**Factors influencing adherence in a trial of early introduction of allergenic food**

**Michael R. Perkin, PhD,**a **Henry T. Bahnson, MPH,b Kirsty Logan, PhD,**c **Tom Marrs, MB BS,c Suzana Radulovic, MD,c Rebecca Knibb, PhD,d Joanna Craven, MPH,c Carsten Flohr, PhD,e E. N. Mills, PhDf, Serge A. Versteeg,g Ronald van Ree, PhD,gh and Gideon Lack, M.B. B.Ch,**c **on behalf of the EAT Study Team**

From athe Population Health Research Institute, St George's, University of London, bthe Benaroya Research Institute, Seattle, c the Paediatric Allergy Research Group Department of Women and Children’s Health, School of Life Course Sciences, King’s College London, dthe Department of Psychology, Aston University, ethe Unit for Population-Based Dermatology Research, St John’s Institute of Dermatology, School of Basic and Medical Biosciences, Faculty of Life Sciences & Medicine, King’s College London, fthe School of Biological Sciences, Division of Infection, Immunity and Respiratory Medicine, Manchester Academic Health Science Centre, Manchester Institute of Biotechnology, University of Manchester, gthe Department of Experimental Immunology, Academic Medical Center, Amsterdam; hthe Department of Otorhinolaryngology, Academic Medical Center, Amsterdam

**Conflict of interest:** none

World count: 4392

Figures/Tables: 2 Tables & 4 Figures

**Corresponding author:**

Gideon Lack

Professor of Paediatric Allergy, King's College London

Head of the Clinical Academic Paediatric Allergy Service

Guy’s & St Thomas’ NHS Foundation Trust

Children's Allergies Department

St Thomas’ Hospital

Westminster Bridge Road

London SE1 7EH

Tel: +44 (0)20 7188 9730

Fax: +44 (0)20 7188 9782

Email: gideon.lack@kcl.ac.uk

**Funding**

The main components of the EAT study were jointly funded by the UK Food Standards Agency (FSA, contract code T07051) and the Medical Research Council (MRC, grant MC\_G1001205). Additionally we would like to thank the Davis Foundation. The skin-related aspects of the EAT study were supported by the UK National Institute for Health Research (NIHR). CF held an NIHR Clinician Scientist Award (NIHRCS/01/2008/009). The analyses presented in this paper were supported by a subsequent grant from the FSA (contract code FS101178) and the European Union (Integrated Approaches to Food Allergen and Allergy Risk Management (iFAAM), Grant Agreement N° 312147).

**Abstract (244 words)**

**Background:** The Enquiring About Tolerance (EAT) study examined whether the early introduction of six allergenic foods from three months of age in exclusively breastfed infants prevented the development of food allergy. The intervention was effective in the per-protocol analysis for allergy to one or more foods and for egg and peanut individually, but only 42% of early introduction group (EIG) children met the per-protocol criteria.

**Objective**: To identify which factors were responsible for non-adherence in the EAT study.

**Methods**: Factors influencing adherence within the key early introduction period in the EIG (up to six months of age) were divided into enrollment and post-enrollment factors and their association with non-adherence was explored.

**Results**: In an adjusted analysis, at enrollment, increased maternal age, non-white ethnicity and lower maternal quality of life were independently and significantly associated with overall non-adherence in the EIG. Enrollment eczema and enrollment serum allergen-specific IgE sensitization to one or more foods (≥0.1 kU/l) were not related to overall non-adherence.

Post enrollment two factors were significantly related with EIG overall non-adherence: parent reported IgE type symptoms with infant allergenic food consumption by 6 months of age and reported feeding difficulties by 4 months of age.

**Conclusion**: If early introduction of allergenic foods were to be considered as a strategy to prevent food allergy, families of non-white ethnicity, those with older mothers and those with infants with reported feeding difficulties or early onset eczema would benefit from support to promote early and sustained consumption.

**Clinical implications:**

Non-white families, those with older mothers and those with infants with reported feeding difficulties or early onset eczema would benefit from support to achieve early and sustained allergenic food consumption.

**Capsule summary:**

Poor adherence was associated with older maternal age, non-white ethnicity and lower maternal quality of life. Encouraging e adherence in non-white families and infants with early onset eczema might reduce the prevalence of food allergy.

**Key words**

Food allergy; diet; allergens; infancy; breastfeeding; randomized controlled trial; adherence

**Abbreviations**

IFS2010 Infant Feeding Survey 2010

EIG Early Introduction Group

SIG Standard Introduction Group

EAT Enquiring About Tolerance

AD Atopic Dermatitis

ISAAC International Study of Asthma and Allergies in Childhood

SCORAD Scoring Atopic Dermatitis index

TEWL Transepidermal water loss

**Introduction**

The Enquiring About Tolerance (EAT) study was a large randomised food allergy prevention trial of the early introduction of six allergenic foods from three months of age in exclusively breastfed infants recruited from the general population.1,2 The EAT study achieved markedly different rates of exposure to allergenic foods between the randomized groups (the Early Introduction Group; EIG and the Standard Introduction Group; SIG) before six months of age.1 However the study did not show statistically significant efficacy in an intention-to-treat analysis but did show a significant per-protocol effect for allergy to one or more foods and for egg and peanut individually.2 There are two explanations for this discrepancy. 1) Per-protocol was effective because the population adhered to the intervention. 2) Intention-to-treat was not effective because amongst the large group of children who didn’t adhere, those with nascent allergy with food sensitization developed sub-clinical symptoms and/or food aversion and were therefore unable to adhere. Further analyses suggested that food allergy prevention through the early introduction of multiple allergenic foods in normal breastfed infants may depend on adherence and dosage.2

## The EAT study per-protocol criteria for the EIG were stringent. By six months of age, EIG infants were expected to have achieved sustained, high dose consumption of five or more of the six early introduction foods. Achieving such per-protocol adherence in the EIG proved difficult. Only 42% (223/529) of adherence-evaluable EIG children complied entirely with the protocol (34% (223/652) of the whole EIG group).

Following the completion of the study, we measured serum allergen-specific IgE sensitization in the EAT participants and have demonstrated in an intention-to-treat analysis that the intervention successfully reduced the development of food allergy amongst EIG infants who were sensitised on specific IgE testing at enrollment. Infants with the early emergence of food specific IgE sensitization to foods are known to be at high risk of developing a food allergy.3,4

In this paper we explore how this and other data collected in the EAT study influenced the issue of non-adherence with the recommended level of consumption of the six early introduction foods (overall non-adherence) as well as non-adherence with consumption of individual foods (food specific non-adherence). We determine whether occult sensitization and early symptoms were responsible for the high non-adherence rate.

The UK Scientific Advisory Committee on Nutrition (SACN) has issued the following statement following its review on the evidence on feeding in the first year of life: "The available evidence indicates that the deliberate exclusion or delayed introduction of peanut or hen’s egg beyond 6 to 12 months of age may increase the risk of allergy to the same foods".5 We address how barriers to the prompt introduction of allergenic foods might be mitigated, thereby enhancing the possibility of food allergy prevention.

**Method**

**Participants**

1303 three-month old infants were recruited from the general population in England and Wales through direct advertising and were enrolled between November 2009 and July 2012. Details of the EAT study methodology have been published elsewhere.1 Maternal age at enrollment ranged from 19 to 46 years (median 33 years) and there was no difference in maternal age between study groups. The median age was used as the cut off for dividing mothers into younger (<33 years) and older (≥33 years). All children were generally well, exclusively breastfed and born at term (≥37 weeks gestation). Ethnic origin of the child was based on their parent-defined ethnicity coded using the classification used in the 2001 UK Census.6 1104 of the enrolled infants were white (84.7%), 119 mixed (9.1%) and 80 (6.1%) were black, Asian or Chinese. The trial was registered with the ISRCTN (registration number: 14254740). Ethical approval for the EAT study was provided by St Thomas’ Hospital REC (REC Reference 08/H0802/93) and informed consent was obtained from the parents of all children enrolled in the study.

**Procedures**

Participants were randomized to the SIG or the EIG. The SIG was asked to exclusively breastfeed to around six months of age in accordance with the recommendation in place in the UK since 2003.7 Beyond six months, allergenic food consumption was at parental discretion.

The EIG were asked to introduce six allergenic foods to their infant: cow’s milk (yogurt), peanut, cooked (boiled) hen’s egg, sesame, white fish and wheat.1 Cow's milk was always introduced first, as yogurt. The order of introduction of the next four foods was randomly determined, to avoid any bias from one food being introduced consistently before another. Wheat was introduced last and not before four months of age (see section: *EIG early introduction regimen* in the Methods section in this article's Online Repository).

An online questionnaire was sent to each family monthly to one year of age and then every three months until the child reached three years of age. Each questionnaire allowed families to report any suspected symptoms with food ingestion and to list suspected foods. Clinical judgement was used to divide these into IgE and non-IgE type symptoms. The online questionnaires also ascertained maternal quality of life using the WHO Quality of Life BREF questionnaire,8 infant sleep using the Brief Infant Sleep Questionnaire,9 and parent reporting of feeding difficulty and aversive feeding behaviour using questions based on previously published work.10 Clinic visits took place at enrollment, one and three years of age. Further information on the online questionnaire and clinic visit data collected are presented in the section: *Information collected* in the Methods section in this article's Online Repository.

Food specific IgE to each of the six foods was measured at enrollment, one and three years of age in both groups using ImmunoCap (Phadia) assays.

The primary outcome of the EAT study was the proportion of participants with challenge proven food allergy to one or more of the six early introduction foods between one and three years of age.2

**Per-protocol adherence**

The definitions of overall per-protocol adherence are given in Table E1 in this article's Online Repository. The key criterion (C) for overall adherence in the EIG was the consumption of at least five of the allergenic foods in at least 75% of the recommended amount (3g allergen protein/week), for at least five weeks between three months and six months of age. Food specific per-protocol adherence was based on the same criteria (i.e. consumption of at least 75% of the recommended amount of the specific food for at least five weeks between three and six months of age). The window in which five or more weeks of consumption could be achieved was narrow, as explained in more detail in the section: *Restricted window to achieve per-protocol status* in the Methods section in this article's Online Repository.

**Statistical analyses**

Univariate and multivariable logistic regression models were used to identify factors associated with non-adherence. Penalized logistic regression was used were appropriate for situations with very sparse data. Eczema was analysed as presence of visible eczema at enrollment using the UK diagnostic criteria ("visible eczema").11 Eczema severity was determined by the Scoring Atopic Dermatitis (SCORAD) index and grouped using the accepted SCORAD categories.12 Data were analysed using STATA version 15, SAS version 9.4, and JMP Pro 14. The EAT dataset (ITN900AD) is available through TrialShare, a public website managed by the Immune Tolerance Network (www.itntrialshare.org).

**Results**

Overall per-protocol adherence status could only be determined in 81% (529/652) of the EIG participants (Table E1). An exploration of the likely true adherence status of the 123 EIG participants (19% of the EIG) whose adherence status was non-evaluable, as well as the impact of including or excluding them in the analyses undertaken for this paper, are reviewed in detail in the section: *EIG adherence non-evaluable participants* in the Results section in this article's Online Repository, Table E2 and Figs E1 and E2.

Whilst overall adherence to the EAT early introduction regimen was low at 42%, families found it easier to introduce some foods than others (Fig 1), the result being that food specific adherence varied by food: milk, 84% (451/537); peanut, 61% (336/549); whitefish, 59% (318/543); sesame, 52% (288/550); egg, 42% (234/551); and wheat, 39% (216/553) (Table E3). Whilst randomization had been effective in ensuring the median age of introduction of peanut, egg, sesame and fish was the same at 19.6 weeks, there remained the possibility that the position in the order in which a specific food was introduced might be associated with overall or food specific adherence. Specific foods introduced later in the sequence reduced the likelihood of being per-protocol adherent to that food (Fig E3). However, order of introduction of each of the foods was unrelated to overall per-protocol adherence.

The key period for defining per-protocol adherence was consumption through to six months of age. However, Fig 1 clearly indicates that there were certain foods where the ability to meet the per-protocol threshold (3g/week of allergen protein) continued to improve between six and twelve months of age. High sustained levels of consumption were achieved by six months of age for milk and shortly after six months for wheat. Per-protocol consumption of fish and egg continued to improve beyond six months, plateauing at 9 months for fish and 10 months for egg. Most remarkable were the patterns observed for sesame and peanut. The level of consumption of these two foods that had been achieved by six months of age did not materially change throughout the rest of the first year of life. Hence by one year of age there was still a significant minority who were not eating peanut or sesame at the per-protocol recommended level.

**Enrollment factors associated with EIG overall and food specific non-adherence (univariate analysis)**

Non-white ethnicity, increased maternal age and lower enrollment maternal quality of life scores were significantly associated with not being per-protocol adherent in the EIG (Table E4 - univariate analysis). Non-white ethnicity and increased maternal age were associated with delaying the introduction of solids in both the SIG and EIG infants (Fig E4). Differences were observed in other enrollment demographic characteristics between ethnic groups: visible eczema and enrollment sensitization were both more common in non-white ethnic groups and a history of a sibling having a parent-reported food allergy was more common in infants of Asian, black or Chinese ethnicity (Table E5) and are reviewed in the section: *Association between ethnicity and baseline demographic characteristics* in the Results section in this article's Online Repository.

Eczema severity (SCORAD as a continuous variable) was significantly associated with non-adherence, whilst any visible eczema at enrollment was of borderline significance (p=0.07) (Table E4). More detail about the associations between enrollment factors and overall non-adherence, are presented in the section: *Enrollment factors associated with overall non-adherence* in the Results section in this article's Online Repository. The associations between enrollment factors and food specific non-adherence are presented in the corresponding section: *Enrollment factors associated with food specific non-adherence* in the Results section in this article's Online Repository.

**Enrollment sensitization in the EIG**

In the EAT study there were too few EIG participants sensitized on skin prick testing at enrollment to individual foods (ranging from none for sesame to 24 for raw egg white) to be able to determine reliably the effect on subsequent food specific adherence (Table I). More EIG participants were shown to be sensitized to specific foods based on serum food-specific IgE testing using a 0.1 kU/l threshold (response to one or more foods of ≥0.1 kU/l: 15.7%, 93/593), than were identified to be skin prick test positive (SPT >0mm: 5.1%, 33/652) (Table I).

Food specific IgE sensitization at enrollment strongly predicted the development of food allergy to the same food, and sensitization to one or more foods strongly predicted overall food allergy (Fig E5). Sensitization to one food also predicted food allergy developing to other foods. The group of infants with early food specific IgE sensitization accounted for 69% of the food allergy cases that developed in the EAT study. We have shown that the EAT study early introduction intervention was effective in an intention-to-treat analysis of this high risk population.13

The great majority of EIG infants sensitized to a specific food at enrollment did not report any symptoms when that food was introduced into their diet (for example, 92% (18/22) for peanut). Similarly, the great majority of infants whose families reported symptoms with a specific food were not sensitised to that food at enrollment (for example, 81% (17/21) for peanut). Both are reviewed in detail in the section: *IgE type symptom reporting and enrollment sensitization* in the Results section in this article's Online Repository. Serum food specific sensitization to one or more foods did not predict overall non-adherence in the univariate analysis (Fig 2). In contrast, in univariate analysis, food specific sensitization predicted food specific non-adherence for egg and was of borderline significance for peanut (Fig 2 & Fig E6), both likely to be a consequence of the study design, and discussed in more detail in the section: *Consumption of each allergenic food by enrollment specific IgE sensitization status* in the Results section in this article's Online Repository.

**Enrollment factors associated with EIG overall non-adherence (multivariable analysis)**

A multivariable analysis was undertaken to see if overall non-adherence in the EIG could have been predicted from certain enrollment characteristics (Table II, left column). There was no significant relationship between enrollment sensitization to one or more foods and overall non-adherence.

Non-white ethnicity, increased maternal age and lower enrollment maternal quality of life (psychological domain) all remained significantly related to increased EIG overall non-adherence. There was no statistically significant relationship with any measure of eczema at enrollment, be this visible eczema, eczema severity (SCORAD severity group) or SCORAD itself, although all the odds ratios were greater than 1.0.

**Enrollment factors associated with EIG food specific non-adherence (multivariable analysis)**

Models were created for each individual food (Table II, other columns). Results were broadly similar to overall non-adherence. Ethnicity and maternal age were most strongly associated with non-adherence. Enrollment eczema SCORAD was significantly related to sesame and fish non-adherence but not to other foods. In contrast to the univariate associations, once potential confounding factors were adjusted for, the relationship between enrollment sensitization to any individual food and subsequent non-adherence to these foods was attenuated (peanut OR 1.18, 95% CI 0.39-3.59, p=0.77 and egg OR 2.32, 95% CI 0.85-6.31, p=0.10) and not statistically significant. Amongst the other variables, night waking frequency was significantly associated with egg non-adherence.

**Post enrollment factors associated with non-adherence (univariate analysis)**

We explored three post enrollment factors in the key early introduction period up to six months of age, to assess their association with non-adherence in the EIG (Table E6). These were the new onset of parent-reported eczema after enrollment but before six months, maternal reporting of feeding difficulties at the very beginning of solid food introduction (assessed at 4 months of age) (Table E7), and the reporting of IgE and non-IgE type symptoms with consumption of the early introduction foods before 6 months of age (Table E8 and Fig E7). Whilst new onset eczema showed no association with overall or food specific adherence, there was a strong association between adherence and early reported feeding difficulties, and between adherence and the reporting of IgE type symptoms to the early introduction foods in the key early introduction period (Fig 3). The three factors are reviewed in detail in the section *Post enrollment factors associated with non-adherence* in the Results section in this article's Online Repository.

The association between the reporting of IgE and non-IgE type symptoms and the development of food allergy is reviewed in the section: *Parent suspected IgE or non-IgE type symptoms with food introduction in the EIG and the effect on food allergy* in the Results section in this article's Online Repository and Fig E8.

**Targeted intervention to reduce the overall food allergy burden**

The EAT study SIG participants can be used to explore the natural history of the development of food allergy, independent of the early food introduction intervention. Children with visible eczema or food sensitization at enrollment or those of non-white ethnicity, although representing a small sub-group of the overall population, contributed disproportionately to the burden of overall food allergy (Fig 4 Part A and Fig E9).

SIG participants with eczema at enrollment made up 24.3% of the study population but were responsible for 61.9% of the food allergy cases. Likewise, 15.6% of the SIG were sensitized on IgE testing at baseline to one or more foods, but were responsible for 69.2% of food allergy cases in the SIG. 15.3% of the SIG were of non-white ethnicity but accounted for 28.6% food allergy cases in the SIG and a significantly greater proportion of non-white participants had visible eczema and/or IgE food specific sensitization at enrollment (Table E5 & Fig E9). Furthermore, in the EIG, adherence was significantly lower in those participants of non-white ethnicity (Fig 4 Part A).

We modelled the effects of improved adherence in infants at high risk of developing food allergy (non-white infants, those with enrollment eczema or those with enrollment sensitization (≥0.1kU/l)) and how this might affect the prevalence of food allergy (Fig 4 Part B). Certain assumptions were made: an 80% intervention effect was assumed given the high efficacy observed in the EAT per-protocol analysis and the efficacy seen in the LEAP study intention to treat analysis.14 Assuming that a higher level of adherence could be achieved in these subgroups at high risk of developing food allergy than the 42% observed in the adherence-evaluable EIG children, we determined what the impact might be if an adherence rate of 85% is assumed. Fig 4 Part B displays the percent reduction in total allergy burden and the number needed to treat within the different subgroups.

Targeting the intervention to the group of non-white and/or eczematous infants would comprise a high-risk population of 71.4% of the food allergy burden. If 50%, 75%, or 85% adherence rates can be achieved in this high-risk group, reduction in the overall burden of food allergy in the whole population would be approximately 29%, 43%, and 49% respectively. **Discussion**

Whilst 5.6% of EIG participants developed a food allergy in the EAT study, 58% were non-adherent with the early introduction protocol. Hence the non-adherence rate was ten-fold higher than the food allergy rate. Notably the non-adherence rate also significantly exceeded the prevalence rate of risk factors associated with developing a food allergy: visible eczema at enrollment (25%), enrollment sensitization to one or more foods on specific IgE testing (16%) and non-white ethnicity (15%).

In univariate analysis, non-white ethnicity, older maternal age, lower enrollment maternal quality of life scores and increasing SCORAD were associated with non-adherence to the EIG protocol. The enrollment factors that were found to remain significantly associated with non-adherence in the adjusted analysis were non-white ethnicity, older maternal age and lower enrollment maternal psychological quality of life. Non-white ethnicity and older maternal age were associated in both study groups with postponing the introduction of allergenic foods, compromising the ability to be per-protocol adherent, as the window for per-protocol defined adherence was so short. This delay being present in the SIG could have been anticipated, having been reported in the Infant Feeding Survey undertaken in 2010 (IFS2010),15 and considered in more detail in the section: *Comparison with the Infant Feeding Survey 2010 findings* in the Discussion in this article's Online Repository. However, unexpectedly this delay was present in the EIG as well, despite all EIG families having being asked to introduce the allergenic foods as rapidly as possible.

Post enrollment, whilst the reporting of IgE type symptoms in EIG participants in the key early introduction period by was common (16%), this too fell far short of the 58% non-adherence rate. Furthermore, the great majority of EIG participants reporting such symptoms were neither sensitised to any food at enrolment (76%), nor did they develop a food allergy (82%). The strongest association with non-adherence was the early emergence of feeding difficulties with 40% of non per-protocol EIG families reporting some or great difficulty feeding their infant at four months of age compared with 20% of the per-protocol EIG families.

Enrollment eczema was not associated with overall adherence in the adjusted analyses (although it was associated with food specific adherence to sesame and fish). This is likely to reflect the mild phenotype of infants with eczema in the EAT study. Of the 160 EIG infants with enrollment eczema, 123 were mild (SCORAD <15), 31 moderate (15 to <40) and only 6 were severe (40+). Having eczema in childhood is strongly associated with dietary restriction and a reluctance to include allergenic foods in the diet. In a study of 100 children attending a paediatric dermatology clinic, 75% were having some form of parent instigated dietary exclusion and allergenic foods, including dairy products, eggs and cow's milk were being omitted by 48%, 27% and 25% respectively.16

It might have been anticipated that enrollment sensitization could lead to subclinical symptoms resulting in a subclinical form of pre-existing food allergy that prevented adherence. This was not the case. Enrollment sensitization was not associated with overall or food specific adherence. Furthermore the EAT intervention was effective in an intention-to-treat analysis in the enrollment sensitized EIG infants.13

The early emergence of parental perceived feeding difficulties and aversive feeding behaviour by four months of age, when families had only just started introducing solids to their EIG infant, had the strongest associations with non-adherence in the EIG and were also associated with later introduction of allergenic foods. This finding suggests that families were trying to feed their infant the allergenic food, but if the family perceived that their infant was not ready or mature enough, and they were struggling to achieve the study's stipulated consumption levels, then, particularly for certain foods, having reached a specific level of consumption in the key early introduction period, they did not attempt to escalate this level further beyond six months.

That infant maturity may be a key factor was demonstrated in our recent analysis of sleep data within the cohort. In this study, we showed in an intention-to-treat analysis that early introduction in the EIG was associated with greater duration and quality of sleep.17 However, EIG infants who were sleeping better at enrollment were more likely to subsequently be per-protocol adherent, suggesting that infant maturity is the link between the ability to sleep better and to eat better.17

Feeding difficulties were also shown in the IFS2010 to have a strong association with ethnicity (considered in more detail in the section: *Comparison with the Infant Feeding Survey 2010* findings in the Discussion in this article's Online Repository).15 However, survey questions about feeding difficulties in the context of a randomized controlled trial where the intervention sets high expectations for the introduction of foods, are likely to over-estimate the prevalence of true feeding difficulties which might be seen if a parent were left to introduce solids at a time and in a way of their choosing.

The primary strength of this analysis is that the EAT study cohort was recruited from the general population. The children were meticulously studied and have been shown to have demographic characteristics broadly similar to the population of England and Wales.1 The potential weakness of our findings is the extent to which it can be concluded that factors pertaining to the difficulty in following the highly prescriptive EAT early introduction regimen might relate to the success of early allergenic food introduction in the real world. However, we have previously shown with modelling of our consumption data that that mean weekly consumption of 2 g of peanut protein (50% of the recommended EAT weekly dose) was associated with prevention of peanut allergy and a dose response relationship for protection against peanut allergy and egg allergy was apparent.2

It has been recognised by others that when clinical efficacy has been demonstrated in trials such as EAT and particularly LEAP, translating this into a public health intervention is complex and the results are likely to be subject to effect modification in different populations.18 Hence the call for plausibility trials to evaluate the impact of large-scale public health programs. Such trials serve to identify the barriers and facilitators of the intervention in the real world.18

Our findings suggest that there are certain groups who could benefit from directed support should the recommendation of early introduction of allergenic foods be adopted as a way to prevent food allergy. Specifically, the important factors were found to be: non-Caucasian ethnicity, older mothers and mothers with poorer quality of life. This also applies to infants with early onset eczema in that whilst their adherence to per-protocol consumption of specific foods was not compromised compared to children without eczema, it is within this group that the majority of food allergy develops. While these factors explain only a small part of the 58% of EIG families who were non-adherent, these groups of infants contributed disproportionately to the overall prevalence of food allergy in the EAT population. Indeed our modelling shows that improved adherence in infants manifesting early eczema and from ethnic minorities, raises the possibility of a substantial reduction in the burden of food allergy with a 49% reduction if 85% adherence were achievable. Sufficiently high adherence rates with an early introduction regimen in these populations will be more challenging yet of great value.

The issue of ethnic differences in adherence to public health recommendations is well recognised.19 There is less of a literature on ethnic differences in adherence within the context of a randomised trial that individuals have consented to enrol on.

A recent study of 1000 expecting and 1000 new caregivers of infants under one year of age reported questionable support for early allergenic solid food recommendations.20 However, it has been shown in Australia that updated guidelines issued in 2008 removing recommendations to delay allergenic solids have been associated with reduced delay in parents introducing egg and peanut into the diet.21 Cultural factors may well be important. Whilst US caregivers may perceive early peanut introduction to be difficult, the majority of Israeli infants are eating 2 grams of peanut protein per week without the support of guidelines or a public health campaign.22

A number of countries including the USA,23 Australia24 and the UK5,25,26 have issued new infant feeding guidelines in light of the EAT and LEAP study findings. Where a public health policy of early allergenic food introduction is being recommended, a significant amount of public health support is likely to be necessary to help specific groups at risk of low adherence in order to achieve a substantial reduction in the prevalence of food allergy.

**Conflicts of interest**

The authors declare that there are no conflicts of interest.

 The views expressed in this publication are those of the authors and not necessarily those of the FSA, MRC, the NHS, the NIHR, the Wellcome Trust, the European Union or the UK Department of Health.

**Acknowledgements**

We would like to thank the parents and children of the EAT study for taking part.

We thank our Trial Steering Committee which included Graham Roberts (chair), David Strachan (vice chair), Mary Fewtrell, Christine Edwards, David Reading, Ian Kimber, Anne Greenough and Andy Grieve, for all their work; Mary Feeney, Kate Grimshaw, Judy More, Debbie Palmer and Carina Venter for their contributions to the study design; Monica Basting and Gemma Deutsch for project management coverage; Helen Fisher, Una O’Dwyer-Leeson, Amy Nixon, Louise Coverdale, and Muhsinah Adam for nursing support; Alicia Parr for dietetic support; George Du Toit and Susan Chan for assistance with medical supervision; Jenna Heath and Kathryn Hersee for play-specialist support; and Joelle Buck, Sarah Hardy, Elizabeth Kendall, and Shuhana Begum, of the Food Standards Agency, for their support and commitment to the trial; Alyssa Ylescupidez for her review and edits of the manuscript.

**Members of the EAT Study Team include:**

**Nursing Staff:** Louise Young, RN Children, Victoria Offord, BSc Nursing, Mary DeSousa, BSc Nursing, Jason Cullen, BSc Nursing, Katherine Taylor, MRes. **Dietitians:** Anna Tseng, MPH Nutrition, Bunmi Raji, MSc Nutrition, Sarah Byrom, BSc Human Nutrition and Dietetics, Gillian Regis, BSc Human Nutrition and Dietetics, Charlie Bigwood, Charlotte Stedman, PG Dip Dietetics. **Study management and administration:** Sharon Tonner, PhD, Emily Banks, Yasmin Kahnum, Rachel Babic, BA, Ben Stockwell, BSc, Erin Thompson, BSc, Lorna Wheatley, BSc. **Phlebotomist:** Devi Patkunam. **Laboratory projects:** Kerry Richards, MSc Medicine, Ewa Pietraszewicz, MSc, Alick Stephens, PhD, Asha Sudra, MSc, and Victor Turcanu, PhD.

**References**

1. Perkin MR, Logan K, Marrs T, Radulovic S, Craven J, Flohr C et al. Enquiring About Tolerance (EAT) study: Feasibility of an early allergenic food introduction regimen. J Allergy Clin Immunol 2016; 137(5):1477-86.

2. Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J et al. Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants. N Engl J Med 2016; 374(18):1733-43.

3. Schnabel E, Sausenthaler S, Schaaf B, Schafer T, Lehmann I, Behrendt H et al. Prospective association between food sensitization and food allergy: results of the LISA birth cohort study. Clin Exp Allergy 2010; 40(3):450-7.

4. Du Toit G, Roberts G, Sayre PH, Plaut M, Bahnson HT, Mitchell H 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(1):135-43.

5. Scientific Advisory Committee on Nutrition. Feeding in the first year of life. 2018.

6. Ethnicity categories and the 2011 census. Office of National Statistics . 2018.

7. Department of Health. Infant Feeding Recommendation. 2003.

8. 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(2):299-310.

9. Sadeh A. A brief screening questionnaire for infant sleep problems: validation and findings for an Internet sample. Pediatrics 2004; 113(6):e570-e577.

10. Knibb RC, Smith DM, Booth DA, Armstrong AM, Platts RG, Macdonald A et al. No unique role for nausea attributed to eating a food in the recalled acquisition of sensory aversion for that food. Appetite 2001; 36(3):225-34.

11. Weiland SK, Bjorksten B, Brunekreef B, Cookson WO, von ME, Strachan DP. Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC II): rationale and methods. Eur Respir J 2004; 24(3):406-12.

12. Kunz B, Oranje AP, Labrèze L, Stalder JF, Ring J, Taïeb A. Clinical Validation and Guidelines for the SCORAD Index: Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology 1997; 195(1):10-9.

13. Perkin MR, Logan K, Bahnson HT, Marrs T, Radulovic S, Craven J et al. Efficacy of the EAT study amongst infants at high risk of developing food allergy *(in submission)*. Journal of Allergy and Clinical Immunology 2019.

14. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med 2015; 372(9):803-13.

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

16. Johnston GA, Bilbao RM, Graham-Brown RAC. The use of dietary manipulation by parents of children with atopic dermatitis. Br J Dermatol 2004; 150(6):1186-9.

17. Perkin MR, Bahnson HT, Logan K, Marrs T, Radulovic S, Craven J et al. Association of Early Introduction of Solids With Infant Sleep: A Secondary Analysis of a Randomized Clinical Trial. JAMA Pediatr 2018;e180739.

18. Victora CG, Habicht JP, Bryce J. Evidence-Based Public Health: Moving Beyond Randomized Trials. American Journal of Public Health 2004; 94(3):400-5.

19. Kirkpatrick SI, Dodd KW, Reedy J, Krebs-Smith SM. Income and Race/Ethnicity Are Associated with Adherence to Food-Based Dietary Guidance among US Adults and Children. Journal of the Academy of Nutrition and Dietetics 2012; 112(5):624-35.

20. Greenhawt M, Chan ES, Fleischer DM, Hicks A, Wilson R, Shaker M et al. Caregiver and expecting caregiver support for early peanut introduction guidelines. Ann Allergy Asthma Immunol 2018; 120(6):620-5.

21. Tey D, Allen KJ, Peters RL, Koplin JJ, Tang ML, Gurrin LC et al. Population response to change in infant feeding guidelines for allergy prevention. J Allergy Clin Immunol 2014; 133(2):476-84.

22. Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. J Allergy Clin Immunol 2008; 122(5):984-91.

23. Togias A, Cooper SF, Acebal ML, Assa'ad A, Baker JR, Beck LA et al. Addendum guidelines for the prevention of peanut allergy in the United States. Pediatr Dermatol 2017; 34(1):5-12.

24. ASCIA Guidelines: Infant feeding and allergy prevention. 2016.

25. Turner PJ, Feeney M, Meyer R, Perkin MR, Fox AT. Implementing primary prevention of food allergy in infants: New BSACI guidance published. Clin Exp Allergy 2018; 48(8):912-5.

26. Scientific Advisory Committee on Nutrition, Committee on Toxicity of Chemicals in Food CPatE. Assessing the health benefits and risks of the introduction of peanut and hen's egg into the infant diet before six months of age in the UK. 17-7-2017.

**Figure Legends**

**FIG 1. Adherence with the introduction of allergenic foods in the EIG up to one year of age**

The figure presents the relative proportions of the EIG consuming 100%, 75%, 50%, 25%, or not having started consuming each of the six early introduction foods, from enrollment through to 12 months of age. The food specific per-protocol adherence percentage (amongst those whose food specific adherence status was evaluable) is shown in brackets.

**FIG 2. EIG enrollment IgE sensitization and overall and food-specific per-protocol adherence**

Penalized logistic regression of the association between enrollment IgE sensitization (0.1 kU/l or greater) to specific foods, or to one or more of the six early introduction foods, and the association with food specific and overall non-adherence

**FIG 3. The reporting in the key early introduction period (up to six months) of IgE type symptoms to specific foods, IgE or non-IgE type symptoms to any of the early introduction foods, and the association with food specific and overall per-protocol adherence**

Penalized logistic regression of the association between symptoms with consumption of the six allergenic foods and food specific and overall non-adherence. Symptoms manifesting by six months of age are presented for IgE type symptoms for each specific food, IgE type symptoms to one or more of the six early introduction foods and non-IgE type symptoms to one or more of the six early introduction foods.

**FIG 4. Contributions of subgroups to the proportion of food allergy cases in the SIG**

The bar charts in Part A provide the prevalence calculations used to estimate the reduction in total allergy burden and number needed to treat. The per-protocol adherence rates are shown for those EIG participants whose adherence rate was evaluable and also as a proportion of the whole EIG (percentages in brackets). Part B assumes an 80% treatment effect and 85% adherence across all risk factors for allergy. For example, infants in EAT with visible eczema comprised 61.9% of the total food allergy burden. Hypothetically, if per-protocol adherence could be achieved in 85% of this subgroup then 52.6% (61.9%\*85%) of the allergic burden would experience the intervention. Moreover, if an intervention effect of 80% is assumed, then the total reduction in food allergy that would be realized from intervening on this subgroup would be 42.1% (52.6%\*80%).

**TABLE I. Enrollment sensitization data from the EAT study**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Any food** | **Peanut** | **Egg** | **Milk** | **Sesame** | **Fish** | **Wheat** |
| **SPT >0mm** |  |  |  |  |  |  |  |
| **EIG** | 5.1% (33/652) | 1.2% (8/652) | 3.7% (24/652) | 1.4% (9/652) | 0% (0/652) | 0.2% (1/652) | 0.2% (1/652) |
| *EIG Per-protocol* | 4.0% (9/223) | 0.3% (1/336) | 2.6% (6/234) | 0.4% (2/451)† | 0% (0/288) | 0% (0/318) | 0% (0/216) |
| *EIG Non Per-protocol* | 4.0% (12/302) | 1.9% (4/211) | 4.4% (14/315) | 4.9% (4/82) | 0% (0/262) | 0% (0/225) | 0% (0/336) |
| *EIG Adherence Non-evaluable* | 4.2% (5/120) | 1.0% (1/103) | 2.0% (2/101) | 0% (0/115) | 0% (0/102) | 0% (0/109) | 0% (0/99) |
| **SpIgE ≥0.1 kU/l** |  |  |  |  |  |  |  |
| **All participants** | 15.6% (182/1170) | 3.6% (42/1166) | 6.7% (78/1170) | 6.0% (70/1169) | 2.0% (23/1151) | 0% (0/1164) | 4.3% (50/1165) |
| **SIG** | 15.4% (89/577) | 3.1% (18/576) | 7.3% (42/577) | 6.6% (38/576) | 1.4% (8/572) | 0% (0/575) | 4.3% (25/576) |
| **EIG** | 15.7% (93/593) | 4.1% (24/590) | 6.1% (36/593) | 5.4% (32/593) | 2.6% (15/579) | 0% (0/589) | 4.2% (25/589) |
| *EIG Per-protocol* | 13.6% (28/206) | 2.3% (7/305)\* | 3.3% (7/214)\* | 3.9% (16/414) | 2.3% (6/263) | 0% (0/289) | 5.5% (11/201) |
| *EIG Non Per-protocol* | 15.4% (42/273) | 5.7% (11/193) | 8.0% (23/287) | 8.3% (6/72) | 3.1% (7/227) | 0% (0/204) | 3.7% (11/301) |
| *EIG Adherence Non-evaluable* | 15.0% (16/107) | 4.4% (4/90) | 4.4% (4/90) | 5.8% (6/103) | 2.3% (2/89) | 0% (0/96) | 2.3% (2/86) |
| **SpIgE ≥0.35 kU/l** |  |  |  |  |  |  |  |
| **All participants** | 6.4% (74/1170) | 1.6% (19/1166) | 3.9% (45/1170) | 2.8% (33/1169) | 0% (0/1151) | 0% (0/1164) | 0.9% (10/1165) |
| **SIG** | 6.9% (40/577) | 1.6% (9/576) | 4.7% (27/577) | 3.3% (19/576) | 0% (0/572) | 0% (0/575) | 0.7% (4/576) |
| **EIG** | 5.7% (34/593) | 1.7% (10/590) | 3.0% (18/593) | 2.4% (14/593) | 0% (0/579) | 0% (0/589) | 1.0% (6/589) |
| *EIG Per-protocol* | 2.9% (6/206) | 0% (0/305)\* | 1.4%(3/214) | 0.7% (3/414)\* | 0% (0/263) | 0% (0/289) | 0.5% (1/201) |
| *EIG Non Per-protocol* | 5.1% (14/273) | 2.1% (4/193) | 3.8% (11/287) | 5.6% (4/72) | 0% (0/227) | 0% (0/204) | 1.3% (4/301) |
| *EIG Adherence Non-evaluable* | 6.5% (7/107) | 4.4% (4/90) | 2.2% (2/90) | 2.9% (3/103) | 0% (0/89) | 0% (0/96) | 0% (0/86) |

\*p<0.05 †p<0.01 (p values EIG per-protocol and EIG non per-protocol groups)

The rows showing the EIG divided into the per-protocol, non per-protocol and adherence non-evaluable subgroups show overall adherence status for the any food column, and food specific adherence status for the individual food columns.

Specific IgE was measured in 1170 children. However some infants had very small amounts of serum obtained and all six individual foods could not be measured. Hence the denominator for individual foods varies (ranging from N=1151 for sesame to N=1170 for egg).

The seven EIG participants who had positive enrollment challenges to a food are excluded from the adherence rows (4 to milk, 1 to wheat, 2 to peanut and 2 to egg) as they were unable to be adherent already being allergic to the food.

**TABLE II. Logistic regression modelling of enrollment factors influencing EIG overall and food specific non-adherence**

|  |  |  |
| --- | --- | --- |
|  | **EIG overall****non-adherence** | **EIG specific food non-adherence** |
| **Peanut** | **Egg** | **Milk** | **Sesame** | **Fish** | **Wheat** |
| **OR** | **p value** | **OR** | **p value** | **OR** | **p value** | **OR** | **p value** | **OR** | **p value** | **OR** | **p value** | **OR** | **p value** |
| Ethnicity(non-white) | 2.19(1.13-4.25) | 0.02 | 2.16(1.20-3.91) | 0.01 | 1.67(0.90-3.10) | 0.11 | 1.67(0.79-3.50) | 0.18 | 1.68(0.93-3.02) | 0.08 | 2.06(1.14-3.73) | 0.02 | 1.68(0.90-3.14) | 0.10 |
| Visible eczema at enrollment(continuous SCORAD) | 1.02(0.99-1.06) | 0.16 | 1.02(0.99-1.05) | 0.21 | 1.02(0.99-1.05) | 0.27 | 1.01(0.98-1.05) | 0.41 | 1.04(1.01-1.07) | 0.02 | 1.04(1.01-1.07) | 0.01 | 1.01(0.98-1.04) | 0.43 |
| QOL psychological domain(<mean) | 1.51(1.02-2.22) | 0.04 | 1.17(0.79-1.72) | 0.44 | 1.21(0.82-1.77) | 0.34 | 0.99(0.57-1.69) | 0.96 | 1.06(0.72-1.54) | 0.77 | 1.02(0.70-1.50) | 0.91 | 1.42(0.97-2.07) | 0.07 |
| Food specific IgE at enrollment\*(≥0.1 kU/l) | 0.88(0.48-1.60) | 0.68 | 1.18(0.39-3.59) | 0.77 | 2.32(0.85-6.31) | 0.10 | 1.33(0.39-4.56) | 0.65 | 0.94(0.28-3.14) | 0.92 | - | - | 0.47(0.18-1.24) | 0.13 |
| Maternal age(≥median - 33 years) | 1.59(1.08-2.33) | 0.02 | 1.85(1.25-2.76) | 0.002 | 2.32(1.58-3.41) | <0.001 | 1.85(1.04-3.30) | 0.04 | 1.27(0.87-1.85) | 0.22 | 1.54(1.04-2.27) | 0.03 | 1.28(0.88-1.87) | 0.19 |
| Nocturnal sleep duration at enrollment (hours) | 0.92(0.79-1.06) | 0.23 | 0.88(0.76-1.01) | 0.07 | 0.91(0.79-1.04) | 0.17 | 0.94(0.78-1.14) | 0.54 | 0.95(0.83-1.09) | 0.47 | 0.92(0.80-1.06) | 0.26 | 0.90(0.79-1.04) | 0.15 |
| Night time wakings at enrollment(number of wakings) | 1.14(0.97-1.34) | 0.11 | 1.06(0.91-1.25) | 0.44 | 1.18(1.01-1.39) | 0.04 | 1.00(0.81-1.25) | 0.98 | 1.09(0.93-1.27) | 0.31 | 1.13(0.97-1.32) | 0.13 | 1.10(0.93-1.29) | 0.26 |
| Parent reported sleep problem at enrollment(None/Small problem/Very serious problem) | 1.11(0.73-1.67) | 0.63 | 1.27(0.85-1.90) | 0.25 | 0.87(0.58-1.30) | 0.49 | 1.21(0.69-2.10) | 0.50 | 0.95(0.64-1.42) | 0.80 | 0.84(0.56-1.26) | 0.40 | 0.98(0.66-1.46) | 0.92 |

\* Food specific IgE (≥0.1 kU/l) to any food for EIG overall non-adherence, and to the specific food for individual specific food non-adherence.

If sensitization status was included in the model based on skin prick test response at enrollment the result was statistically non-significant for overall non-adherence and food specific non-adherence to any individual food, with the exception of milk (milk positive skin prick test response OR 13.8, 95% CI 1.68-112, p=0.01).

For each outcome all the variables listed were included in the same logistic regression model.