events recorded 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.

## Study attributions

Research attribution: study design MP, KL, CF, GL; data gathering MP, KL, AT, BR, HB, TM, SR, JC, CF, GL; data analysis MP, KL, JC, SA, JP, GL; vouching of data and analysis all authors, drafting of manuscript MP, GL; decision to publish all authors. No commercial entities donated food. All mothers self-purchased the foods. No commercial entity was involved in study design, data accrual, data analysis or manuscript preparation. There were no contractual agreements denying the research team the right to examine the data independently or to submit a manuscript for publication without first obtaining the consent of the sponsor.

# 3. Supplement to the Results

## Per-Protocol Adherence

In the standard-introduction group 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 standard-introduction group.[19]

The primary outcome status could not be determined for 42 of the 606 standard-introduction group participants in whom adherence was evaluable. Hence, 92.9% (524/564) of the standard-introduction group participants whose primary outcome status could be determined were per-protocol adherent (Fig. S1). This represents 80.5% (524/651) of the enrolled standard-introduction group.

In the early-introduction group 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 early-introduction group.[19]

The primary outcome status could not be determined for 43 of the 529 early-introduction group participants in whom adherence was evaluable. Hence, 42.8% (208/486) of the early-introduction group participants whose primary outcome status could be determined were per-protocol adherent (Fig. S1). This represents 31.9% (208/652) of the enrolled early-introduction group.

## Cow's milk formula consumption in the standard-introduction group

Infant formula introduction in the standard-introduction group was minimal under six months: 2% in the standard-introduction group ever having had cow's milk formula by 4 months and 7% by 5 months. By six months of age 14.4% in the standard-introduction group had ever had cow's milk formula which was broken down further into 5.6% of evaluable standard-introduction group participants having been given cow's milk formula in a volume exceeding 300mls for one day or more (rendering them non per-protocol) and 8.8% had been given less than 300mls per day. Thus 85.6% of the standard-introduction group 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 early-introduction group recommended dose of cow's milk protein was 4g per week. By 4 months of age 1.6% (10/621) standard-introduction group 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) standard-introduction group participants consumed this amount or more before six months of age.

## Voluntary withdrawals

43 participants in the standard-introduction group and 69 participants in the early-introduction group 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).

## Food allergy

The primary outcome was non-significantly lower in the early-introduction group in participants with and without visible eczema at enrollment (Table S6).

A secondary outcome was to assess the total number of foods to which EAT participants were allergic (Table S7). Multiple food allergy occurred more frequently in the standard-introduction group (1.31 versus 1.12 food allergies per food allergic participant) but the difference in mean number of food allergies per food allergic child was not statistically significant (p=0.17).

### *Adjusted per-protocol analysis*

For the primary outcome, food allergy to one or more of the early introduction foods, the relative reduction in the adjusted per-protocol analysis in the early-introduction group was 61% (p=0.03), for peanut 100% (p=0.003) and for egg 73% (p=0.02) (Fig. 1).

## Dust sample results

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 $\mu$g per gram of dust (interquartile range, 2.6 to 40.1) in the standard-introduction group and 7.6 $\mu$g per gram of dust (interquartile range, 2.4 to 14.1) in the early-introduction group (Fig. S7). At 12 months of age, the levels were respectively 77.0 $\mu$g per gram of dust (interquartile range, 11.3 to 383) and 387.9 $\mu$g 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 early-introduction group was significantly higher in the per-protocol participants' beds compared to the non per-protocol participants' beds ($p=0.04$).

## Non-IgE mediated allergy type symptoms

The two broad categories of immune mediated food reactions are IgE-mediated and non-IgE-mediated. The former involve acute onset symptoms (such as urticarial or angioedema), the latter are typically delayed in onset and include gastrointestinal symptoms (such as diarrhoea) and rashes (such as eczema flaring). Early-introduction group 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 (Table S8). However the situation reversed in the subsequent time periods with significantly more reports occurring in the standard-introduction families 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): standard-introduction group 25.7% versus early-introduction group 26.5% ($p=0.72$).

## Food Protein Induced Enterocolitis Syndrome

There were 10 participants whose families reported food protein induced enterocolitis syndrome like reactions (Table S9), seven in the early-introduction group (six reporting egg as the trigger, one sesame) and three in the standard-introduction group (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 early-introduction group participants, five had negative challenges, one was positive and one did not return for the challenge. Of the three standard-introduction group participants, two had positive challenges and one had a negative challenge.

## Proctocolitis

There were three cases suggestive of proctocolitis, all in the standard-introduction group and all to cow's milk.

## Serious Adverse Events

In the EAT study it was determined that any participant who had an epinephrine auto-injector administered fulfilled this criterion. Five such serious adverse events were recorded - four in standard-introduction group participants, one in an early-introduction group participant. Two of these events took place on separate occasions in the community in one standard-introduction group participant. On both occasions the mother administered an EpiPen for choking episodes. Three participants received epinephrine auto-injector administration during food challenges on the clinical trials unit, none during enrollment challenges in the early-introduction group (out of 553 food challenges undertaken altogether).

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

## Adverse Events

There were no overall significant differences between the two groups for posseting (Fig. S10 and Table S18), colic (Fig. S12 and Table S20), parent reported wheeze (Fig. S13 and Table S21), upper respiratory tract infections (Fig. S14 and Table S22), parent reported bronchiolitis (Fig. S16 and Table S24), reports of other infections (Fig. S17 and Table S25) and mean days affected by diarrhoea (Fig. S18 and Table S26) or constipation (Fig. S19 and Table S27).

Overall parent reports of vomiting were significantly more frequent in the early-introduction group with a difference at 4-6 months of age being responsible for the overall significant difference (Fig. S11 and Table S19). The difference was largely accounted for by more early-introduction group participants reporting vomiting monthly or less, or weekly. There was no difference between the two groups in posseting frequency during this period.

Conversely the other symptom for which there was a significant overall difference observed was lower respiratory tract infections, with these being more common in the standard-introduction group at every time period, although the absolute difference between the two groups at each time point was small (Fig. S15 and Table S23). Wheezing was significantly more commonly reported in the early-introduction group between 4-6 months of age but in the standard-introduction group between 7-12 months of age (with no statistically significant difference overall) (Fig. S13 and Table S21). Similarly, upper respiratory tract infection symptoms were reported more frequently between 4-6 months in the early-introduction group but there was no statistically significant difference overall (Fig. S14 and Table S22).

There was a non-significant increase in days affected by diarrhoea in the standard-introduction group in the period between 12 and 36 months of age (Fig. S18 and Table S26). Conversely, in the period between 4 and 6 months the early-introduction group reported significantly more days affected by constipation (Fig. S19 and Table S27). In both cases the absolute difference between the two groups was small.

With regards to the anthropometric measurements in Table S28, none of the comparisons between the two groups were statistically significant. There was a tendency towards the early-introduction group 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.

## Baseline skin-prick and allergy status

All 33 of the baseline sensitised early-introduction group participants were invited for food challenges to the relevant foods: seven had positive challenges (to one or more foods), 22 had negative challenges (to one or more foods) and four failed to return (Table S29A). 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 S29C).

# 4. Supplement to the Discussion

## Baseline comparison of the study groups

The two groups were balanced in all respects at baseline with the exception of their having been more early-introduction group participants born by Caesarean section (27.6% in the early-introduction group versus 22.7% in the standard-introduction group, p=0.04) (Table S4). Caesarean section has been associated with an increased likelihood of food allergy[22] and therefore this imbalance would render the early-introduction group at increased risk of food allergy thus not introducing a bias in favour of the early-introduction group participants.

## Paradoxical reduction in egg and peanut allergy in per-protocol analysis

We anticipated seeing our principal effect for the primary outcome which we estimated would have a prevalence of 8% in the standard-introduction group, 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 overall per-protocol adherence in the early-introduction group (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. This was unexpected.

## Per-Protocol adherence to cow's milk formula avoidance in the standard-introduction group

One possible 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 standard-introduction group 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 standard-introduction group before six months of age was minimal (see Supplementary Results) and thus could not have accounted for the low rate of cow's milk allergy in this group.

## Dose-response relationship

In the EAT study, consumption of 2 g of peanut protein per week for at least 4 weeks also reduced peanut allergy tenfold, from 2.5% to 0.2%. 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.

## Reverse causality

In the EAT study it is possible that the individuals in the early-introduction group 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 early-introduction group per protocol food allergy rate by shifting food allergic patients early on towards non per-protocol adherence.

In order to address this issue we compared the rates of allergies to overall and individual foods in the non per-protocol early-introduction group 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 standard-introduction group, which constitutes 93% of the evaluable standard-introduction group participants, represents the spontaneous rate of food allergy in the normal exclusively breastfed population. Table S10B compares the standard-introduction per-protocol and the early-introduction non per-protocol and adherence non-evaluable groups. 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). 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. The same arguments are applicable to the early-introduction adherence non-evaluable group who had very similar rate for the primary outcome compared to the standard-introduction per-protocol group (Table S10B)

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 early-introduction group participants. This is because only the early-introduction group 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 early-introduction group compared with the per-protocol early-introduction group. Despite this potential bias, Table S10B indicates a bias towards increased food allergy in the early introduction non per-protocol group did not exist.

That early-introduction group participants who were non per-protocol were not concealing raised levels of food allergy is further illustrated by the adherence grids in Table S16. Whilst the food specific per-protocol adherence rate for peanut was 61.9% (310/501) and for egg 43.1% (215/499) (blue highlighted cells in Table S16), 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 85% for peanut (419/491) and 76% for egg (370/490). These increased levels of adherence were still associated with statistically significant reductions in both allergies (0.2% for peanut and 1.9% for egg).

Another argument against reverse causation is that the children who were skin-prick test positive at 3 months in the early-introduction group 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 is not the case. Consumption of the allergenic food to which the participant had a negative challenge by six months of age was good (Table S29B) as was overall per-protocol adherence.

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 had excellent adherence in the consumption group and a significantly reduced rate of peanut allergy.[15]

## Bias

Only 31.9% (208/652) of all the enrolled early-introduction group participants were primary outcome evaluable and adhered to the protocol versus 80.5% (524/651) in the standard-introduction group. There are three levels at which attrition of the enrolled population occurred:

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

The differential attrition at all three categories was higher in the early-introduction group than the standard-introduction group all potentially contributing towards a bias between the two groups.

1. **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 category of participants. We can, however, compare their baseline demographics to see whether primary outcome non-evaluable early-introduction group 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 early-introduction group participants.

Table S31 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 baseline atopy status 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 S31 shows that, despite non-white early-introduction group participants being statistically more likely to be primary outcome non-evaluable compared with white early-introduction group participants, there was no food allergy as determined by challenge in any of the non-evaluable participants in both groups at 12 months of age. This is the age by which point we would have expected most cases of food allergy, particularly in the early-introduction group participants, to be apparent.

2. **Participants whose per-protocol status was non-evaluable (EIG 81, SIG 31)**
3. **Participants who were non per-protocol (EIG 278, SIG 40)**

We can also compare the baseline characteristic of the early-introduction group and standard-introduction group participants by per-protocol adherence status (Category 2 - adherence non-evaluable and Category 3 - per-

protocol and non per-protocol) and this data is presented in Table S12. This indicates that non per-protocol and adherence non-evaluable early-introduction group participants were statistically significantly more likely to be non-white. Non per-protocol early-introduction group 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 S5). However, there was no significantly increased rate of food allergy in both the non per-protocol and adherence non-evaluable participants in the early-introduction group (Table S10B). Thus the differential atopic status did not lead to a bias in the primary outcome.

## Timing of IgE and Non-IgE type symptoms reported in the first year

The most important observation from Table S8 is that when the period between enrollment and one year is considered in its entirety, there were no significant differences for any of the comparisons between the groups. The first three columns divide this period into three monthly divisions. Within these we see that the early-introduction group families observed significantly more symptoms at the time they were introducing symptoms (4-6m, the first column), but that the situation reversed in the second column when the standard-introduction group families were introducing foods to their children (7-9m, second column), with significantly more symptoms in the standard-introduction group. These differences were cancelled out when the overall period was analysed. 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 the table) at 26% in both groups, significantly exceeds the rate of food allergy that we confirmed in the two groups.

## EAT results and other early introduction trials

The EAT study is one of eight studies taking place investigating the hypothesis that the early introduction of allergenic foods can induce oral tolerance, the others being: Learning Early About Peanut allergy (LEAP) (high risk population, peanut),[15] Solids Timing for Allergy Research (STAR) (high risk population, egg),[23] Hen's Egg Allergy Prevention (HEAP) (general population, egg),[24] 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).

Three studies have published their results. LEAP has been discussed in the main paper.[15] The STAR (Solids Timing for Allergy Research) study 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.[23] It 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.

HEAP (Hen's Egg Allergy Prevention) trial is looking at early hen's egg introduction in the general population.[24] The study did not find any effect of early consumption of pasteurized hen's egg white powder 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.

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 early-introduction group there was a great than 75% reduction in the prevalence of egg allergy by age 3. While we do not know whether intervention in this group with 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 the intervention resulted in a comparable level of reduction in skin-prick test reactivity to both commercial egg extract and raw egg white at age 3.

The STEP (Starting Time for Egg Protein) and BEAT (Beating Egg Allergy) trials are expected to publish shortly 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.

## Individual food adherence

Some foods were introduced with greater ease than others. Individual food per-protocol adherence in the early-introduction group 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 standard-introduction group 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

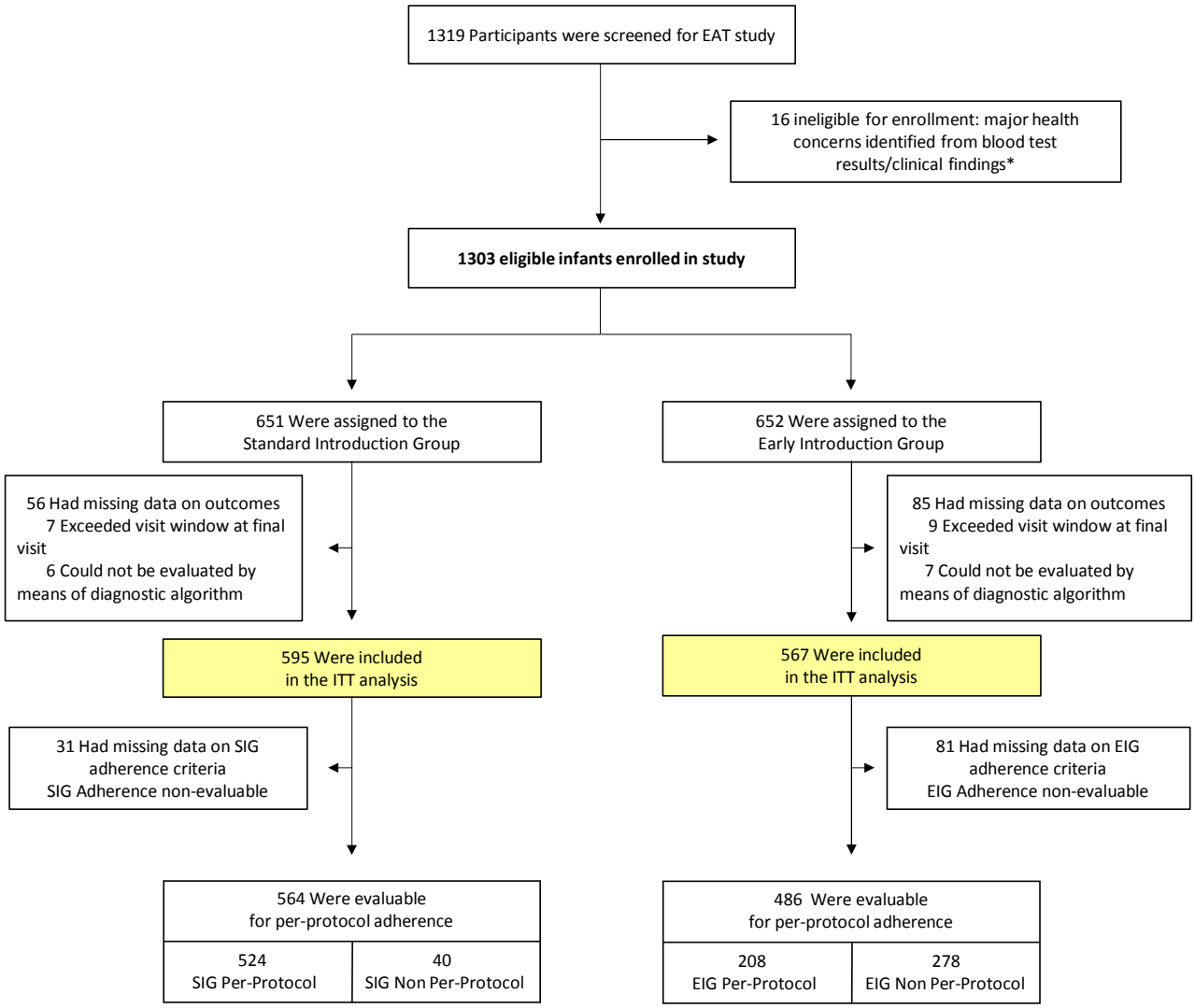
are regarded as secondary outcomes, and interpreted as such. The components of the composite are not usually corrected for multiple testing.[25]

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.

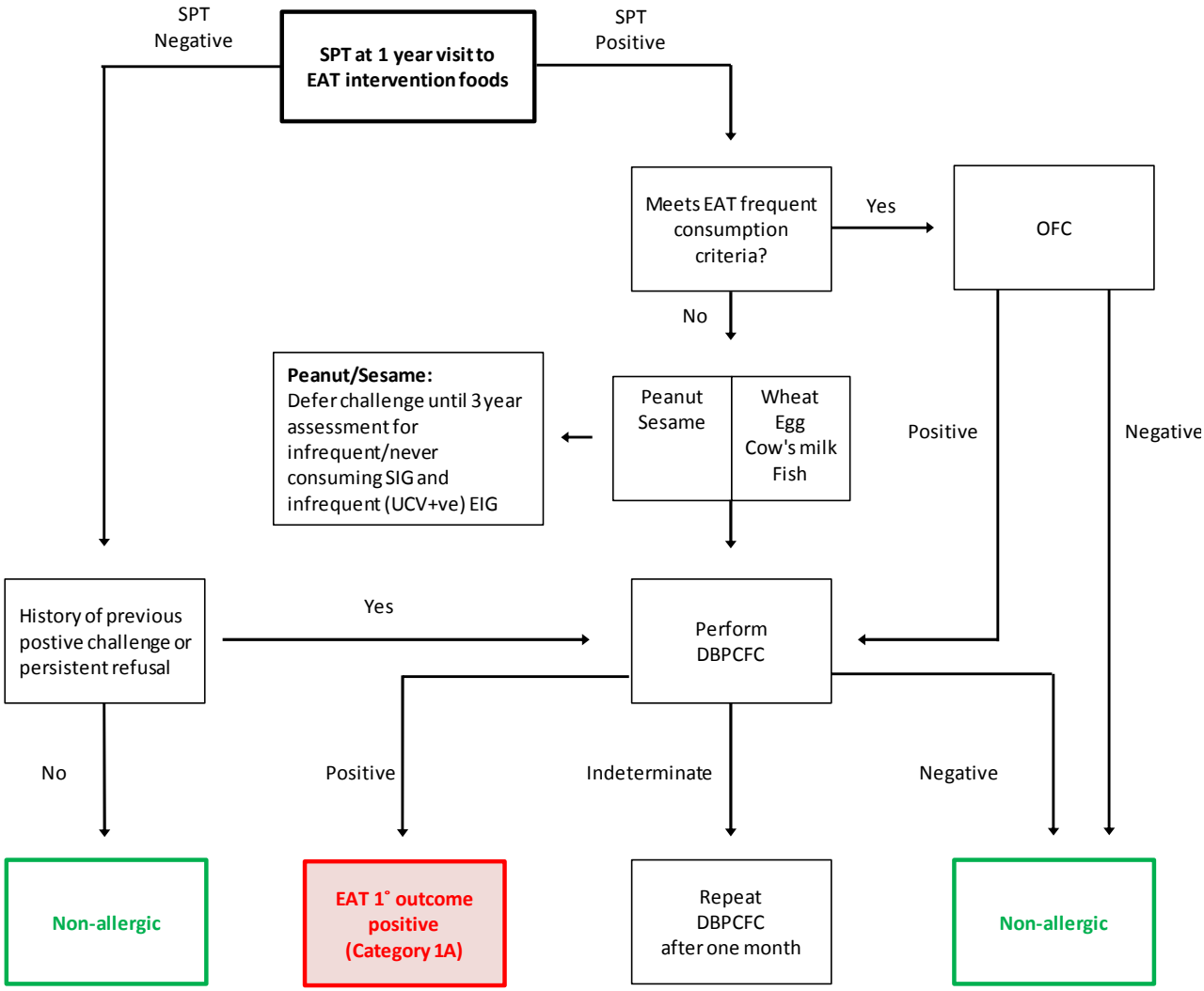
# 5. Supplementary Figures




## Figure S1. Enrollment and Randomization

Baseline visits occurred when participants were 3 months of age.
*Eight infants randomized to each group were found to have significant health issues either on blood testing or the clinical examination at the enrollment visit rendering them ineligible for enrollment: conditions included severe vitamin D deficiency, severe iron deficiency, severe failure to thrive, familial hypercholesterolemia, congenital stridor, epidermolysis bullosa and cartilage hair hypoplasia syndrome.
† Reasons for withdrawal are given in the Supplementary Results
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).

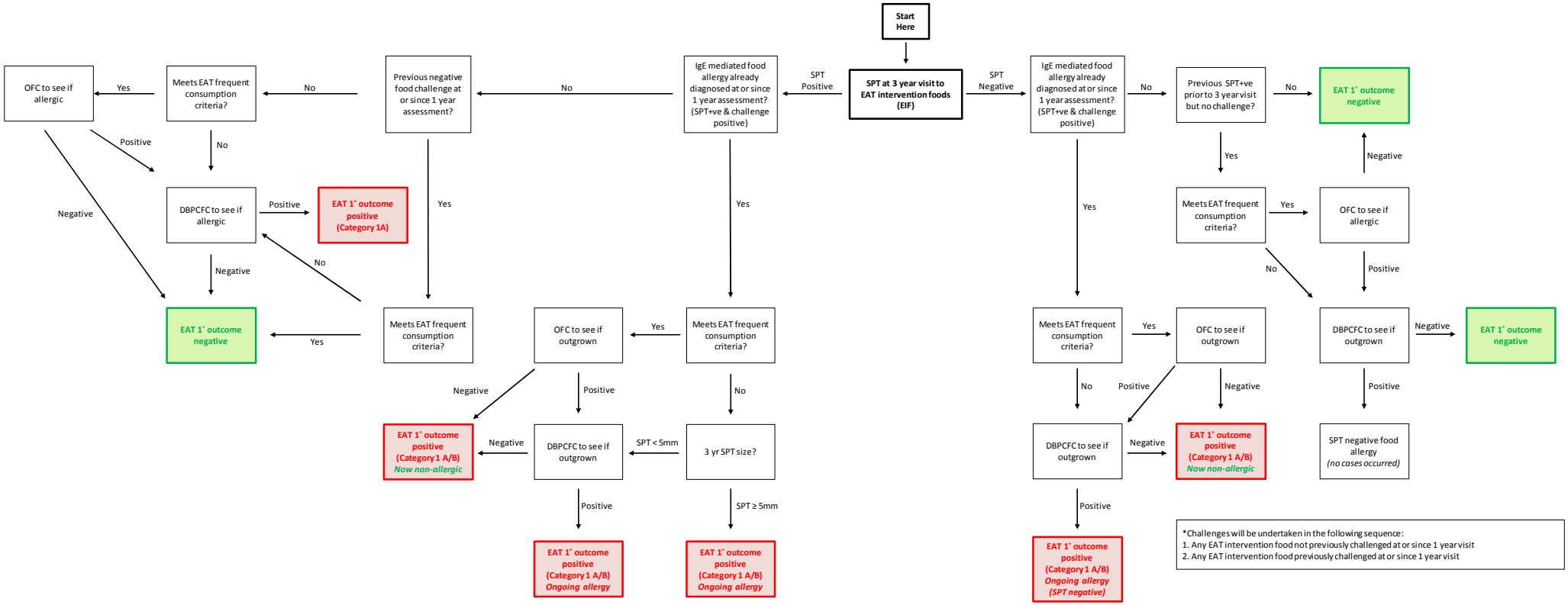
The per-protocol population for food specific allergy used the same consumption criterion, i.e. consumption for at least 5 weeks between three and six months of age of at least 75% of the recommended dose of that food (i.e. 3 g per week of allergenic protein).




## Figure S2. Food Challenge Algorithm - 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 (see Table S2 and Supplementary Methods). Participants with a double-blind, placebo-controlled positive food challenge fulfilled the primary outcome definition (Category 1 - see Supplementary Methods), 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.

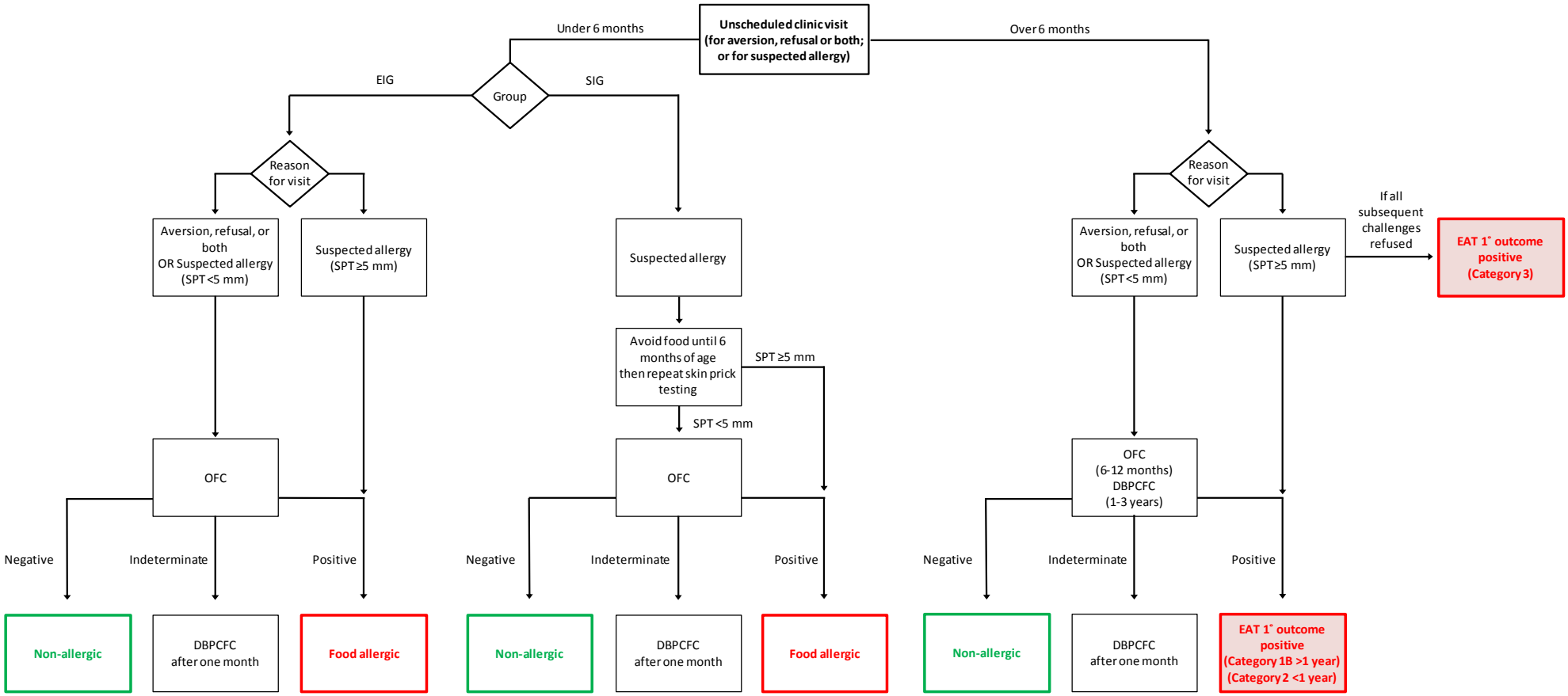
Key: SPT skin-prick test, UCV unscheduled clinic visit, OFC open food challenge, DBPCFC double-blind, placebo-controlled food challenge




## Figure S3. Food Challenge Algorithm - Three Year Assessment

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 (Supplementary Methods). The *frequent consumption criteria* are described in the Supplementary Methods.

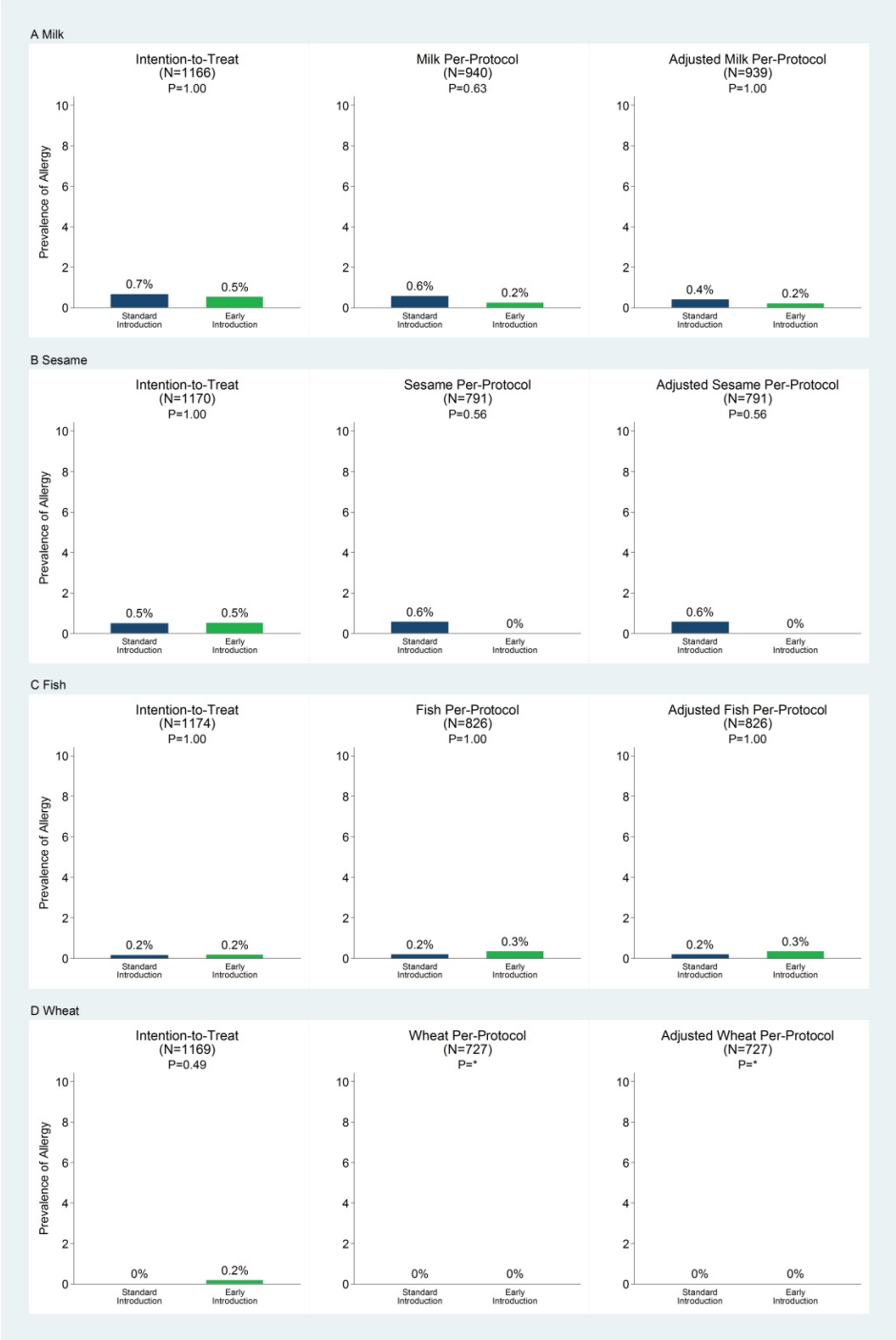
Key: SPT skin-prick test, OFC open food challenge, DBPCFC double-blind, placebo-controlled food challenge




## Figure S4. Food Challenge Algorithm - Unscheduled Clinic Visit

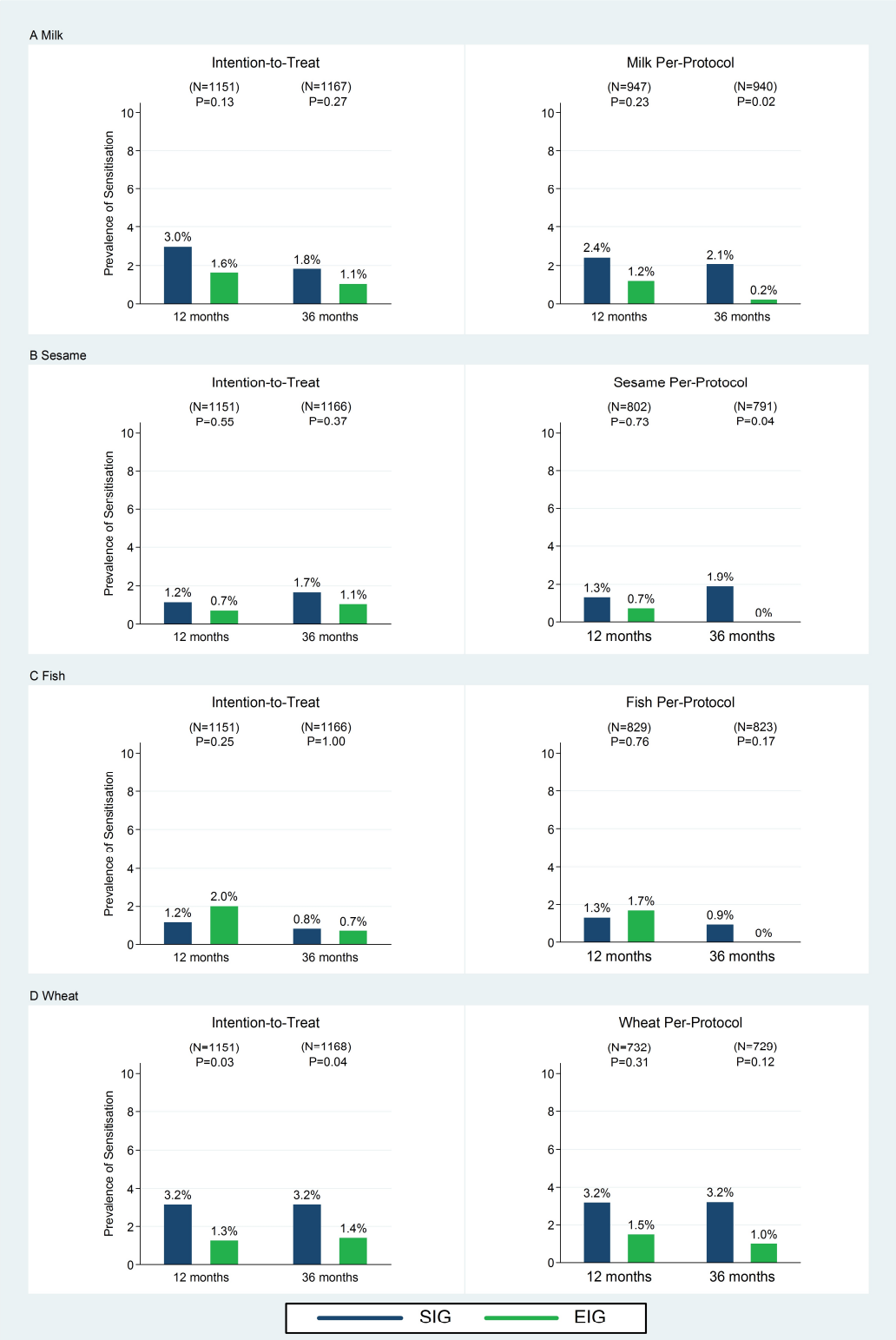
Participants attending an unscheduled clinic visit for food aversion, refusal or suspected allergy followed this algorithm. Early introduction group participants with positive open food challenges under six months of age were designated food allergic but this did not constitute EAT primary outcome positive status as this would have introduced a bias because only early-introduction group participants were challenged under six months of age (Supplementary Methods). 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 (Supplementary Methods). 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 (Supplementary Methods). 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



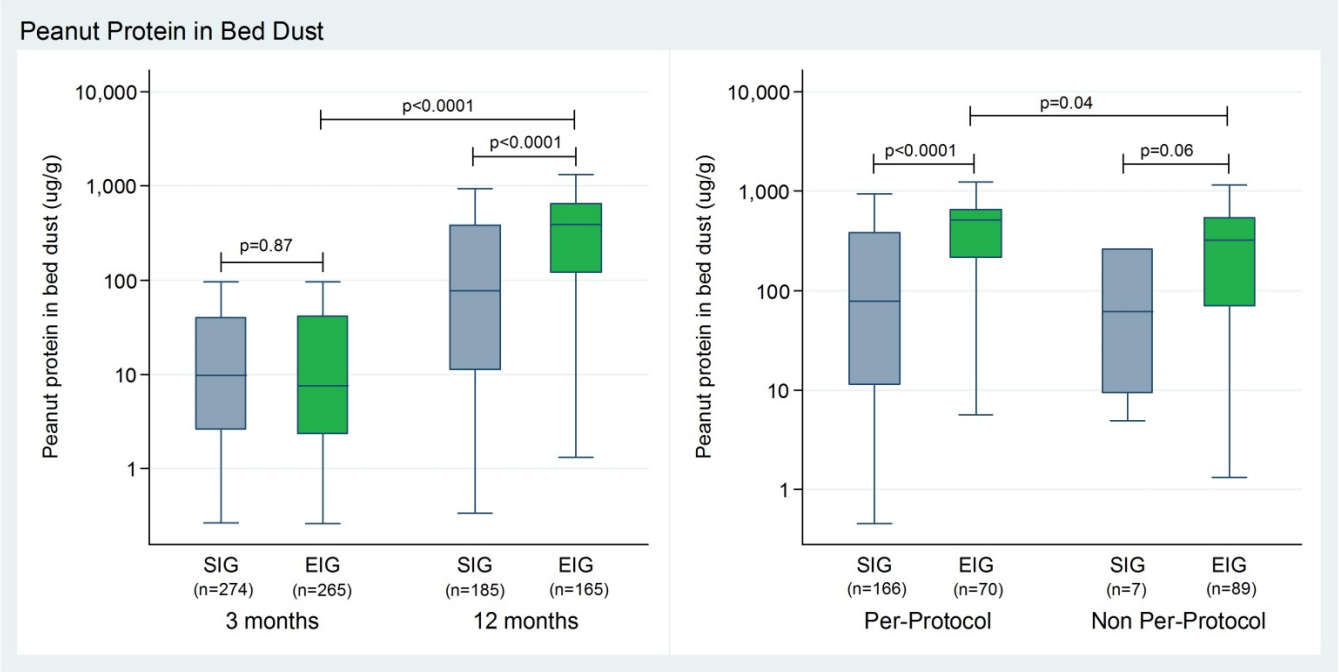

## Figure S5. Secondary Outcomes of Allergy to Other Early Introduction Foods

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. The latter was a conservative per-protocol analysis that adjusted the standard-introduction group food allergy prevalence by subtracting the number of baseline early-introduction group participants who were challenge positive at enrollment and completed the study with a confirmed food allergy from both the numerator (the number of allergic standard-introduction group participants) and the denominator (the number of standard-introduction group per-protocol adherent participants). P values are based on Fisher's exact test (2 tailed). Group specific denominators are given in Table S6 (intention-to-treat analysis) and Table S10A (per-protocol analysis).




## Figure S6. Secondary Outcome of Results on Skin-Prick Testing to Other Early Introduction Foods

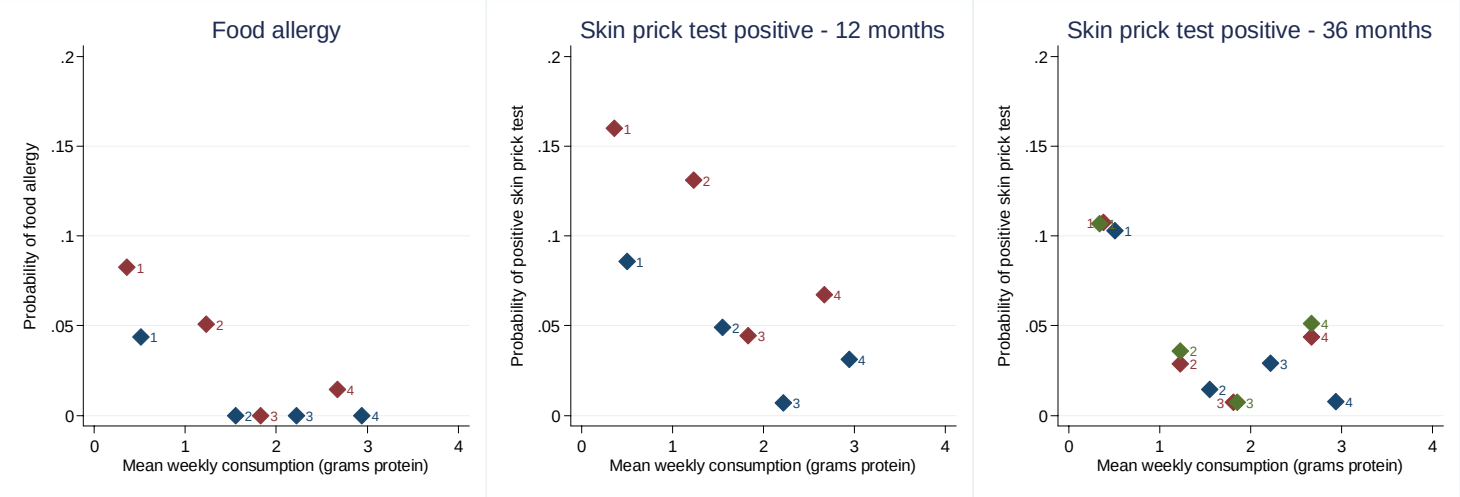
The prevalence of a positive skin-prick test (any sized wheal) is shown to milk (Panel A), sesame (Panel B), white fish (Panel C) and wheat (Panel D). The first column shows the intention-to-treat analysis, the second column the per-protocol analysis. P values are based on chi-square analyses (or Fisher's exact test where appropriate). The group specific denominators and relative risk reduction with 95% CI are given in Table S11.



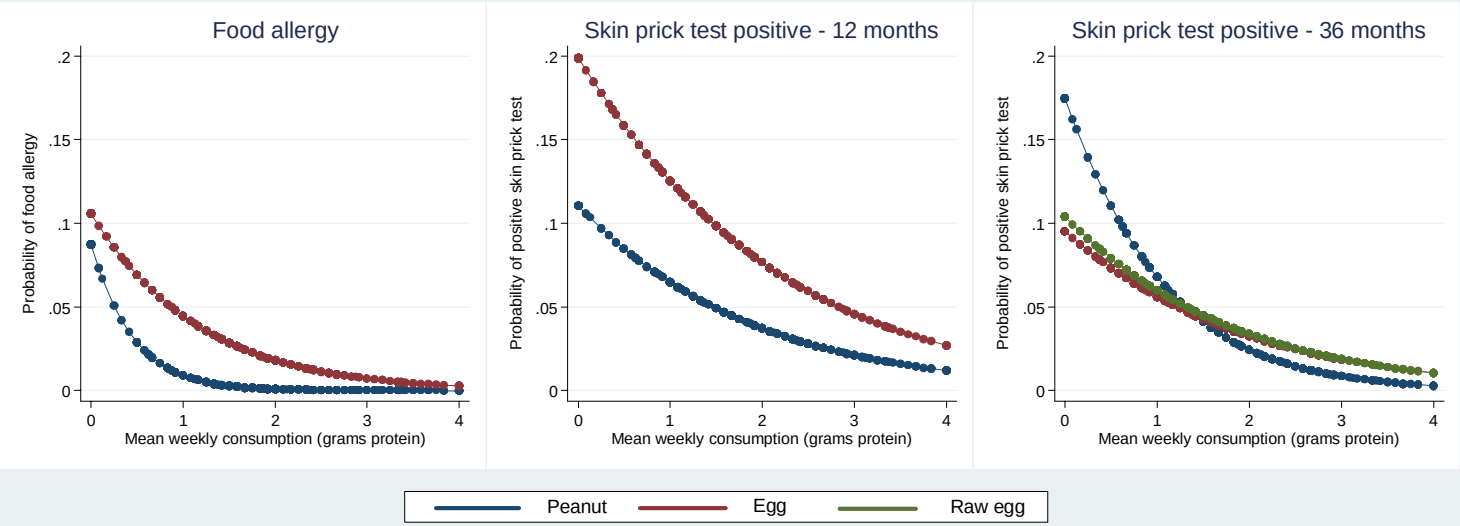

## Figure S7. Peanut Protein in Bed Dust at 3 and 12 Months of Age

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 early-introduction group by one year of age. In the right panel, peanut protein levels were significantly higher in the early-introduction group 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 early-introduction group per-protocol participants compared with the non per-protocol early-introduction group participants.

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 S8. 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 logistical 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.

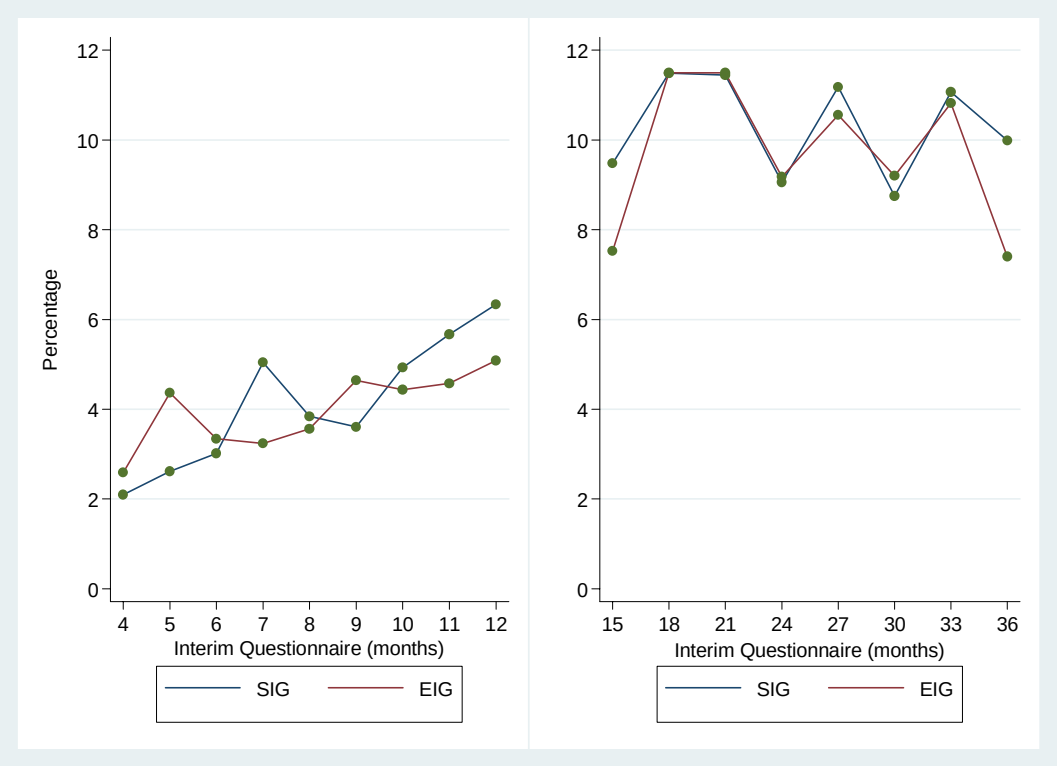
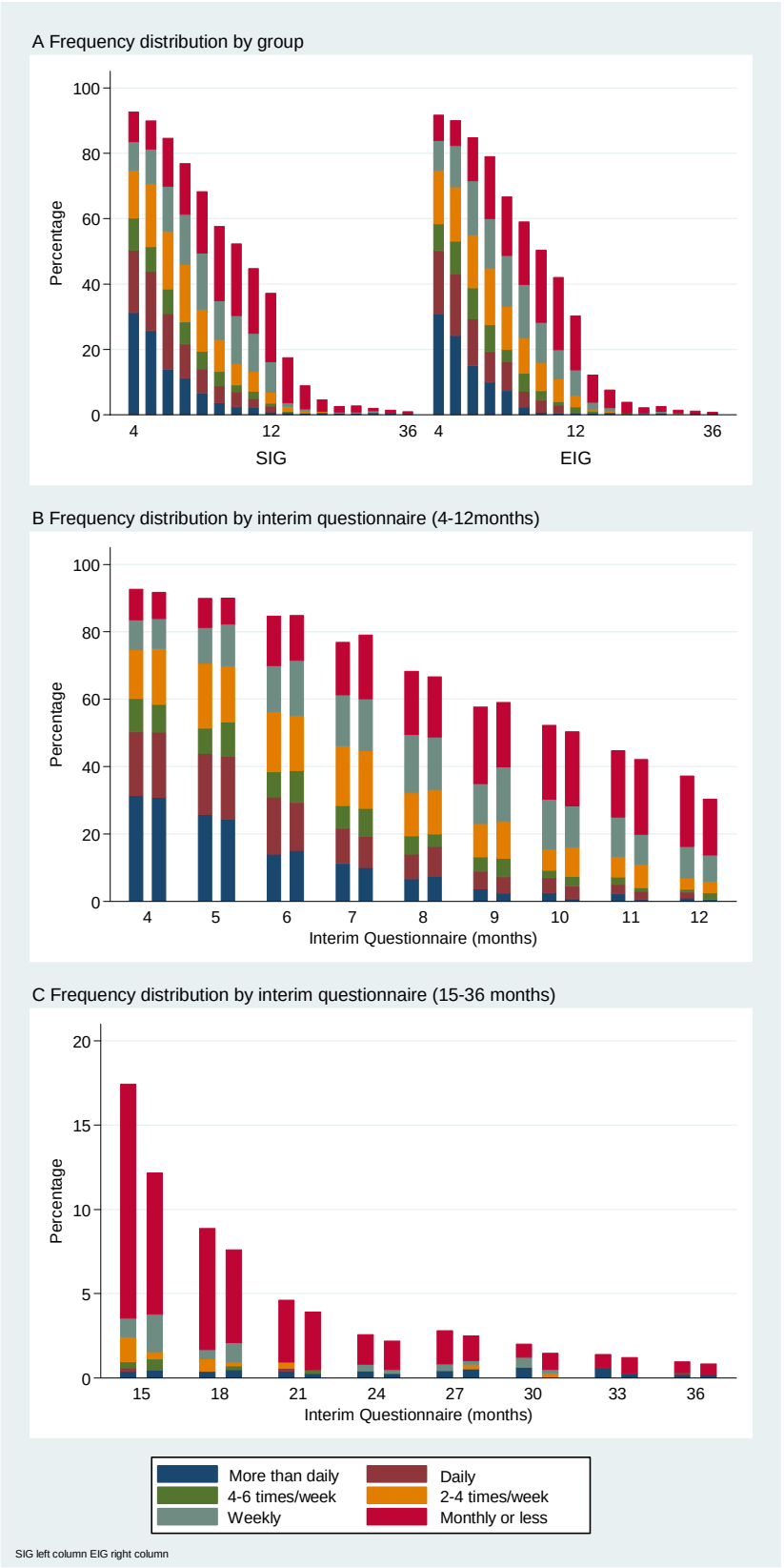


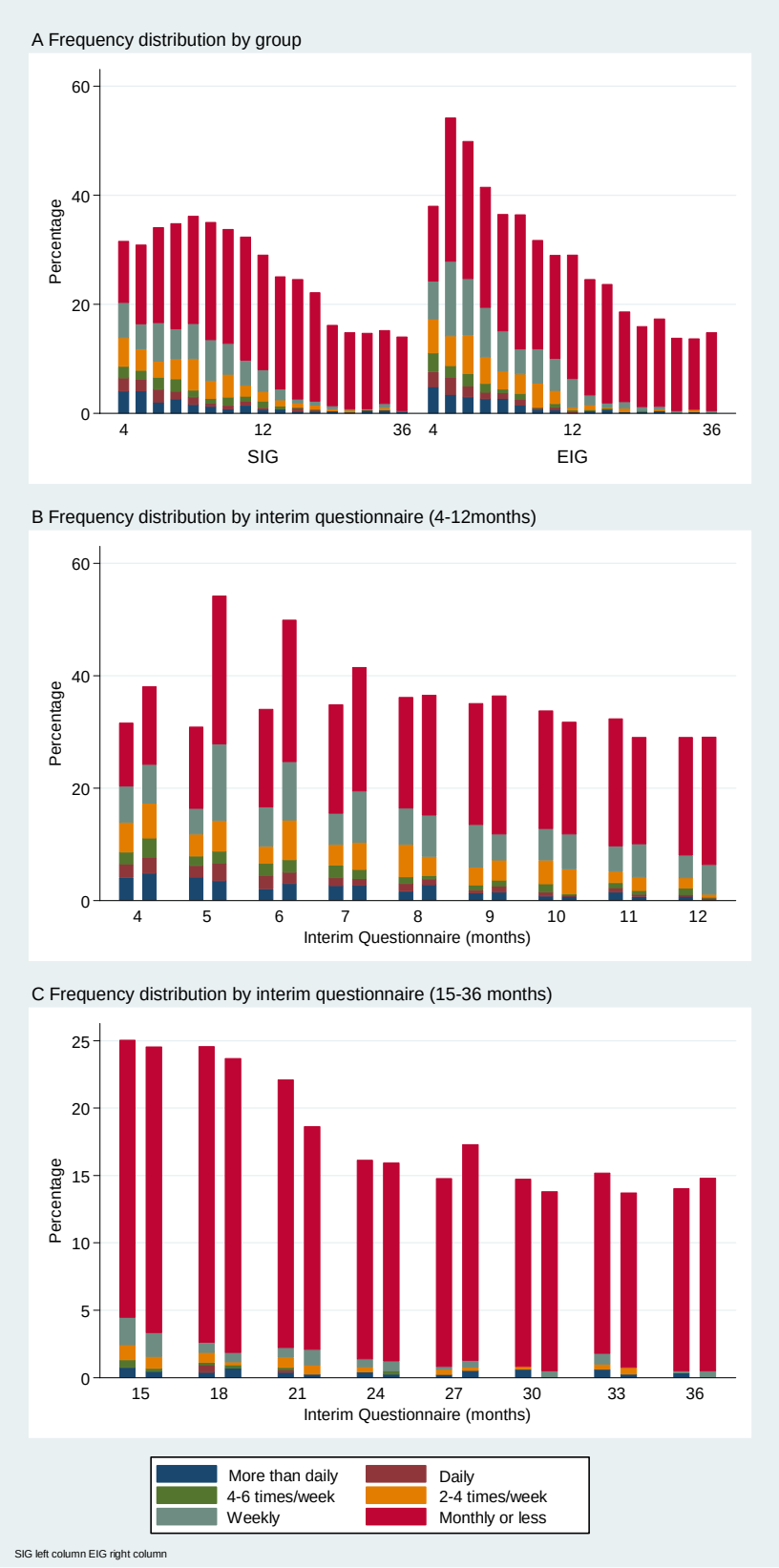

**Figure S9. Adverse Event: Parent Reported Emergency Department Attendances**

The percentage of participants attended an Emergency Department since the last interim questionnaire was completed is shown for each interim questionnaire time point, stratified by study group.



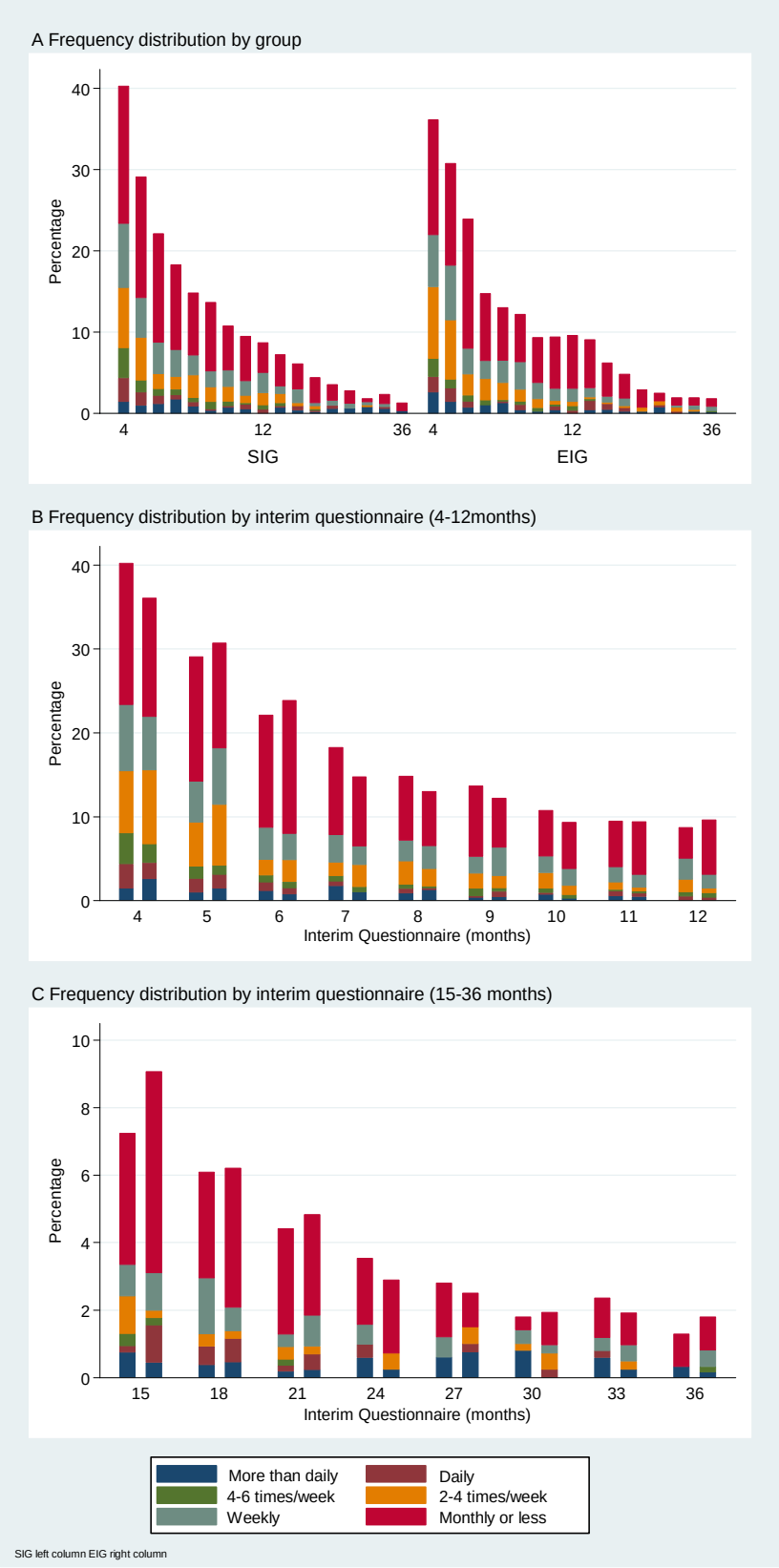

## Figure S10. Adverse Event: Parent Reporting Posseting

The overall distribution of posseting frequency reported in each interim questionnaire by study group (Panel A). The distribution of posseting frequency reported by interim questionnaire for months 4 to 12 (Panel B) and months 15 to 36 (Panel C). Comparisons between posseting frequency in each group are presented in Table S18.



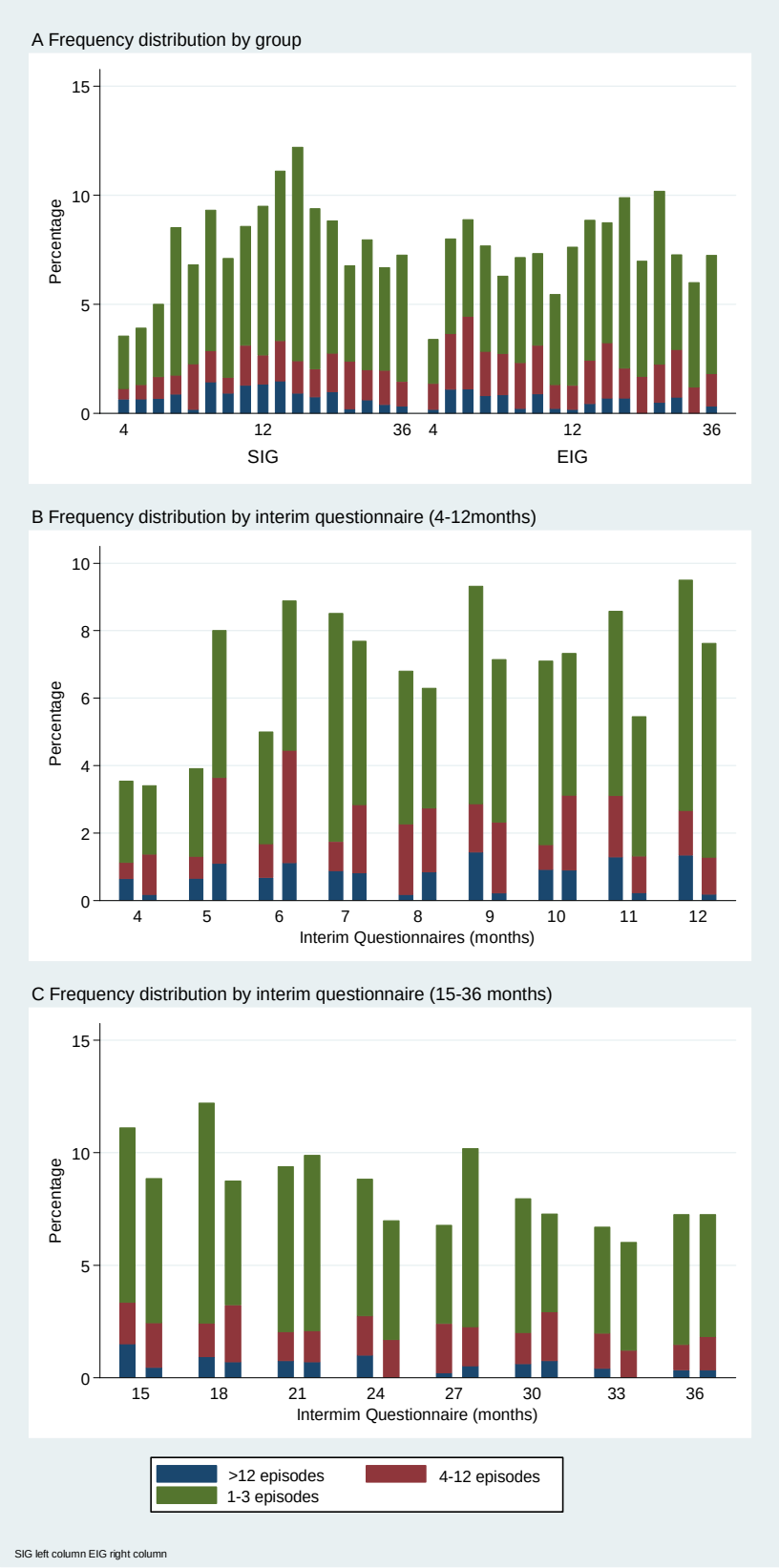

## Figure S11. Adverse Event: Parent Reported Vomiting

The overall distribution of vomiting frequency reported in each interim questionnaire by study group (Panel A). The distribution of vomiting frequency reported by interim questionnaire for months 4 to 12 (Panel B)and months 15 to 36 (Panel C). Comparisons between vomiting frequency in each group are presented in Table S19.



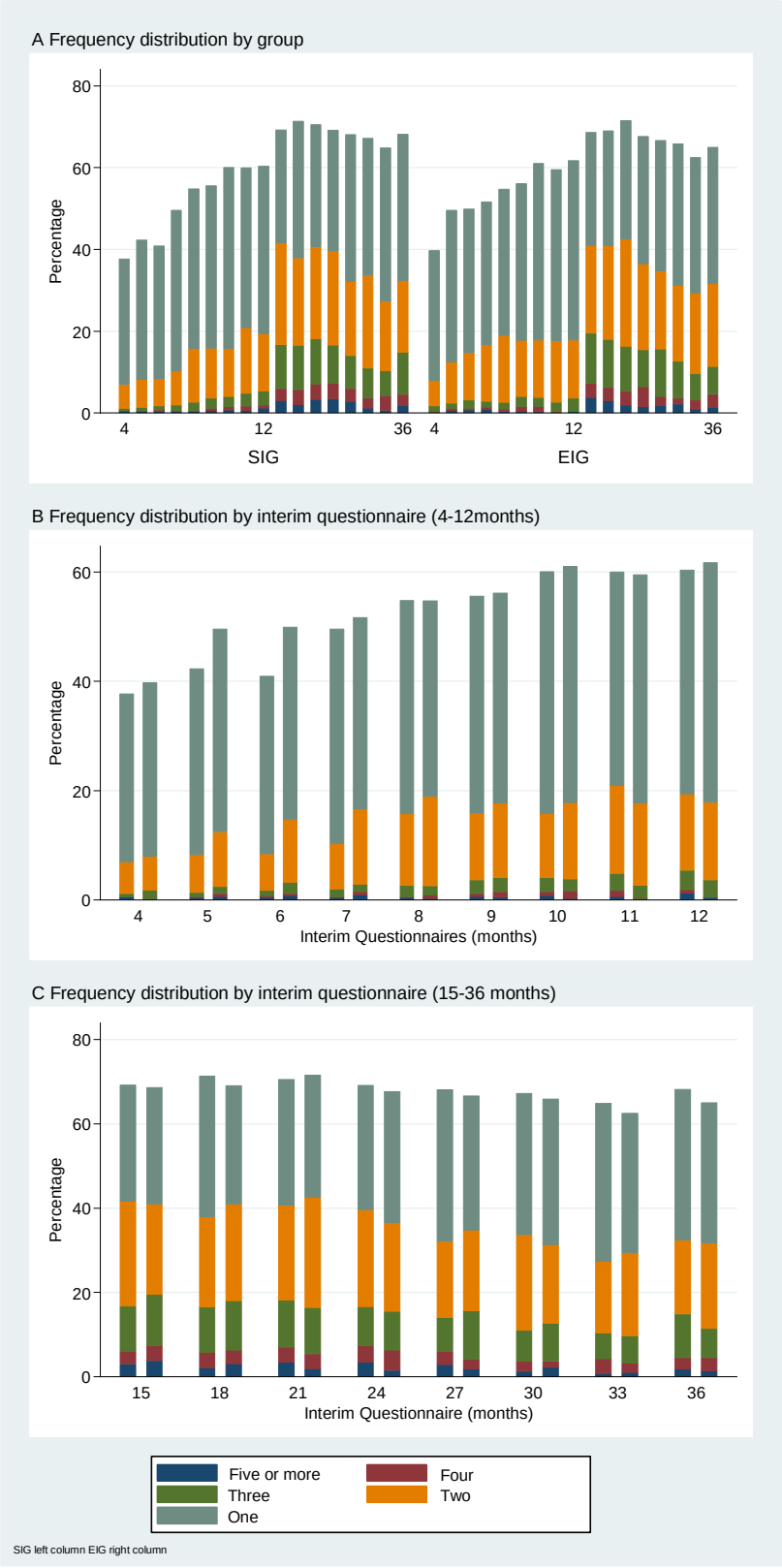

## Figure S12. Adverse Event: Parent Reported Colic

The overall distribution of colic frequency reported in each interim questionnaire by study group (Panel A). The distribution of colic frequency reported by interim questionnaire for months 4 to 12 (Panel B) and months 15 to 36 (Panel C). Comparisons between colic frequency in each group is presented in Table S20.



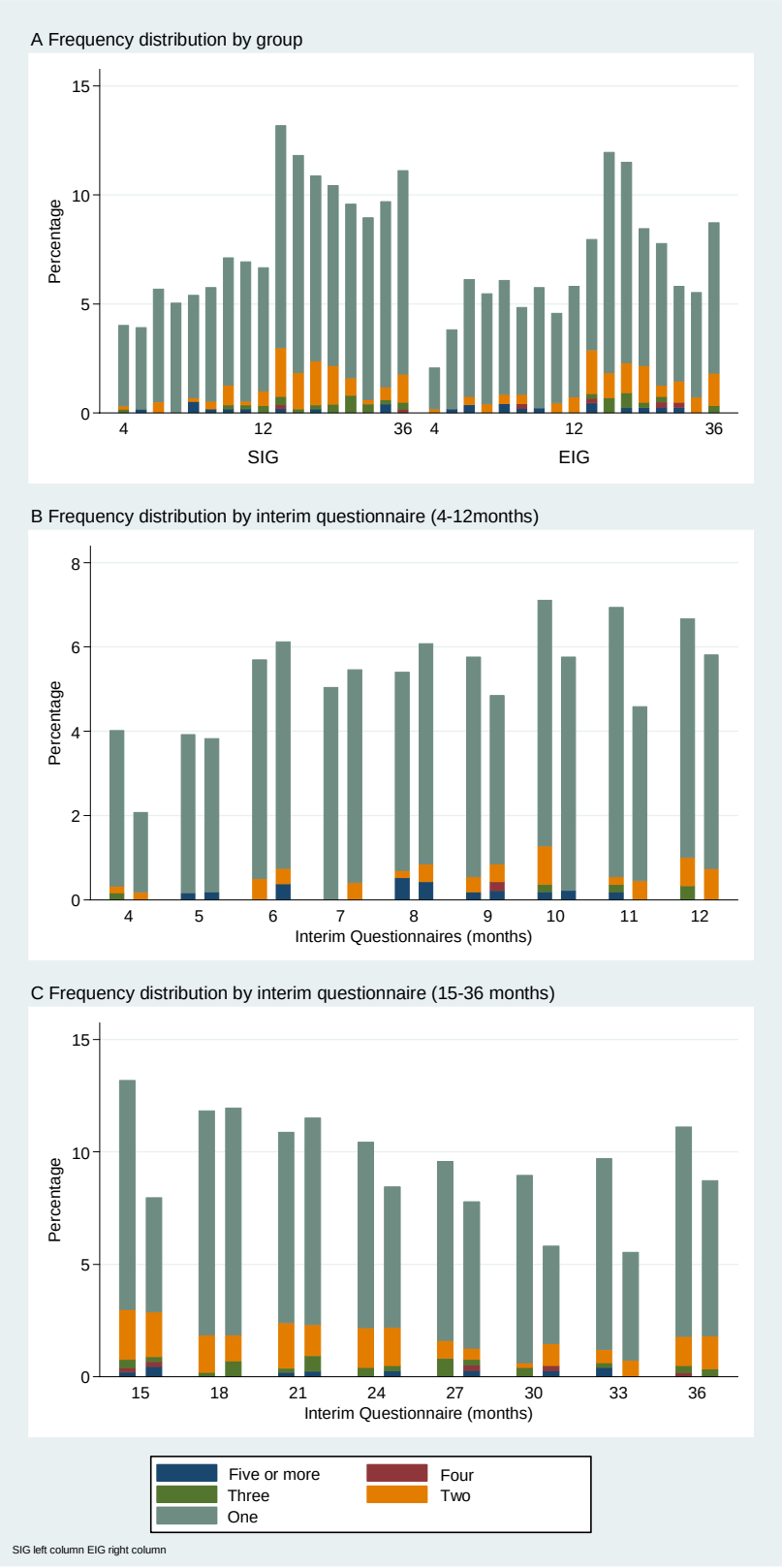

## Figure S13. Adverse Event: Parent Reported Episodes of Wheeze

The overall distribution of wheeze frequency reported in each interim questionnaire by study group (Panel A). The distribution of colic frequency reported by interim questionnaire for months 4 to 12 (Panel B) and months 15 to 36 (Panel C). Comparisons between groups are presented in Table S21.



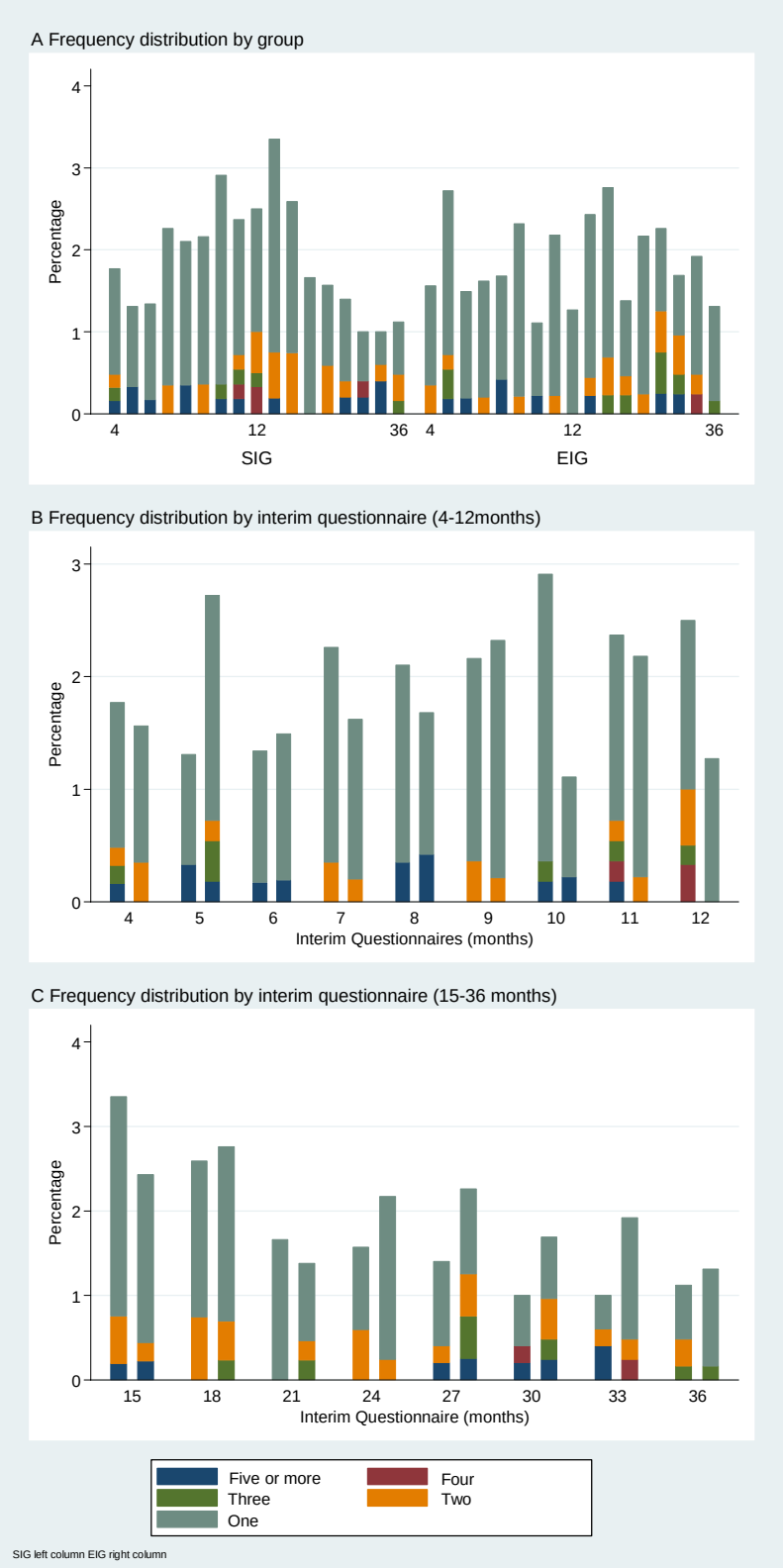

## Figure S14. Adverse Event: Parent Reported Upper Respiratory Tract Infection

The overall distribution of upper respiratory tract infection frequency reported in each interim questionnaire by study group (Panel A). The distribution of upper respiratory tract infection frequency reported by interim questionnaire for months 4 to 12 (Panel B) and months 15 to 36 (Panel C). Comparisons between upper respiratory tract infection frequency between each group are presented in Table S22.



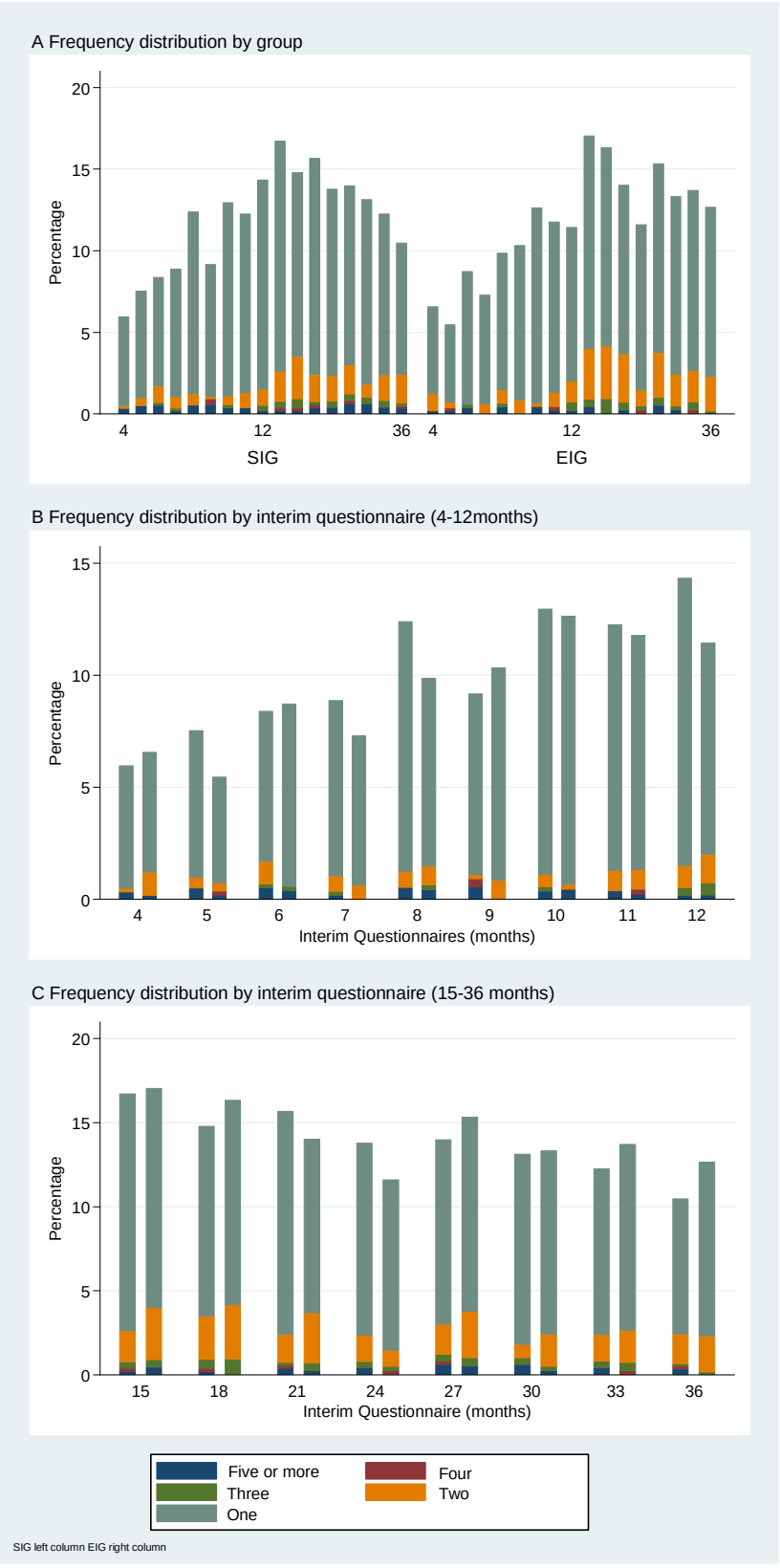

## Figure S15 Adverse Event: Parent Reported Lower Respiratory Tract Information

The overall distribution of lower respiratory tract infection frequency reported in each interim questionnaire by study group (Panel A). The distribution of lower respiratory tract infection frequency reported by interim questionnaire for months 4 to 12 (Panel B) and months 15 to 36 (Panel C). Comparisons between lower respiratory tract infection frequency between each group are presented Table S23.




## Figure S16. Adverse Event: Parent Reported Bronchiolitis

The overall distribution of bronchiolitis frequency reported in each interim questionnaire by study group (Panel A). The distribution of bronchiolitis frequency reported by interim questionnaire for months 4 to 12 (Panel B) and months 15 to 36 (Panel C). Comparisons between bronchiolitis frequency between each group are presented Table S24.




## Figure S17. Adverse Event: Parent Reported Other Infections

The overall frequency distribution of other infections reported in each interim questionnaire by study group (Panel A). The frequency distribution of other infections reported by interim questionnaire for months 4 to 12 (Panel B) and months 15 to 36 (Panel C). Comparisons between reported frequency of other infections in each group are presented Table S25.

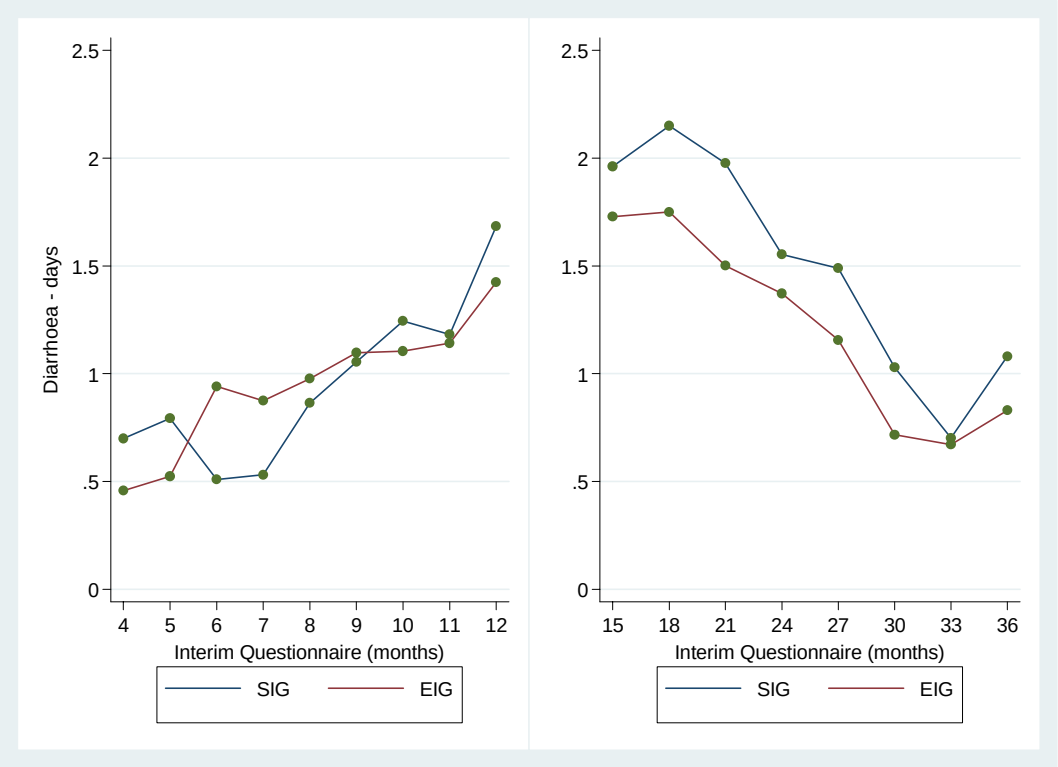



**Figure S18. Adverse Event: Parent Reported Days Affected by Diarrhoea**

In each interim questionnaire families recorded the mean number of days a participant had experienced diarrhoea since completing the last interim questionnaire. Comparisons between mean duration of diarrhoea between groups are presented in Table S26.

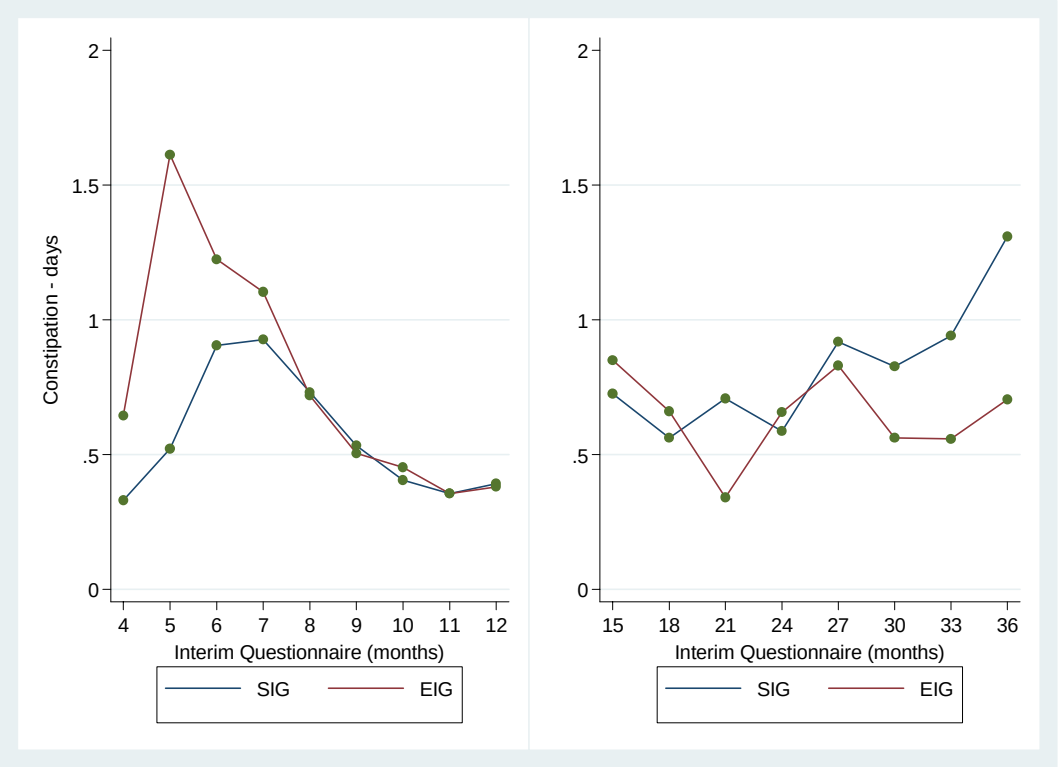



**Figure S19. Adverse Event: Parent Reported Days Affected by Constipation**

In each interim questionnaire families recorded the mean number of days a participant had experienced constipation since completing the last interim questionnaire. Comparisons between mean duration of constipation between groups are presented in Table S27.

# 6. Supplementary Tables

## Table S1. 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

## Table S2. 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)<br>Infrequent (UCV-ve)<br>Never | DBPCFC | 4.3 g (0.1, 0.4, 1.3, 2.5) |
| | | S P | SIG | Infrequent<br>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)<br>Infrequent (UCV-ve)<br>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)<br>Infrequent (UCV-ve)<br>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). See *Food challenges - unscheduled clinic visits* in the Supplementary Methods for more details about the interval between successive challenges. Active dose were interspersed with placebo doses (see Online Protocol).

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 S3. 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 (see Online Protocol).

## Table S4. Baseline data

| | | SIG<br>% (n/N) | EIG<br>% (n/N) |
|---|---|---|---|
| **Number in group** | | 651 | 652 |
| **Demography** | | | |
| Mean age at enrollment (months)<br>(SD) | | 3.39 (n=651)<br>(0.24) | 3.38 (n=652)<br>(0.22) |
| Mean age at three year visit (months)<br>(SD) | | 37.9 (n=601)<br>(3.3) | 37.9 (n=572)<br>(3.4) |
| Sex: | Male | 52.1 (339/651) | 48.2 (314/652) |
| | Female | 47.9 (312/651) | 51.8 (338/652) |
| Ethnicity: | White | 84.0 (547/651) | 85.4 (557/652) |
| | Black | 2.9 (19/651) | 3.4 (22/652) |
| | Asian† | 1.7 (11/651) | 2.6 (17/652) |
| | Chinese | 0.5 (3/651) | 1.2 (8/652) |
| | Mixed | 10.9 (71/651) | 7.4 (48/652) |
| Pet ownership | | 44.6 (290/650) | 40.6 (264/651) |
| Maternal education:<br>(age at leaving full-time education) | ≤16 | 6.2 (40/650) | 5.2 (34/652) |
| | 17-18 | 13.7 (89/650) | 12.7 (83/652) |
| | >18 | 80.2 (521/650) | 82.1 (535/652) |
| **Smoking** | | | |
| Maternal | | 3.1 (20/650) | 3.4 (22/651) |
| Paternal | | 10.9 (71/650) | 10.8 (70/651) |
| **Family history** | | | |
| Median maternal age (years): | | 33 (n=650)<br>(range 19 – 46) | 33.5 (n=652)<br>(range 19 – 45) |
| Siblings | 0 | 38.3 (249/651) | 37.3 (243/652) |
| | 1 | 36.9 (240/651) | 39.3 (256/652) |
| | 2 | 16.4 (107/651) | 14.9 (97/652) |
| | 3+ | 8.5 (55/651) | 8.6 (56/652) |
| **Birth history** | | | |
| Mean birth weight grams<br>(SD) | | 3560 (n=651)<br>(487) | 3570 (n=651)<br>(489) |
| Mode of delivery:* | Vaginal | 77.3 (503/651) | 72.4 (472/652) |
| | Caesarean | 22.7 (148/651) | 27.6 (180/652) |
| Mean gestational age (weeks) | | 39.7 (n=651) | 39.9 (n=652) |
| **Participant enrollment atopy status** | | | |
| Skin-prick test positive (>0 mm) | | N/A | 5.1 (33/652) |
| Visible eczema | | 24.2 (157/650) | 24.5 (160/652) |
| Median SCORAD<br>(infants with eczema) | | 7.5 (n=157)<br>(range 3.5 – 49.2) | 7.5 (n=160)<br>(range 3.5 – 75.0) |
| **EIG median age of allergenic food first consumption (weeks)** | | | |

| | **SIG**<br>% (n/N) | **EIG**<br>% (n/N) |
|---|---|---|
| Dairy | - | 17.3 |
| Egg | - | 19.6 |
| Fish | - | 19.6 |
| Sesame | - | 19.6 |
| Peanut | - | 19.6 |
| Wheat | - | 20.6 |
| **Family atopy status (self-reported)** | | |
| ***Maternal*** | | |
| Eczema | 34.2 (222/650) | 34.9 (227/651) |
| Asthma | 26.8 (174/650) | 25.8 (168/651) |
| Maternal atopy‡ | 63.2 (411/650) | 61.9 (403/651) |
| ***Paternal*** | | |
| Eczema | 21.1 (137/650) | 18.9 (123/651) |
| Asthma | 23.5 (153/650) | 21.8 (142/651) |
| Paternal atopy‡ | 55.7 (362/650) | 50.5 (329/651) |
| **Maternal allergenic food consumption** | | |
| During pregnancy | 100.0 (639/639) | 100.0 (631/631) |
| During breastfeeding | 100.0 (639/639) | 100.0 (631/631) |

* $P < 0.05$

† Asian refers to Indian, Pakistani and Bangladeshi

‡Eczema, asthma or hay fever

## Table S5. Logistic Modelling and Dominance Analysis 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 (early-introduction group) | 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 |

An analysis was undertaken to see if developing the primary outcome, food allergy to one or more foods, could have been predicted from certain baseline characteristics. A logistic model was run with non-adherence being the dependent variable and key atopy and socio-demographic variables included as independent variables. The number of these that could be included was restricted by the number of dependent events there were.
Dominance analysis was then undertaken to discern the relative importance of the independent variables in the logistic model based on each variable's contribution to overall model fit statistics.

## Table S6. Primary Outcome: Intention-to-Treat

| | SIG ITT % (n/N) | EIG ITT % (n/N) | EIG vs SIG Relative risk (95% CI) | p value |
|---|---|---|---|---|
| ***1. Overall primary outcome positive (one or more foods)*** | | | | |
| Overall | 7.1 (42/595) | 5.6 (32/567) | 0.80 (0.51-1.25) | p=0.32[1] |
| ***2. Risk stratified - visible eczema at enrollment*** | | | | |
| 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] |
| ***3. Food specific primary outcome positive*** | | | | |
| 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 S7. Number of Participants with One or More Allergies to the Early Introduction Foods

| | | SIG<br>N=42<br>% (n) | EIG<br>N=32<br>% (n) | |
|---|---|---|---|---|
| **Number of study foods primary outcome positive to** | | | | |
| | 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) | |
| **Mean number of food allergies per food allergic child** | | 1.31 | 1.12 | |

Mann-Whitney test

## Table S8. Parental Reporting of IgE and Non-IgE Type Symptoms

| | | 4-6m<br>% (n/N) | 7-9m<br>% (n/N) | 8-12m<br>% (n/N) | 4-12m<br>% (n/N) |
|---|---|---|---|---|---|
| **(A) IgE type symptoms** | | | | | |
| (1) To one or more of early | **EIG** | 11.7 (72/615) | 6.7 (37/551) | 5.6 (32/571) | 16.0 (101/633) |
| introduction foods | **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 | **EIG** | 8.6 (53/615) | 4.4 (24/551) | 1.8 (10/571) | 11.9 (75/633) |
| introduction foods | **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 | **EIG** | 16.4 (101/615) | 10.2 (56/551) | 7.2 (41/571) | 21.8 (138/633) |
| introduction foods | **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 S9. 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)<br>Recurrent vomiting - (?after prawn cracker at nursery) | 2 hours | Fish (cod)<br>Seafood (prawn) | 7 & 11m (cod)<br>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)<br>"Huge" vomits, pale, subdued (rice) | 2 hours | Milk Soya Rice | 3m (cow's milk)<br>4m (soya)<br>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

## Table S10A. 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) |
| ***Risk stratified - visible eczema at enrollment*** | | | | | | | | |
| 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) |
| **Food specific 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 S10B. 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** % (n/N) | **EIG Non Per-Protocol** % (n/N) | **p value SIG PP vs EIG Non-PP** | **EIG Adherence Non-Evaluable** % (n/N) | **p value SIG PP vs EIG Adherence Non-Evaluable** |
|---|---|---|---|---|---|
| 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** | **SIG Per-Protocol** % (n/N) | **EIG Food Specific Non Per-Protocol** % (n/N) | | **EIG Food Specific Adherence Non-Evaluable** % (n/N) | |
| 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) | - |

## Table S11. Skin-Prick Test Results

| | SIG ITT % (n/N) | EIG ITT % (n/N) | EIG vs SIG Relative Risk (95% CI) | p value |
|---|---|---|---|---|
| ***Intention-to-treat analyses*** | | | | |
| **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] |
| | **SIG PP** % (n/N) | **EIG PP** % (n/N) | **EIG vs SIG Relative Risk** (95% CI) | **p value** |
| ***Per-protocol analyses*** | | | | |
| **12 months** | | | | |
| Any food sensitisation | 17.3 (92/532) | 10.1 (21/208) | 0.58 (0.37-0.91) | p=0.01[1] |
| Peanut | 6.0 (32/532) | 2.9 (9/311) | 0.48 (0.23-0.99) | p=0.04[1] |
| Egg | 12.6 (67/532) | 6.1 (13/214) | 0.48 (0.27-0.85) | p=0.009[1] |
| Milk | 2.4 (13/532) | 1.2 (5/415) | 0.49 (0.18-1.37) | p=0.23[2] |
| Sesame | 1.3 (7/532) | 0.7 (2/270) | 0.56 (0.12-2.69) | p=0.73[2] |
| Fish | 1.3 (7/532) | 1.7 (5/297) | 1.28 (0.41-4.00) | p=0.76[2] |
| Wheat | 3.2 (17/532) | 1.5 (3/200) | 0.47 (0.14-1.58) | p=0.31[2] |
| **36 months** | | | | |
| Any food sensitisation | 10.2 (54/529) | 3.3 (7/210) | 0.33 (0.15-0.71) | p=0.002[1] |
| Peanut | 5.9 (31/527) | 1.9 (6/310) | 0.33 (0.14-0.78) | p=0.007[1] |
| Egg | 6.3 (33/527) | 3.3 (7/215) | 0.52 (0.23-1.16) | p=0.10[1] |
| Milk | 2.1 (11/527) | 0.2 (1/413) | 0.12 (0.02-0.89) | p=0.02[2] |
| Sesame | 1.9 (10/527) | 0.0 (0/264) | 0.00 (-) | p=0.04[2] |
| Fish | 0.9 (5/527) | 0.0 (0/296) | 0.00 (-) | p=0.17[2] |
| Wheat | 3.2 (17/527) | 1.0 (2/202) | 0.31 (0.07-1.32) | p=0.12[2] |
| Raw egg white | 7.3 (38/524) | 3.7 (8/215) | 0.51 (0.24-1.08) | p=0.07[1] |

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

## Table S12. Baseline Characteristics by Per-Protocol Status

| | Standard-Introduction Group | | | Early-Introduction Group | | |
|---|---|---|---|---|---|---|
| | 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 (5040† | 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 |
| **Family 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 median (IQR) | | | | | | |
| Physical QOL | 14 (12-15) | 14 (12-15) | 13 (11-15) | 14 (12-15) | 14 (12-15) | 14 (12-15) |
| Psychological QOL | 13 (12-14) | 12 (12-14) | 12 (10-13)† | 13 (12-14) | 13 (12-14)‡ | 13 (11-14)† |
| Social QOL | 10 (8-11) | 9 (8-11) | 9 (7-10) † | 10 (9-11) | 10 (8-11) | 10 (8-11) |
| Environment QOL | 14 (12-15) | 14 (13-15) | 12 (10-14) ‡ | 14 (13-15) | 14 (12-15) | 13 (12-15) |

| | | | | | | |
|---|---|---|---|---|---|---|
| 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 standard-introduction group or early-introduction group as appropriate

## Table S13. Logistic Modelling and Dominance Analysis of Factors Influencing Standard-Introduction Group 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 |

An analysis was undertaken to see if per-protocol adherence in the standard-introduction group could have been predicted from certain baseline characteristics. A logistic model was run with non-adherence being the dependent variable and key socio-demographic variables included as independent variables. The number of these that could be included was restricted by the number of dependent events there were.
Dominance analysis was then undertaken to discern the relative importance of the independent variables in the logistic model based on each variable's contribution to overall model fit statistics.

## Table S14. Logistic Modelling and Dominance Analysis of Factors Influencing Early-Introduction Group Non-Adherence

| | **EIG non-adherence** 56.6% (286/505) | | **EIG dominance analysis** | |
|---|---|---|---|---|
| | OR (95% CI) | p value | Dominance statistic | Rank |
| Ethnicity (non-white) | 2.21 (1.18-4.14) | 0.01 | 27.4% | 1 |
| Visible eczema at 3m visit | 1.38 (0.87-2.19) | 0.18 | 10.9% | 4 |
| New onset eczema (4-6m) | 1.35 (0.75-2.41) | 0.32 | 3.8% | 7 |
| Maternal atopy | 1.23 (0.84-1.79) | 0.29 | 5.1% | 5 |
| Maternal education (≤18 years) | 1.12 (0.68-1.83) | 0.66 | 0.5% | 13 |
| Maternal smoking | 0.78 (0.27-2.28) | 0.65 | 1.4% | 11 |
| Caesarean delivery | 1.21 (0.80-1.83) | 0.38 | 3.9% | 6 |
| Sex (female) | 1.21 (0.84-1.75) | 0.39 | 3.3% | 8 |
| Siblings (any) | 1.10 (0.76-1.61) | 0.70 | 1.6% | 10 |
| QOL psychological domain (>median) | 0.69 (0.47-1.00) | 0.05 | 17.8% | 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 (1.02-2.86) | 0.04 | 22.2% | 2 |
| Any symptoms to other foods (4-6m) | 1.34 (0.53-3.35) | 0.54 | 1.7% | 9 |

An analysis was undertaken to see if per-protocol adherence in the early-introduction group could have been predicted from certain baseline characteristics. A logistic model was run with non-adherence being the dependent variable and key socio-demographic variables included as independent variables. Given non-adherence was significantly more common in the early-introduction group than the standard-introduction group, the number of independent variables that could be incorporated in the model was greater.
Dominance analysis was then undertaken to discern the relative importance of the independent variables in the logistic model based on each variable's contribution to overall model fit statistics.

## Table S15A. Overall Adherence Determined by Number of Foods Consumed, Quantity and Frequency of Consumption in the Early-Introduction Group

**≥4 foods**

| | ≥50% | ≥75% | 100% |
|---|---|---|---|
| ≥4 weeks | 81% (393/483) | 69% (333/480) | 54% (256/474) |
| ≥5 weeks | 68% (327/483) | 54% (262/484) | 35% (169/483) |
| ≥6 weeks | 57% (277/488) | 42% (207/491) | 25% (123/490) |

**≥5 foods**

| | ≥50% | ≥75% | 100% |
|---|---|---|---|
| ≥4 weeks | 74% (358/484) | 58% (280/481) | 40% (189/475) |
| ≥5 weeks | 58% (282/485) | **43%** (208/486) | 25% (120/485) |
| ≥6 weeks | 45% (222/494) | 26% (131/496) | 16% (77/494) |

**6 foods**

| | ≥50% | ≥75% | 100% |
|---|---|---|---|
| ≥4 weeks | 57% (279/488) | 41% (201/485) | 24% (117/479) |
| ≥5 weeks | 42% (208/496) | 25% (123/496) | 12% (60/494) |
| ≥6 weeks | 25% (126/500) | 13% (67/501) | 6% (32/498) |

## Table S15B. Effect of Adherence on Primary Outcome in the Early-Introduction Group: Comparison with the Per-Protocol Standard-Introduction Group Primary Outcome Allergy Prevalence 7.3%

**≥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 | 3.3%* (9/277) | 1.9%** (4/207) | 1.6%* (2/123) |

**≥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) |

*p<0.05 **p<0.01

Table S15A shows the percentage, and corresponding numbers, of early-introduction group participants achieving varying levels of study food consumption amongst those early-introduction group 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[19] because of the additional requirement in Table S15A 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 (see *Measuring Adherence* in the Supplementary Methods). The shaded blue square represents the level of consumption defined as overall 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. Table S15B presents the primary outcome allergy prevalence for the corresponding level of consumption in the respective cells in the grid in Table S15A. The shaded blue square represents the allergy prevalence among those early-introduction group participants complying with the study protocol, i.e. among the 43% of children in Table S15A 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 early-introduction group with the allergy prevalence rate in the standard-introduction group adherent group where 7.3% (38/524) were found to meet the primary outcome. The same adherence grids are shown for each specific food in Table S16.

## Table S16. Adherence Grids for Each Specific Food

| | | Specific Food Consumption | | | Specific Food Allergy | | | Per-Protocol SIG Allergy |
|---|---|---|---|---|---|---|---|---|
| | | ≥50% | ≥75% | 100% | ≥50% | ≥75% | 100% | |
| **Peanut** | ≥4 weeks | 85% (419/491) | 75% (363/487) | 63% (304/481) | 0.2%** (1/419) | 0.0%** (0/363) | 0.0%** (0/304) | 2.5% (13/525) |
| | ≥5 weeks | 73% (359/490) | 62% (310/501) | 51% (252/496) | 0.3%* (1/359) | 0.0%** (0/310) | 0.0%* (0/252) | |
| | ≥6 weeks | 65% (320/492) | 54% (266/497) | 39% (196/501) | 0.3%* (1/320) | 0.0%* (0/266) | 0.0%* (0/196) | |
| **Egg** | ≥4 weeks | 76% (370/490) | 59% (286/484) | 43% (207/478) | 1.9%** (7/370) | 2.1%* (6/286) | 1.0%** (2/207) | 5.5% (29/525) |
| | ≥5 weeks | 63% (306/488) | 43% (215/499) | 29% (142/499) | 2.3%* (7/306) | 1.4%* (3/215) | 1.4%* (2/142) | |
| | ≥6 weeks | 50% (246/495) | 33% (165/498) | 21% (106/505) | 0.8%** (2/246) | 1.2%* (2/165) | 1.9% (2/106) | |
| **Milk** | ≥4 weeks | 95% (478/503) | 91% (449/494) | 86% (421/491) | 0.2% (1/478) | 0.2% (1/449) | 0.2% (1/421) | 0.6% (3/525) |
| | ≥5 weeks | 91% (441/486) | 85% (415/487) | 77% (374/487) | 0.2% (1/441) | 0.2% (1/415) | 0.3% (1/374) | |
| | ≥6 weeks | 87% (425/486) | 79% (385/489) | 70% (344/490) | 0.2% (1/425) | 0.3% (1/385) | 0.3% (1/344) | |
| **Sesame** | ≥4 weeks | 79% (385/489) | 66% (323/486) | 52% (248/480) | 0.0% (0/385) | 0.0% (0/323) | 0.0% (0/248) | 0.6% (3/525) |
| | ≥5 weeks | 68% (334/494) | 51% (266/505) | 38% (188/499) | 0.0% (0/334) | 0.0% (0/266) | 0.0% (0/188) | |
| | ≥6 weeks | 58% (290/499) | 42% (213/504) | 29% (145/504) | 0.0% (0/290) | 0.0% (0/213) | 0.0% (0/145) | |
| **Fish** | ≥4 weeks | 85% (419/493) | 75% (367/490) | 59% (283/482) | 0.2% (1/419) | 0.3% (1/367) | 0.0% (0/283) | 0.2% (1/529) |
| | ≥5 weeks | 74% (361/491) | 60% (297/495) | 43% (212/498) | 0.3% (1/361) | 0.3% (1/297) | 0.0% (0/212) | |
| | ≥6 weeks | 63% (309/492) | 47% (232/497) | 34% (171/503) | 0.3% (1/309) | 0.0% (0/232) | 0.0% (0/171) | |
| **Wheat** | ≥4 weeks | 81% (393/483) | 69% (333/480) | 54% (256/474) | 0.0% (0/371) | 0.0% (0/314) | 0.0% (0/244) | 0.0% (0/525) |
| **7** | ≥5 weeks | 68% (327/483) | 40% (202/505) | 35% (169/483) | 0.0% (0/278) | 0.0% (0/202) | 0.0% (0/132) | |
| | ≥6 weeks | 57% (277/488) | 42% (207/491) | 25% (123/490) | 0.0% (0/186) | 0.0% (0/131) | 0.0% (0/80) | |

*p<0.05 **p<0.01

Table S16 shows in the left grid the percentage, and corresponding numbers, of early-introduction group participants achieving varying levels of consumption of each specific food amongst those early-introduction group participants in whom the primary outcome was determined. Each grid varies 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, ≥ 3g and 4 g of the specific allergenic protein per week respectively. Consumption is measured over a 12 week period from enrollment to 6 months of age (see *Measuring Adherence* in the Supplementary Methods). The shaded blue square represents the level of consumption defined as food specific per-protocol adherent, i.e. consumption of 75% or more of the weekly recommended dose of allergenic protein, for 5 or more weeks before 6 months of age. The corresponding right hand column presents the food specific allergy prevalence for the corresponding level of consumption in the respective cells in the left hand column grid. The shaded blue square represents the food specific allergy prevalence among those early-introduction group participants complying with the study protocol for that specific food. P values are based on Fisher's exact test (2 tailed) comparing each specific food allergy prevalence rate in the early-introduction group with the food specific allergy prevalence in the standard-introduction group adherent group which is indicated in the right hand larger cell of the right hand column grids for each specific food.

## Table S17. Serious Adverse Events: Hospital Admissions

| | | SIG (N=651) n (%) | EIG (N=652 n (%) | p value |
|---|---|---|---|---|
| **Death** | | 0 (0%) | 0 (0%) | - |
| **Life threatening SAE** | | 3 (0.5%)* | 0 | 0.12 |
| **Number of Hospitalizations** | | | | |
| | 0 | 560 (86%) | 576 (88%) | 0.28[1] |
| | 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 | |
| **Any Hospitalizations** | | | | |
| | No | 560 (86.0%) | 576 (88.3%) | 0.22[2] |
| | Yes | 91 (14.0%) | 76 (11.7%) | |

* heart valve damage (1), extensive burns (1), prolonged febrile convulsion (1)
[1]Chi-Square [2]Fisher Exact

## Table S18. 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) |
| $\chi^2$ 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

## Table S19. Adverse Event: Parent Reported Vomiting

| | 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) |
| $\chi^2$ 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

## Table S20. 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) |
| $\chi^2$ 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.

## Table S21. 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) |
| $\chi^2$ 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

## Table S22. Adverse Event: Parent Reported Upper Respiratory Tract Infection

| | 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) |
| $\chi^2$ 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

## Table S23. Adverse Event: Parent Reported Lower Respiratory Tract Infection

| | 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) |
| $\chi^2$ 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

## Table S24. 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) |
| $\chi^2$ 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

## Table S25. 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) |
| $\chi^2$ 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

## Table S26. 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 |

## Table S27. 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 |

## Table S28. Growth: Anthropometry at 3, 12 Months and Three Years.

| Anthropometric outcome, mean (SD) | 3 months SIG | 3 months EIG | 12 months SIG | 12 months EIG | | 36 months SIG | 36 months 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. Body Mass Index | 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. Body Mass Index-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 |

*MUAC: Mid Upper Arm Circumference

## Table S29A. Skin-Prick Test and Challenge Results of Baseline Food Allergic and Skin-prick Test Positive Participants

| | Enrollment visit | | 12 month visit | | | 36 month visit | | | |
|---|---|---|---|---|---|---|---|---|---|
| ID | 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 | Study 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 |

Key: M Milk E Egg RE raw egg white C cod S Sesame P Peanut W Wheat + positive challenge - negative challenge ic incomplete challenge ind indeterminate challenge

dna did not attend dna(fc) did not attend (frequently consuming) ne non-evaluable ts skin-prick test too significant

*SPT-ve †Unwell on day of challenge

In Table S29A, a detailed exposition is given of the progress through the study of the 33 early-introduction group participants (5.1%, 33/652) who were skin-prick test positive to one or more foods at the enrollment visit. 7 returned for food challenges and were positive to one or more foods (ID's 1 to 7), 22 returned for one or more food challenges and were negative (ID's 8 to 29). Four refused to return for the enrollment food challenge (ID's 30 to 33). The 33 participants' subsequent skin-prick test results at the 12 month and 36 month assessments are given in the table for every food that was positive. The result of subsequent food challenges generated by these positive skin-prick tests at the two assessment visits is also given, with the food for which the participant had a positive challenge to being indicated. In the penultimate column on the right the final study primary outcome status is given. In the far right column, the participant's per-protocol adherence status is given.

Negative challenges and primary outcome status are indicated by green shading and positive challenges and primary outcome status by red shading. It can be clearly seen that the seven baseline food challenge participants remained food allergic bar one participant (with one not having a determinable primary outcome status). Conversely, the great majority of the 22 participants with negative enrollment challenges remained positive. Demographic differences between the enrollment challenge positive, challenge negative and challenge not attended groups amongst the 33 participants are shown in Table S29C.

## Table S29B. 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 S29B, 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 Supplementary Discussion: Reverse Causality).

## Table S29C. Demographics of Baseline Food Allergic and Skin-prick Test Positive Early-Introduction Group 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

## Table S30. Details of the Seven Children with Positive Open-Label Food Challenges at Enrollment

| 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) |

*Indeterminate result: refused to return for repeat challenge

## Table S31. Baseline and Post-Enrollment 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 |
| **Family atopy status** | | | | | | | |
| Maternal asthma (%) | 26.6 | 23.6 | 0.47 | 22.9 | 0.57 | 24.0 | 0.62 |

| | 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** |
| 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 (median)* | | | | | | | |
| Physical | 14 (12-15) | 14 (12-15) | 0.77 | 14 (12-15) | 0.25 | 14 (12-15) | 0.56 |
| Psychological | 13 (12-14) | 13 (11-14) | 0.46 | 13 (11-14) | 0.38 | 13 (10-14) | 0.79 |
| Social | 10 (8-11) | 10 (8-11) | 0.11 | 9 (7-10) | 0.006 | 10 (8-11) | 0.86 |
| Environment | 14 (12-15) | 13 (12-15) | 0.14 | 13 (11-14) | 0.001 | 14 (12-16) | 0.42 |
| 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 |
| Duration of exclusive breastfeeding (median weeks) | 18 | 17 | 0.11 | 20 | 0.32 | 16 | 0.005 |
| **Compliance** | | | | | | | |
| EIG complied | 43.1 (212/492) | 29.7 (11/37) | 0.11 | - | - | 29.7 (11/37) | 0.11 |
| SIG complied | 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)

† Primary outcome evaluable vs non-evaluable

IQ Interim Questionnaires

## Table S32. Distribution of Cases of Food Allergy in the Standard-Introduction Group by Eczema Status and Severity at Enrollment

| Standard Introduction Group | Cases | No eczema at enrollment 76% of SIG (451/594) A | New onset eczema from 4-6 months 11% of SIG (66/587) A1 | No eczema by 6 months 78% of SIG (355/458) A0 | No visible eczema at enrollment or 12 months 66% of SIG (352/532) A00 | Any visible eczema at enrollment 24% of SIG (143/594) B | SCORAD 1-14 18% of SIG (110/143) B1 | SCORAD 15-40 5% of SIG (30/143) B2 | SCORAD >40 1% of SIG (3/143) 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 standard-introduction group 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 standard-introduction group 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 standard-introduction group participants who had no eczema, who constitute 76% of the whole standard-introduction group.

**A** and **B** are the standard-introduction group 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 standard-introduction group, **B** is those with visible eczema at enrollment, constituting 24% of the standard-introduction group
**A1** is a subgroup of **A**, and represents standard-introduction group 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 standard-introduction group.
**A0** is a subgroup of **A,** and represents standard-introduction group 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 standard-introduction group 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 standard-introduction group.

**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 standard-introduction group participants.

**References**


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

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

3 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)

4 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)

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

6 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.

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

8 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)

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

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

11 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.

12 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.

13 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.

14 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.

15 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.

16 Weiland SK, Bjorksten B, Brunekreef B, et al. Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC II): rationale and methods. *Eur Respir J* 2004; **24:** 406-12.

17 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.

18 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.

19 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. Available from: http://www.sciencedirect.com/science/article/pii/S0091674916001354

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

21 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/)

22 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.

23 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.

24 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;

25 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.