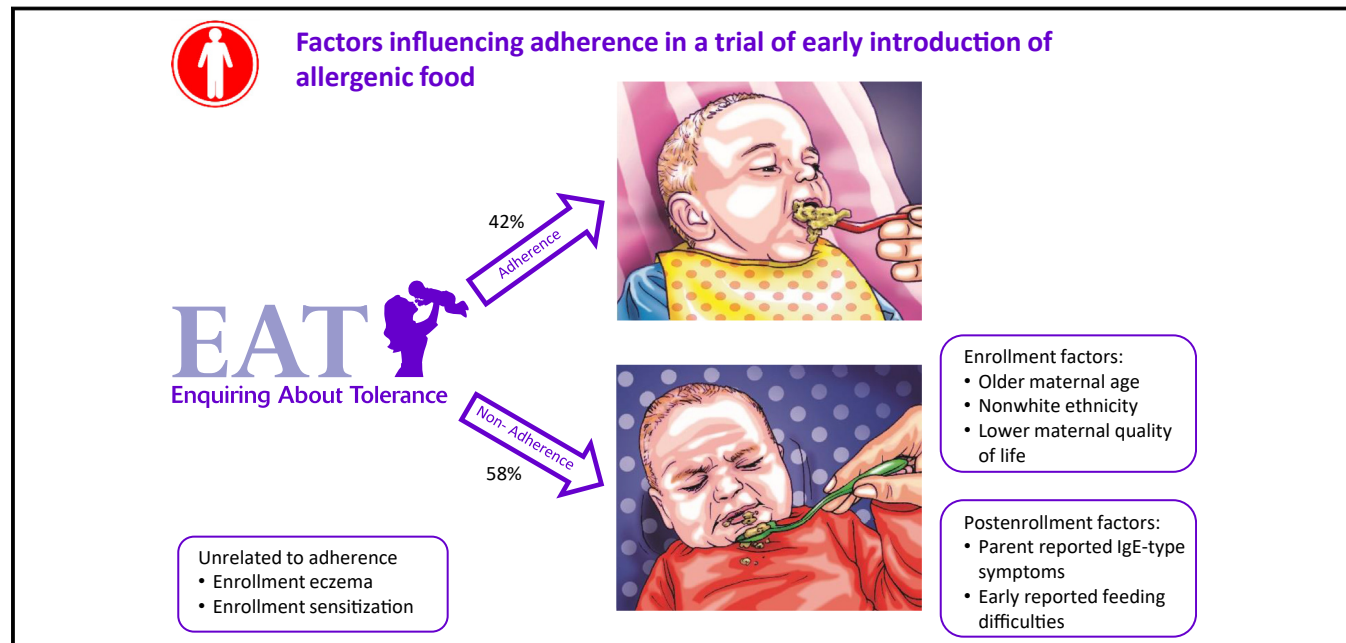


Factors influencing adherence in a trial of early introduction of allergenic food



Michael R. Perkin, PhD,^a Henry T. Bahnson, MPH,^b Kirsty Logan, PhD,^c Tom Marrs, PhD,^c Suzana Radulovic, MD,^c Rebecca Knibb, PhD,^d Joanna Craven, MPH,^c Carsten Flohr, PhD,^e E. N. Mills, PhD,^f Serge A. Versteeg, BSc,^g Ronald van Ree, PhD,^{g,h} and Gideon Lack, MB BCH,^c on behalf of the Enquiring About Tolerance (EAT) study team
London, Birmingham, and Manchester, United Kingdom; Seattle, Wash; and Amsterdam, The Netherlands

GRAPHICAL ABSTRACT



Background: The Enquiring About Tolerance (EAT) study examined whether the early introduction of 6 allergenic foods from 3 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 1 or more foods and for egg and peanut individually, but only 42% of early introduction group (EIG) children met the per-protocol criteria.

Objective: We sought to identify which factors were responsible for nonadherence in the EAT study.

Methods: Factors influencing adherence within the key early introduction period in the EIG (up to 6 months of age) were divided into enrollment and postenrollment factors, and their association with nonadherence was explored.

Results: In an adjusted analysis, at enrollment, increased maternal age, nonwhite ethnicity, and lower maternal quality of

From ^athe Population Health Research Institute, St George's, University of London; ^bthe Benaroya Research Institute, Seattle; ^cthe 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, Birmingham; ^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, and the Manchester Institute of Biotechnology, University of Manchester; and the Departments of ^gExperimental Immunology and ^hOtorhinolaryngology, Academic Medical Center, Amsterdam.

The main components of the Enquiring About Tolerance (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 thank the Davis Foundation. The skin-related aspects of the EAT study were supported by the UK National Institute for Health Research (NIHR). C.F. held a National Institute for Health Research Clinician Scientist Award (NIHRCS/01/2008/009). The analyses presented in this article 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 no. 312147). The views expressed in this publication are those of the authors and not necessarily those of the FSA, MRC, the National Health Service, the NIHR, the Wellcome Trust, the European Union, or the UK Department of Health.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication September 11, 2018; revised June 6, 2019; accepted for publication June 14, 2019.

Corresponding author: Gideon Lack, MB BCH, Paediatric Allergy, King's College London, Clinical Academic Paediatric Allergy Service, Guy's & St Thomas' NHS Foundation Trust, Children's Allergies Department, St Thomas' Hospital, Westminster Bridge Rd, London SE1 7EH, United Kingdom. E-mail: gideon.lack@kcl.ac.uk.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749

© 2019 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

<https://doi.org/10.1016/j.jaci.2019.06.046>

life were independently and significantly associated with overall nonadherence in the EIG. Enrollment eczema and enrollment serum allergen-specific IgE sensitization to 1 or more foods (≥ 0.1 kU/L) were not related to overall nonadherence. After enrollment, 2 factors were significantly related to EIG overall nonadherence: 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 a strategy to prevent food allergy, families of nonwhite 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. (J Allergy Clin Immunol 2019;144:1595-605.)

Key words: Food allergy, diet, allergens, infancy, breastfeeding, randomized controlled trial, adherence

The Enquiring About Tolerance (EAT) study was a large randomized food allergy prevention trial of the early introduction of 6 allergenic foods from 3 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 6 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 1 or more foods and for egg and peanut individually.²

There are 2 explanations for this discrepancy. First, the per-protocol analysis was effective because the population adhered to the intervention. Second, the intention-to-treat analysis was not effective because among the large group of children who did not adhere to treatment, those with nascent allergy with food sensitization had subclinical symptoms, food aversion, or both and were therefore unable to adhere. Further analyses suggested that food allergy prevention through early introduction of multiple allergenic foods in normal breastfed infants might depend on adherence and dosage.²

The EAT study per-protocol criteria for the EIG were stringent. By 6 months of age, EIG infants were expected to have achieved sustained high-dose consumption of 5 or more of the 6 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).

After the completion of the study, we measured serum allergen-specific IgE sensitization in the EAT participants and demonstrated in an intention-to-treat analysis that the intervention successfully reduced the development of food allergy among EIG infants who were sensitized 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 article we explore how these and other data collected in the EAT study influenced the issue of nonadherence to the recommended level of consumption of the 6 early introduction foods (overall nonadherence), as well as nonadherence to consumption of individual foods (food-specific nonadherence). We determined whether occult sensitization and early symptoms were responsible for the high nonadherence rate.

Abbreviations used

EAT: Enquiring About Tolerance
EIG: Early introduction group
LEAP: Learning Early About Peanut Allergy
SIG: Standard introduction group

The UK Scientific Advisory Committee on Nutrition has issued the following statement after its review of 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.

METHODS

Participants

One thousand three hundred three 3-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 cutoff for dividing mothers into younger (<33 years) and older (≥ 33 years) groups. 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 by using the classification used in the 2001 UK Census.⁶ One thousand one hundred four (84.7%) of the enrolled infants were white, 119 (9.1%) were mixed, and 80 (6.1%) were black, Asian, or Chinese. The trial was registered with the ISRCTN (registration no. 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 6 months of age in accordance with the recommendation in place in the United Kingdom since 2003.⁷ Beyond 6 months, allergenic food consumption was at parental discretion.

The EIG parents were asked to introduce 6 allergenic foods to their infants: 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 4 foods was randomly determined to avoid any bias from one food being introduced consistently before another. Wheat was introduced last and not before 4 months of age (see the “EIG early introduction regimen” section in the [Methods](#) section in this article’s Online Repository at www.jacionline.org).

An online questionnaire was sent to each family monthly to 1 year of age and then every 3 months until the child reached 3 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-type and non-IgE-type symptoms. The online questionnaires also ascertained maternal quality of life using the World Health Organization Quality of Life BREF questionnaire,⁸ infant sleep using the Brief Infant Sleep Questionnaire,⁹ and parental reporting of feeding difficulty and aversive feeding behavior by using questions based on previously published work.¹⁰ Clinic visits took place at enrollment and at 1 and 3 years of age. Further information on the online questionnaire and clinic visit data collected are presented in the “Information collected” section in the [Methods](#) section in this article’s Online Repository.

Food-specific IgE levels to each of the 6 foods were measured at enrollment and at 1 and 3 years of age in both groups using ImmunoCAP (Phadia, Uppsala, Sweden) assays. The primary outcome of the EAT study was the proportion of participants with challenge-proved food allergy to 1 or more of the 6 early introduction foods between 1 and 3 years of age.²

Per-protocol adherence

The definitions of overall per-protocol adherence are presented in [Table E1](#) in this article's Online Repository at www.jacionline.org. The key criterion for overall adherence in the EIG was consumption of at least 5 of the allergenic foods in at least 75% of the recommended amount (3 g of allergen protein/wk) for at least 5 weeks between 3 and 6 months of age. Food-specific per-protocol adherence was based on the same criteria (ie, consumption of $\geq 75\%$ of the recommended amount of the specific food for at least 5 weeks between 3 and 6 months of age). The window in which 5 or more weeks of consumption could be achieved was narrow, as explained in more detail in the "Restricted window to achieve per-protocol status" section 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 nonadherence. Penalized logistic regression was used where appropriate for situations with very sparse data. Eczema was analyzed as the presence of visible eczema at enrollment by using the UK diagnostic criteria ("visible eczema").¹¹ Eczema severity was determined by using the SCORAD index and grouped by using the accepted SCORAD categories.¹² Data were analyzed with STATA software (version 15; StataCorp, College Station, Tex), SAS software (version 9.4; SAS Institute, Cary, NC), and JMP Pro 14 (SAS Institute). The EAT data set (ITN900AD) is available through TrialShare, a public Web site 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 (see [Table E1](#)). An exploration of the likely true adherence status of the 123 EIG participants (19% of the EIG) whose adherence status was nonevaluable, as well as the effect of including or excluding them in the analyses undertaken for this article, are reviewed in detail in the "EIG adherence nonevaluable participants" section in the [Results](#) section and in [Table E2](#) and [Figs E1 and E2](#) in this article's Online Repository at www.jacionline.org.

Although overall adherence to the EAT early introduction regimen was low at 42%, families found it easier to introduce some foods than others ([Fig 1](#)), with 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, see [Table E3](#) in this article's Online Repository at www.jacionline.org). Although 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 (see [Fig E3](#) in this article's Online Repository at www.jacionline.org). However, the 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 6 months of age. However, [Fig 1](#) clearly

indicates that there were certain foods in which the ability to meet the per-protocol threshold (3 g/wk of allergen protein) continued to improve between 6 and 12 months of age. High sustained levels of consumption were achieved by 6 months of age for milk and shortly after 6 months of age for wheat. Per-protocol consumption of fish and egg continued to improve beyond 6 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 2 foods that had been achieved by 6 months of age did not materially change throughout the rest of the first year of life. Hence by 1 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 nonadherence (univariate analysis)

Nonwhite ethnicity, increased maternal age, and lower enrollment maternal quality-of-life scores were significantly associated with not being per-protocol adherent in the EIG (see [Table E4](#) in this article's Online Repository at www.jacionline.org for univariate analysis). Nonwhite ethnicity and increased maternal age were associated with delaying the introduction of solids in both the SIG and EIG infants (see [Fig E4](#) in this article's Online Repository at www.jacionline.org). Differences were observed in other enrollment demographic characteristics between ethnic groups: visible eczema and enrollment sensitization were both more common in nonwhite 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 (see [Table E5](#) in this article's Online Repository at www.jacionline.org) and are reviewed in the "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 overall nonadherence, whereas any visible eczema at enrollment was of borderline significance ($P = .07$, see [Table E4](#)). More details about the associations between enrollment factors and overall nonadherence are presented in the "Enrollment factors associated with overall nonadherence" section in the [Results](#) section in this article's Online Repository. Associations between enrollment factors and food-specific nonadherence are presented in the "Enrollment factors associated with food-specific nonadherence" section 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 ≥ 1 foods of ≥ 0.1 kU/L; 15.7% [93/593]) than were identified to have positive skin prick test responses (>0 mm; 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 1 or more foods strongly predicted overall food allergy (see [Fig E5](#) in this article's Online Repository at

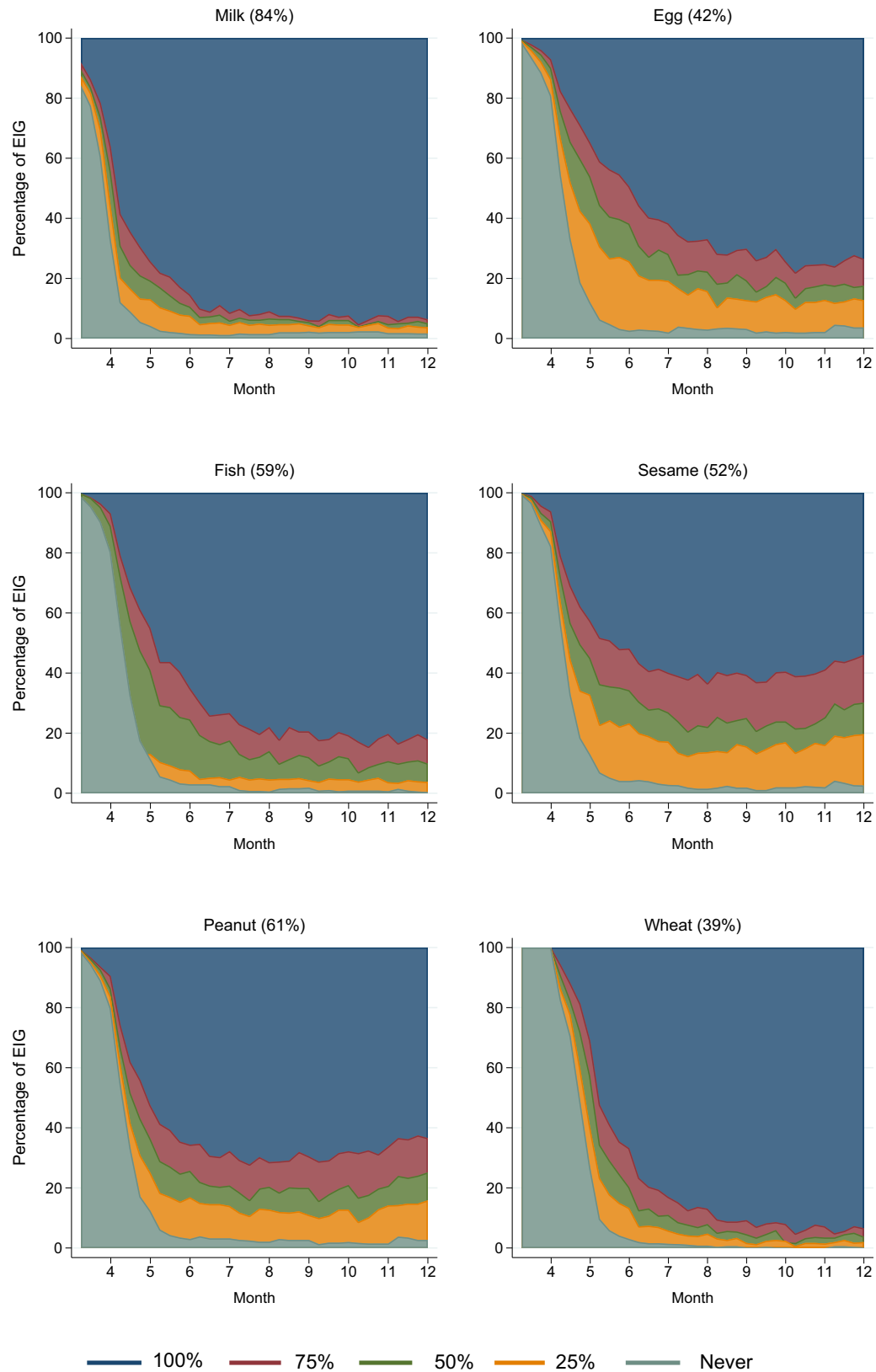


FIG 1. Adherence with introduction of allergenic foods in the EIG up to 1 year of age. The figure presents the relative proportions of the EIG consuming 100%, 75% (the per-protocol threshold), 50%, or 25% or not having started consuming each of the 6 early introduction foods from enrollment through 12 months of age. The food-specific per-protocol adherence percentage (among those whose food-specific adherence status was evaluable) is shown in parentheses.

TABLE I. Enrollment sensitization data from the EAT study

	Any food	Peanut	Egg	Milk	Sesame	Fish	Wheat
SPT >0 mm							
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 nonevaluable	4.2% (5/120)	1.0% (1/103)	2.0% (2/101)	0% (0/115)	0% (0/102)	0% (0/109)	0% (0/99)
Specific IgE ≥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 nonevaluable	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)
Specific IgE ≥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 nonevaluable	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)

Rows showing the EIG divided into the per-protocol, non-per-protocol, and adherence nonevaluable subgroups show overall adherence status for the any food column and food-specific adherence status for individual food columns. Specific IgE levels were measured in 1170 children. However, some infants had very small amounts of serum obtained, and all 6 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 7 EIG participants who had positive enrollment challenge results to a food are excluded from the adherence rows (4 to milk, 1 to wheat, 2 to peanut, and 2 to egg) because they were unable to be adherent being already allergic to the food.

SPT, Skin prick test.

**P* < .05 and †*P* < .01, *P* values for the EIG per-protocol and EIG non-per-protocol groups.

Food-Specific Nonadherence	Overall Nonadherence 57.8%	3.36 (0.95-12.0) 0.06	1.45 (0.63-3.33) 0.38	1.54 (0.61-3.88) 0.36	1.23 (0.40-3.83) 0.72	- - -	0.61 (0.25-1.50) 0.28	1.16 (0.69-1.94) 0.58
	Wheat 60.9%	1.44 (0.54-3.85) 0.47	1.28 (0.60-2.71) 0.52	1.18 (0.51-2.73) 0.70	1.07 (0.34-3.31) 0.91	- - -	0.66 (0.28-1.54) 0.33	1.05 (0.64-1.71) 0.85
	Fish 41.4%	2.70 (1.06-6.90) 0.04	2.22 (1.04-4.71) 0.04	1.43 (0.63-3.26) 0.39	2.34 (0.75-7.27) 0.14	- - -	1.58 (0.68-3.65) 0.29	1.65 (1.01-2.68) 0.04
	Sesame 47.6%	1.73 (0.69-4.31) 0.24	1.86 (0.88-3.92) 0.10	1.36 (0.60-3.09) 0.47	1.36 (0.45-4.12) 0.58	- - -	0.72 (0.31-1.70) 0.46	1.09 (0.67-1.77) 0.73
	Milk 16.0%	1.23 (0.35-4.40) 0.75	3.35 (1.49-7.55) 0.003	2.26 (0.85-5.99) 0.10	1.07 (0.23-4.94) 0.93	- - -	1.73 (0.62-4.83) 0.30	1.30 (0.67-2.52) 0.44
	Egg 57.5%	1.41 (0.55-3.59) 0.48	2.58 (1.08-6.12) 0.03	1.72 (0.73-4.04) 0.21	0.64 (0.21-1.92) 0.42	- - -	1.08 (0.45-2.57) 0.87	1.40 (0.85-2.31) 0.19
	Peanut 38.8%	2.57 (0.98-6.76) 0.06	2.01 (0.97-4.18) 0.06	1.10 (0.46-2.62) 0.83	1.93 (0.64-5.82) 0.25	- - -	0.91 (0.38-2.22) 0.84	1.18 (0.72-1.94) 0.51
		Peanut (n=24)	Egg (n=36)	Milk (n=32)	Sesame (n=15)	Fish (n=0)	Wheat (n=25)	One or more foods (n=93)
		Food-specific IgE sensitization at enrollment (0.1 kU/l or greater)						

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) to specific foods or to 1 or more of the 6 early introduction foods and the association with food-specific and overall nonadherence are shown.

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

	EIG overall nonadherence		EIG-specific food nonadherence			
	OR	P value	Peanut		Egg	
			OR	P value	OR	P value
Ethnicity (nonwhite)	2.19 (1.13-4.25)	.02	2.16 (1.20-3.91)	.01	1.67 (0.90-3.10)	.11
Visible eczema at enrollment (continuous SCORAD score)	1.02 (0.99-1.06)	.16	1.02 (0.99-1.05)	.21	1.02 (0.99-1.05)	.27
QOL psychological domain (< mean)	1.51 (1.02-2.22)	.04	1.17 (0.79-1.72)	.44	1.21 (0.82-1.77)	.34
Food-specific IgE at enrollment* (≥ 0.1 kU/L)	0.88 (0.48-1.60)	.68	1.18 (0.39-3.59)	.77	2.32 (0.85-6.31)	.10
Maternal age ($\geq$ median, 33 y)	1.59 (1.08-2.33)	.02	1.85 (1.25-2.76)	.002	2.32 (1.58-3.41)	<.001
Nocturnal sleep duration at enrollment (h)	0.92 (0.79-1.06)	.23	0.88 (0.76-1.01)	.07	0.91 (0.79-1.04)	.17
Nighttime awakenings at enrollment (no. of awakenings)	1.14 (0.97-1.34)	.11	1.06 (0.91-1.25)	.44	1.18 (1.01-1.39)	.04
Parent-reported sleep problem at enrollment (none/small problem/very serious problem)	1.11 (0.73-1.67)	.63	1.27 (0.85-1.90)	.25	0.87 (0.58-1.30)	.49

OR, Odds ratio.

*Food-specific IgE (≥ 0.1 kU/L) to any food for EIG overall nonadherence and to the specific food for individual food-specific nonadherence. If sensitization status was included in the model based on skin prick test response at enrollment, the result was statistically nonsignificant for overall nonadherence and food-specific nonadherence to any individual food, with the exception of milk (positive milk skin prick test response: OR, 13.8; 95% CI, 1.68-112; $P = .01$). For each outcome, all the variables listed were included in the same logistic regression model.

www.jacionline.org). Sensitization to 1 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 diets (eg, 92% [18/22] for peanut). Similarly, the great majority of infants whose families reported symptoms with a specific food were not sensitized to that food at enrollment (eg, 81% [17/21] for peanut). Both are reviewed in detail in the “IgE-type symptom reporting and enrollment sensitization” section in the [Results](#) section in this article’s Online Repository. Serum food-specific sensitization to 1 or more foods did not predict overall nonadherence in the univariate analysis (Fig 2). In contrast, in the univariate analysis food-specific sensitization predicted food-specific nonadherence for egg and was of borderline significance for peanut (Fig 2 and see Fig E6 in this article’s Online Repository at www.jacionline.org), both of which are likely to be a consequence of the study design and discussed in more detail in the “Consumption of each allergenic food by enrollment-specific IgE sensitization status” section in the [Results](#) section in this article’s Online Repository.

Enrollment factors associated with EIG overall nonadherence (multivariable analysis)

A multivariable analysis was undertaken to determine whether overall nonadherence in the EIG could have been predicted from certain enrollment characteristics (Table II, left column). There was no significant relationship between enrollment sensitization to 1 or more foods and overall nonadherence.

Nonwhite ethnicity, increased maternal age, and lower enrollment maternal quality of life (psychological domain) all remained significantly related to increased EIG overall nonadherence. 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 odds ratios were greater than 1.0.

Enrollment factors associated with EIG food-specific nonadherence (multivariable analysis)

Models were created for each individual food (Table II, other columns). Results were broadly similar to overall nonadherence. Ethnicity and maternal age were most strongly associated with nonadherence. Enrollment eczema SCORAD was significantly related to sesame and fish nonadherence but not to other foods. In contrast to univariate associations, once potential confounding factors were adjusted for, the relationship between enrollment sensitization to any individual food and subsequent nonadherence to these foods was attenuated (peanut odds ratio of 1.18 [95% CI, 0.39-3.59; $P = .77$] and egg odds ratio of 2.32 [95% CI, 0.85-6.31; $P = .10$]) and not statistically significant. Among the other variables, nighttime waking frequency was significantly associated with egg nonadherence.

Postenrollment factors associated with nonadherence (univariate analysis)

We explored 3 postenrollment factors in the key early introduction period up to 6 months of age to assess their association with nonadherence in the EIG (see Table E6 in this article’s Online Repository at www.jacionline.org). These were new onset of parent-reported eczema after enrollment but before 6 months, maternal reporting of feeding difficulties at the very beginning of solid food introduction (assessed at 4 months of age, see Table E7 in this article’s Online Repository at www.jacionline.org), and reporting of IgE-type and non-IgE-type symptoms with consumption of early introduction foods before 6 months of age (see Fig E7 and Table E8 in this article’s Online Repository at www.jacionline.org). Although 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 3 factors are reviewed in detail in the “Postenrollment factors associated with nonadherence” section in the [Results](#) section in this article’s Online Repository.

The association between reporting of IgE-type and non-IgE-type symptoms and development of food allergy is reviewed in the

EIG-specific food nonadherence							
Milk		Sesame		Fish		Wheat	
OR	P value	OR	P value	OR	P value	OR	P value
1.67 (0.79-3.50)	.18	1.68 (0.93-3.02)	.08	2.06 (1.14-3.73)	.02	1.68 (0.90-3.14)	.10
1.01 (0.98-1.05)	.41	1.04 (1.01-1.07)	.02	1.04 (1.01-1.07)	.01	1.01 (0.98-1.04)	.43
0.99 (0.57-1.69)	.96	1.06 (0.72-1.54)	.77	1.02 (0.70-1.50)	.91	1.42 (0.97-2.07)	.07
1.33 (0.39-4.56)	.65	0.94 (0.28-3.14)	.92	—	—	0.47 (0.18-1.24)	.13
1.85 (1.04-3.30)	.04	1.27 (0.87-1.85)	.22	1.54 (1.04-2.27)	.03	1.28 (0.88-1.87)	.19
0.94 (0.78-1.14)	.54	0.95 (0.83-1.09)	.47	0.92 (0.80-1.06)	.26	0.90 (0.79-1.04)	.15
1.00 (0.81-1.25)	.98	1.09 (0.93-1.27)	.31	1.13 (0.97-1.32)	.13	1.10 (0.93-1.29)	.26
1.21 (0.69-2.10)	.50	0.95 (0.64-1.42)	.80	0.84 (0.56-1.26)	.40	0.98 (0.66-1.46)	.92

“Parent-suspected IgE-type or non-IgE-type symptoms with food introduction in the EIG and the effect on food allergy” section in the [Results](#) section and [Fig E8](#) in this article’s Online Repository at www.jacionline.org.

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 nonwhite ethnicity, although representing a small subgroup of the overall population, contributed disproportionately to the burden of overall food allergy ([Fig 4, A](#), and see [Fig E9](#) in this article’s Online Repository at www.jacionline.org).

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 1 or more foods but were responsible for 69.2% of food allergy cases in the SIG. Of the SIG, 15.3% were of nonwhite ethnicity but accounted for 28.6% of food allergy cases in the SIG, and a significantly greater proportion of nonwhite participants had visible eczema and/or IgE food-specific sensitization at enrollment (see [Table E5](#) and [Fig E9](#)). Furthermore, in the EIG adherence was significantly lower in those participants of nonwhite ethnicity ([Fig 4, A](#)).

We modelled the effects of improved adherence in infants at high risk of developing food allergy (nonwhite infants, those with enrollment eczema, or those with enrollment sensitization [≥ 0.1 kU/L]) and how this might affect the prevalence of food allergy ([Fig 4, 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 Learning Early About Peanut Allergy (LEAP) study intention-to-treat analysis.¹⁴ Assuming that a greater 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 effect might be if an adherence rate of 85% is assumed. [Fig 4, B](#), displays the percentage reduction in total

allergy burden and the number needed to treat within the different subgroups.

Targeting the intervention to the group of nonwhite 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 had a food allergy in the EAT study, 58% were nonadherent with the early introduction protocol. Hence the nonadherence rate was 10-fold greater than the food allergy rate. Notably, the nonadherence rate also significantly exceeded the prevalence rate of risk factors associated with developing a food allergy: visible eczema at enrollment (25%), enrollment sensitization to 1 or more foods on specific IgE testing (16%), and nonwhite ethnicity (15%).

In univariate analysis nonwhite ethnicity, older maternal age, lower enrollment maternal quality-of-life scores, and increasing SCORAD were associated with nonadherence to the EIG protocol. The enrollment factors that were found to remain significantly associated with nonadherence in the adjusted analysis were nonwhite ethnicity, older maternal age, and lower enrollment maternal psychological quality of life. Nonwhite 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 because 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 (Infant Feeding Survey 2010),¹⁵ and considered in more detail in the “Comparison with the Infant Feeding Survey 2010 findings” section in the [Discussion](#) section in this article’s Online Repository at www.jacionline.org. 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.

After enrollment, although the reporting of IgE-type symptoms in EIG participants in the key early introduction period was common (16%), this too fell far short of the 58% nonadherence

Food-Specific Nonadherence	Overall Nonadherence 57.8%	2.99 (1.05-8.55) 0.04	1.62 (0.87-2.99) 0.13	2.20 (0.94-5.16) 0.07	2.10 (0.70-6.25) 0.18	9.80 (0.55-175) 0.12	2.74 (0.44-16.8) 0.28	2.26 (1.37-3.71) 0.001	1.50 (0.89-2.51) 0.13
	Wheat 60.9%	2.11 (0.80-5.58) 0.13	1.12 (0.62-2.01) 0.71	1.92 (0.86-4.28) 0.11	2.12 (0.73-6.20) 0.17	8.52 (0.48-152) 0.15	2.38 (0.39-14.6) 0.35	1.67 (1.04-2.67) 0.03	1.07 (0.65-1.77) 0.78
	Fish 41.4%	2.07 (0.89-4.83) 0.09	1.23 (0.69-2.19) 0.48	1.18 (0.58-2.42) 0.65	2.58 (0.97-6.85) 0.06	5.28 (0.86-32.4) 0.07	1.42 (0.32-6.30) 0.65	1.49 (0.95-2.32) 0.08	1.32 (0.81-2.15) 0.26
	Sesame 47.6%	2.91 (1.16-7.33) 0.02	1.37 (0.77-2.44) 0.28	2.04 (0.97-4.29) 0.06	5.11 (1.58-16.5) 0.006	4.09 (0.67-25.1) 0.13	1.10 (0.25-4.89) 0.90	2.32 (1.47-3.66) <0.001	1.34 (0.83-2.18) 0.24
	Milk 16.0%	2.39 (0.93-6.17) 0.07	1.13 (0.52-2.46) 0.76	3.03 (1.33-6.88) 0.008	4.18 (1.59-11.0) 0.004	1.49 (0.24-9.23) 0.67	1.49 (0.24-9.23) 0.67	1.56 (0.88-2.76) 0.13	1.46 (0.78-2.72) 0.23
	Egg 57.5%	1.94 (0.77-4.88) 0.16	9.06 (3.39-24.2) <0.001	1.02 (0.50-2.10) 0.96	1.86 (0.68-5.09) 0.23	2.76 (0.45-16.9) 0.27	9.85 (0.55-176) 0.12	3.23 (1.92-5.41) <0.001	1.55 (0.93-2.56) 0.09
	Peanut 38.8%	5.40 (2.04-14.3) 0.001	0.94 (0.52-1.70) 0.85	1.24 (0.59-2.57) 0.57	2.28 (0.88-5.91) 0.09	1.59 (0.36-7.07) 0.54	0.88 (0.19-4.16) 0.87	1.39 (0.89-2.17) 0.15	1.42 (0.87-2.32) 0.16
		Peanut (n=22)	Egg (n=52)	Milk (n=33)	Sesame (n=18)	Fish (n=6)	Wheat (n=6)	Any IgE-type symptoms (n=99)	Any non-IgE-type symptoms (n=82)

FIG 3. Reporting in the key early introduction period (up to 6 months) of IgE-type symptoms to specific foods, IgE-type 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 6 allergenic foods and food-specific and overall nonadherence. Symptoms manifesting by 6 months of age are presented for IgE-type symptoms for each specific food, IgE-type symptoms to 1 or more of the 6 early introduction foods, and non-IgE-type symptoms to 1 or more of the 6 early introduction foods.

rate. Furthermore, the great majority of EIG participants reporting such symptoms were neither sensitized to any food at enrollment (76%) nor had a food allergy (82%). The strongest association with nonadherence was the early emergence of feeding difficulties, with 40% of non per-protocol EIG families reporting some or great difficulty feeding their infant at 4 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, in 123 it was mild (SCORAD <15), in 31 moderate (SCORAD 15 to <40), and in only 6 was it severe (SCORAD ≥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 pediatric 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 parentally perceived feeding difficulties and aversive feeding behavior by 4 months of age, when families had only just started introducing solids to their EIG infants, had the strongest associations with nonadherence in the EIG and were also associated with later introduction of allergenic foods. This finding suggests that families were trying to feed their infants the allergenic food, but if the family perceived that the infant was not ready or mature enough and they were struggling to achieve the study's stipulated consumption levels, then, particularly for certain foods and having reached a specific level of consumption in the key early introduction period, they did not attempt to escalate this level further beyond 6 months.

That infant maturity might 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 of sleep and fewer night wakings, as well as significantly less parent-reported very serious sleep problems.¹⁷ Notably, 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 and eat better.¹⁷

Feeding difficulties were also shown in the Infant Feeding Survey 2010 to have a strong association with ethnicity (considered in more detail in the "Comparison with the Infant Feeding Survey 2010" section findings in the Discussion section in this article's Online Repository).¹⁵ However, survey questions about feeding difficulties in the context of a randomized controlled trial in which the intervention sets high expectations for the

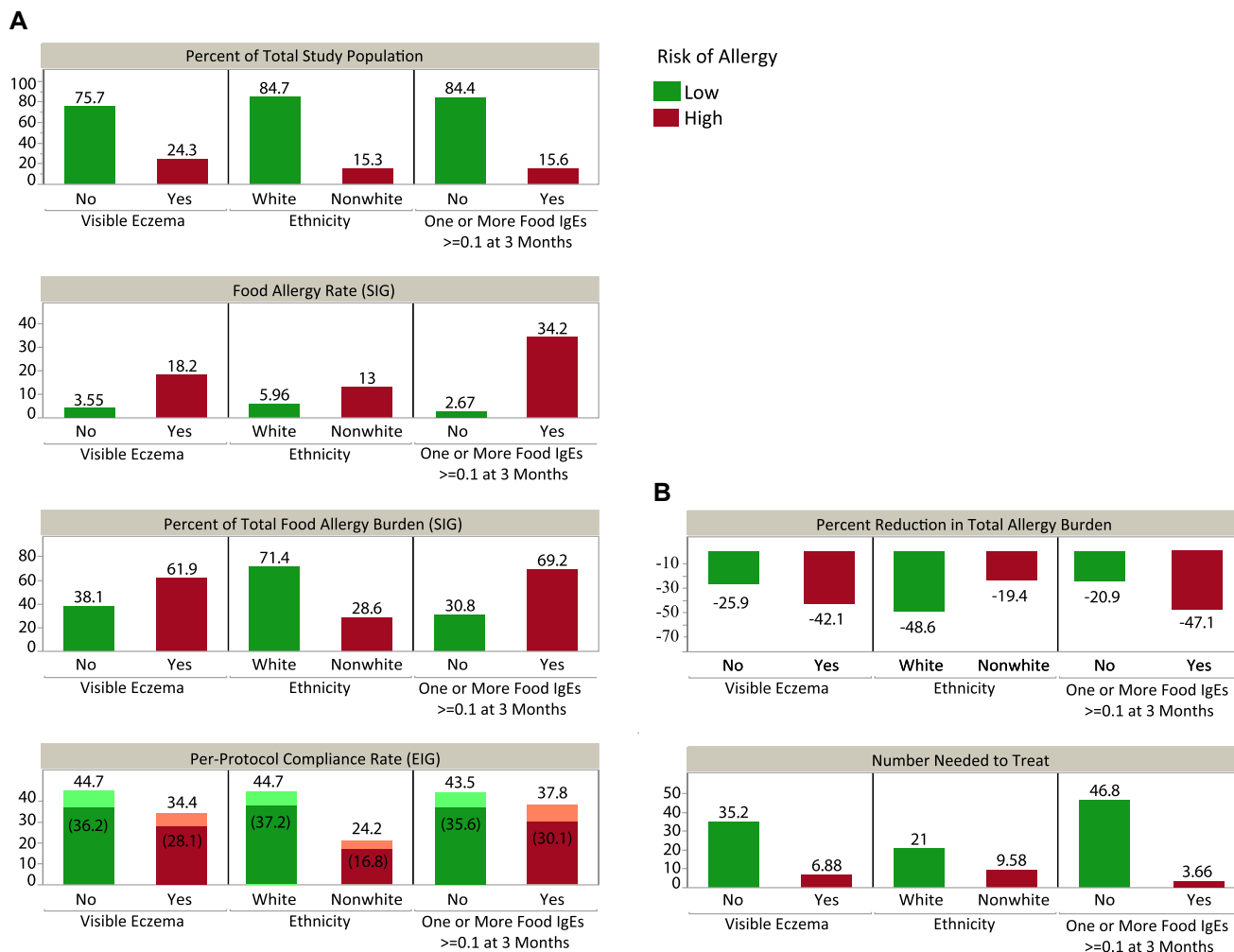


FIG 4. Contributions of subgroups to the proportion of food allergy cases in the SIG. **A**, Bar charts provide prevalence calculations used to estimate the reduction in total allergy burden and number needed to treat. Per-protocol adherence rates are shown for those EIG participants whose adherence rates were evaluable and also as a proportion of the whole EIG (percentages in parentheses). **B**, An 80% treatment effect and 85% adherence across all risk factors for allergy is assumed. 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% ($61.9\% \times 85\%$) 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% ($52.6\% \times 80\%$).

introduction of foods are likely to overestimate 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 those of 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 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 recognized 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 effect 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 nonwhite ethnicity, older mothers, and mothers with poorer quality of life. This also applies to infants with early-onset eczema in that although their adherence to per-protocol consumption of specific foods was not compromised compared with children without eczema, it is within this group that the majority of food allergy develops. Although these factors explain only a small part of the 58% of EIG families who were nonadherent, 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 recognized.¹⁹ There is less of a literature on ethnic differences in adherence within the context of a randomized trial in which subjects have consented to enroll.

A recent study of 1000 expecting and 1000 new caregivers of infants less than 1 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 might well be important. Although US caregivers can perceive early peanut introduction to be difficult, the majority of Israeli infants are eating 2 g of peanut protein per week without the support of guidelines or a public health campaign.²²

A number of countries, including the United States,²³ Australia,²⁴ and the United Kingdom,^{5,25,26} 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.

We 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; and Alyssa Ylescupidez for her review and edits of the manuscript.

Members of the EAT Study Team include the following:

Nursing staff—Louise Young, RN Children; Victoria Offord, BSc Nursing; Mary DeSousa, BSc Nursing; Jason Cullen, BSc Nursing; and 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; and 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; and Lorna Wheatley, BSc.

Phlebotomist—Devi Patkunan.

Laboratory projects—Kerry Richards, MSc Medicine; Ewa Pietraszewicz, MSc; Alick Stephens, PhD; Asha Sudra, MSc; and Victor Turcanu, PhD.

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

REFERENCES

- 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;137:1477-86.
- 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;374:1733-43.
- 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;40:450-7.
- 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;131:135-43.
- Feeding in the first year of life. Public Health England, UK: Scientific Advisory Committee on Nutrition; 2018. Available at: <https://www.gov.uk/government/publications/feeding-in-the-first-year-of-life-sacn-report>. Accessed June 6, 2019.
- Ethnicity categories and the 2011 census. UK: Office of National Statistics; 2011. Available at: <https://www.ethnicity-facts-figures.service.gov.uk/ethnic-groups>. Accessed June 6, 2019.
- Infant feeding recommendation. UK: Department of Health; 2003. Available at: https://webarchive.nationalarchives.gov.uk/20120503221049/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4097197. Accessed June 6, 2019.
- 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.
- Sadeh A. A brief screening questionnaire for infant sleep problems: validation and findings for an Internet sample. *Pediatrics* 2004;113:e570-7.
- 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;36:225-34.
- Weiland SK, Bjorksten B, Brunekreef B, Cookson WO, von Mutius E, Strachan DP. Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC II): rationale and methods. *Eur Respir J* 2004;24:406-12.
- 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;195:10-9.
- Perkin MR, Logan K, Bahnson HT, Marrs T, Radulovic S, Craven J, et al. Efficacy of the Enquiring About Tolerance (EAT) study among infants at high risk of developing food allergy. *J Allergy Clin Immunol* 2019;144:1606-14.
- 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;372:803-13.
- McAndrew F, Thompson J, Fellows L, Large A, Speed M, Renfrew MJ. Infant Feeding Survey 2010. UK: Health and Social Care Information Centre; 2012. Available at: <https://digital.nhs.uk/data-and-information/publications/statistical/infant-feeding-survey/infant-feeding-survey-uk-2010#resources>. Accessed June 6, 2019.
- Johnston GA, Bilbao RM, Graham-Brown RAC. The use of dietary manipulation by parents of children with atopic dermatitis. *Br J Dermatol* 2004;150:1186-9.
- 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;172:e180739.
- Victoria CG, Habicht JP, Bryce J. Evidence-based public health: moving beyond randomized trials. *Am J Public Health* 2004;94:400-5.
- 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. *J Acad Nutr Diet* 2012;112:624-35.

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;120:620-5.
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;133:476-84.
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;122:984-91.
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;34:5-12.
24. ASCIA guidelines—infant feeding and allergy prevention. Brookvale (Australia): Australasian Society of Clinical Immunology and Allergy; 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;48:912-5.
26. 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. UK: Scientific Advisory Committee on Nutrition, Committee on Toxicity of Chemicals in Food, Consumer Products, and the Environment; 2017. Available at: <https://cot.food.gov.uk/sites/default/files/jointsacnecotallergystatementfinal2.pdf>. Accessed June 6, 2019.

Supplementary Appendix

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, PhD,^f 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

Methods

EIG early introduction regimen

The EAT Study tested the hypothesis that the early introduction of multiple allergenic foods would generate an immunologically tolerizing milieu through the induction of regulatory mechanisms.

The mean age of enrollment onto the EAT study was 14.7 weeks.¹ Families in the EIG had to await the return of safety blood results before consumption commenced (up to four days after enrollment). EIG families were then told to first introduce nonallergenic foods such as baby rice and/or pureed fruits or vegetables during the first week until they were established on solid food. They then continued with these solids and additionally introduced cow's milk yogurt on two days of the second week. Hence, median age of introduction of dairy in the EIG was 17.3 weeks.¹

During weeks three and four of the early introduction regimen, peanut, hard-boiled egg, sesame and whitefish (cod) were introduced sequentially in a random order with two new foods introduced per week. Finally, wheat was introduced in week 5, reflecting the guidance on optimal timing of wheat introduction after 4 months of age, and by week 6, infants were ideally consuming the required amount of all 6 allergenic foods each week.

Randomisation was effective and the median age of introduction of the four randomised foods was 19.6 weeks. Wheat, which was always introduced last and not before four months of age had a median age of introduction of 20.6 weeks.¹

Food vehicles chosen for introducing the allergen to the infants were those which families would be familiar and comfortable with using. Yoghurt was used for introducing cow's milk protein. We specifically excluded recommending using cow's milk formula, which might have affected breastfeeding. Boiled egg was used instead of egg powder. Wheat was introduced as a wheat based breakfast cereal (Weetabix), widely consumed in the UK and suitable for infants as it dissolves in milk to form an easily consumed paste. Peanut butter has historically not commonly been given to UK infants, but is the vehicle that virtually all parents of infants would chose, if they were feeding

their infant peanut. The only food that is rarely given to infants, and which many parents were not familiar with, was tahini (ground sesame paste), although hummus (the ingredients of which include tahini) is consumed by many children.

Participants were asked to consume the equivalent of 2 g of each allergenic food protein twice each week (4 g of allergen protein per food per week). Therefore the full weekly amount for the allergenic foods consisted of 2 small 40- to 60-g portions of cow's milk yogurt, 3 rounded teaspoons of peanut butter, 1 small hard-boiled egg (<53 g), 3 rounded teaspoons of sesame paste, 25 g of whitefish, and 2 wheat-based cereal biscuits (eg, Weetabix).

Information collected

Online Questionnaire data

Infant sleep was assessed in every online questionnaire through to two years and again at three years of age using the Brief Infant Sleep Questionnaire (BISQ).² Maternal quality of life was recorded using the WHO Quality of Life BREF questionnaire at three time points: enrollment, one year and three years of age. This is a shorter version of the WHOQOL-100 and includes 26 questions. Two enquire about overall quality of life and general health. The remaining 24 questions are divided into four domains of quality of life: Physical health (7 items: Activities of daily living; Dependence on medicinal substances and medical aids; Energy and fatigue; Mobility; Pain and discomfort; Sleep and rest; Work Capacity), Psychological (6 items: Bodily image and appearance; Negative feelings; Positive feelings; Self-esteem; Spirituality/Religion/Personal beliefs; Thinking, learning, memory and concentration), Social relationships (3 items: Personal relationships; Social support; Sexual activity), and Environment (8 items: Financial resources; Freedom, physical safety and security; Health and social care: accessibility and quality; Home environment; Opportunities for acquiring new information and skills; Participation in and opportunities for recreation/leisure activities; Physical environment - pollution/noise/traffic/climate; Transport).³ Four domain scores can be generated denoting an individual's perception of quality of life in each particular domain. Domain scores are scaled in a positive direction (i.e. higher scores denote higher quality of life). Scores range from 4 to

20. There were no significant differences in quality of life scores in each of the four domains between the two groups at enrollment. Poorer psychological domain quality of life was defined as less than the median score (16).

The online questionnaires allowed families to report any suspected symptoms with food ingestion, and to list suspected foods through responding to a generic question: "Does your child have adverse reactions to any foods, such as eczema, breathing problems or gastrointestinal problems?" If they answered yes, they were asked to describe the problems and identify the suspected food/foods. The answers to these questions were coded by food and symptom type, with clinical judgement used to distinguish between IgE-type symptoms (urticaria, angioedema, acute rash, respiratory symptoms, acute vomiting), and non-IgE-type symptoms (diarrhoea, constipation, reflux, delayed vomiting, delayed rash, eczema). These data were then used to give an indication of the prevalence of parent reported IgE and non-IgE-type food symptoms to specific foods and to grouped foods. Foods were grouped as any of the six early introduction foods, any non-early introduction food, or any food.⁴

Feeding difficulty and aversive feeding behaviour were enquired about at 4, 6, 9 and 12 months and two and three years of age. Questions used were based on previously published work on taste and sensory aversions in adults and were adapted for use in babies and young children.⁵ In this paper, the effect on adherence of symptoms reported at the earliest time point, four months, is assessed and the key question ascertained was whether the family had experienced: "Any difficulty feeding baby what you want them to eat?"

Clinic visit data

Scheduled clinic visits took place at enrollment, one and three years of age. All children were examined for eczema at all three clinic visits, using the UK diagnostic criteria-based photographic protocol of the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Two.⁶

Disease severity was determined by the Scoring Atopic Dermatitis (SCORAD) index.⁷ SCORAD was categorized as mild (<15), moderate (15 to less than 40), and severe (40 or more).⁷ Transepidermal

water loss (TEWL) was measured using the Biox Aquaflux[®] AF200 closed condenser chamber device on the unaffected skin of the volar aspect of the forearm 2009.⁸

Families of participants could report perceived problems with food consumption via a study dedicated telephone line, a study email address or in an interim questionnaire. Any family 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, followed by a food challenge where necessary.

Restricted window to achieve per-protocol status

Per-protocol criterion C for the EIG proved to be particularly challenging (Table E1). The window in which to achieve 5 weeks of 75% consumption of a specific allergenic food by 26 weeks of age (6 months), particularly for the four randomized foods, was narrow, given the average age of first consumption of these foods was 19.6 weeks. For wheat, the window was shorter still, as wheat consumption always commenced last (median age of introduction of 20.6 weeks) and consumption was not allowed before four months of age.

Results

EIG adherence nonevaluable participants

Overall adherence status could only be determined in 81% (529/652) of the EIG participants (Table E1). In the remaining 19% (123/652) of the EIG participants, their adherence could not be determined because insufficient questionnaires had been completed in the key early introduction period (the 4, 5 and 6 month questionnaires). We have previously demonstrated that levels of consumption of the allergenic foods in the overall adherence nonevaluable EIG participants (red line) were similar to the overall nonadherent EIG participants (green line) (Fig E1, left panels).¹

However, food-specific adherence levels varied considerably, ranging from 39% for wheat, to 84% for milk (Table E3). When we assessed weekly food consumption levels by food-specific adherence status (Fig E1, central panels), a different pattern was observed. Compared with the left hand panels, the most notable observation is that the weekly consumption levels in the food-specific nonadherent groups (red line) are at significantly lower levels than those observed in the overall nonadherent group (red line) in the left hand panels. Furthermore, predominantly in the key early introduction period (up to six months of age), weekly consumption levels for certain foods in the nonevaluable group (green line) were much closer to the levels observed in the per-protocol group (blue line) (particularly for peanut and sesame).

This was even more apparent when we analyzed the proportion of EIG participants who were consuming 75% or more of the recommended dose of each early introduction food. (Fig E1, right panels). Participants whose adherence status was nonevaluable for specific foods (green line) were consuming the specific food at or above the per-protocol threshold much more frequently than the food-specific non per-protocol participants (red line).

In Fig E2 we explore the issue of how many foods were being consumed at or above the per-protocol threshold by overall compliance status. The number of foods being consumed at or above the per-

protocol threshold at any particular time point is similar between the overall noncomplied group (red line) and the overall compliance nonevaluable group (green line), other than the data from the 6 month interim questionnaire showing a higher level of consumption in the overall non evaluable group (green line) (Fig E2, Panel A). However, Panel A represents the mean number of foods being consumed at a particular time point, and therefore does not provide any information about how many participants might have been exceeding the overall per-protocol definition of five or more foods being consumed at 75% or more of the recommended dose. This is presented in Panel B and in the key early introduction period, a higher percentage of EIG participants in the overall adherence nonevaluable group (green line) would appear to be achieving this threshold, than in the overall noncomplied group (red line), particularly just before six months.

To have an adherence status that was nonevaluable was entirely related to insufficient interim questionnaires being completed to allow consumption levels to be determined in the key early introduction period (up to six months of age). Questionnaire completion rates in participants whose overall adherence status was nonevaluable continued to be significantly lower throughout the first year of life, compared with the other two groups. It is only those adherence nonevaluable families who completed an interim questionnaire at any specific monthly time point up to one year of age that provide the consumption data for any specific month to compare with the other two groups that is presented in Figs E1 & E2. Therefore, in Fig 2, Panel C, it can be seen that whilst the overall adherence nonevaluable group includes 123 EIG participants, the monthly interim questionnaire completion rates through to one year in this group were very low. The data points for most months between 4 and 12 months are based on less than 30 respondents. Thus considerable caution has to be exercised as to how representative the 30 or so families that were completing these interim questionnaires are of the whole group of 123 overall nonevaluable EIG participants.

When comparing the demographic characteristics of the EIG overall nonadherent and adherence nonevaluable groups, the two groups were broadly similar, for example with both having much

higher proportions of nonwhite participants (Table E2). However, there were some important differences, eczema was significantly less common in the adherence nonevaluable EIG group (Table E2).

Whilst these results suggest that the adherence nonevaluable group's consumption levels were more similar to the adherent group, particularly in the key early introduction period, because the adherence nonevaluable group's precise adherence status was unknown, we undertook the analyses in this paper comparing the per-protocol and non per-protocol groups. We did, however, repeat the analyses with the non per-protocol and the adherence nonevaluable groups combined. The effect of eczema on nonadherence diminished and the effect of ethnicity increased but the results were in general broadly similar.

Association between ethnicity and baseline demographic characteristics

Given that ethnicity was such an important determinant of nonadherence, we explored whether differences existed in other enrollment demographic characteristics between ethnic groups (Table E5). Asian, black and Chinese participants were more likely to come from families with siblings and more likely to have a sibling with a parent-reported history of food allergy. Smoking rates, both in mothers and fathers, were highest in the mixed ethnicity participants. Birth weight significantly diminished across the ethnic categories, with Asian, black or Chinese participants having the lowest birth weight. With regards to atopy there was a stepwise increase in visible eczema across ethnic groups with it being highest in the Asian, black or Chinese group. The eczema that was present was also more severe for the Asian, black or Chinese participants compared with the other two groups. The trend in visible eczema was matched by a similar increase in sensitisation rates at enrollment in the EIG with it being 3.6% in the white participants but 23.4% in the Asian, black or Chinese participants. Conversely, the opposite trend was seen with regards to parental atopy. Maternal asthma, maternal and paternal atopy all showed a stepwise reduction from white, to mixed, to

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

Enrollment factors associated with overall nonadherence (univariate analysis)

Per-protocol adherence in the EIG could be compromised by three independent factors: delayed introduction of allergenic foods resulting in insufficient time to achieve five or more weeks consumption at the requisite amount between enrollment and six months of age, insufficient amount of an allergenic food being consumed (<75% of the recommended amount), and an insufficient total number of foods being consumed at the recommended amount (less than five of the six early introduction foods).

Nonadherence - delayed introduction of allergenic foods

Nonwhite ethnicity and increased maternal age both showed independent and statistically significant associations with postponed introduction of solids into the infant's diet. For the former, the difference between white participants and the Asian, black or Chinese infants amounted to 5.9 days in the SIG ($p=0.15$) and 6.4 days ($p=0.005$) in the EIG. For the latter, the difference in age of solid food introduction when comparing a 20 year old mother with a 45 year old mother amounted to 12.5 days in the SIG and 7.5 days in the EIG.

Nonadherence - insufficient amount of the allergenic foods consumed

Nonwhite ethnicity, increased maternal age and enrollment eczema severity (SCORAD category) were all associated with EIG infants being fed less than the recommended weekly dose of allergenic foods. This reduced consumption persisted throughout the first year of life for several of the foods.

Nonadherence - insufficient total number of foods

The reduction in consumption of individual allergenic foods meant that for nonwhite ethnicity, maternal age and eczema severity (SCORAD category) there was a concomitant reduction in the total number of foods being consumed at the per-protocol level (Fig E4, left hand panels). Particularly for nonwhite participants this reduction persisted throughout the first year of life.

This, in turn, affected the ability of certain subgroups to fulfil the per-protocol definition of adherence on any particularly week, i.e. on a specific week to have consumed five or more of the six foods, at 75% or more of the recommended dose (Fig E4, right hand panels). Again, for ethnicity the effect was particularly marked with 80% of white participants achieving the overall per-protocol threshold from shortly after six months of age, whilst 60% of mixed ethnicity participants were meeting the threshold beyond six months, the figure dropping to around 50% of black, Asian or Chinese participants.

Enrollment factors associated with food-specific nonadherence (univariate analysis)

Factors influencing overall nonadherence in the EIG were similar for individual foods (Table E4). Nonadherence was statistically significantly related to the presence of any visible eczema at enrollment for several of the individual foods.

A strong association with maternal older age was observed for food-specific nonadherence for four of the six foods and for paternal older age with egg and fish non per-protocol adherence. Baseline maternal quality of life factors also appeared significant, particularly for peanut with mothers with lower quality of life scores being significantly more likely to be non per-protocol.

Significant associations with non per-protocol status were also seen with several measures assessed in the BISQ sleep questionnaire completed at enrollment. Increased frequency of night wakings was significantly associated with non per-protocol adherence specifically for peanut and egg. Infants who

were sleeping in the parent's bed at enrollment were significantly more likely to be non per-protocol adherent whilst those who were put to bed alone were significantly less likely to be nonadherent.

IgE-type symptom reporting and enrollment sensitization

There was a statistically significant relationship between being sensitized to a specific food at enrollment and subsequently reporting symptoms to the food. For example, 18% (4/22) of EIG participants sensitized to peanut at enrollment reported IgE-type symptoms with peanut introduction, compared with 3.2% (17/533) of non-peanut sensitized EIG families reporting symptoms with peanut introduction ($p < 0.001$). However, it important to note that 18 out of the 22 peanut sensitized children therefore did not report any symptoms with peanut introduction. IgE-type symptoms were reported with peanut consumption by coincidentally the same number of EIG children (22). One of these did not have IgE data. It is equally important to note that of the remaining 21 children, 17 were not sensitized to peanut at enrollment. Both the number of EIG participants with reported peanut symptoms (22) and the number sensitized to peanut at enrollment (22) significantly exceeded the number of EIG participants who ultimately developed a peanut allergy (7).

Consumption of each allergenic food by enrollment specific IgE sensitization status

Enrollment specific IgE sensitization (0.1kU/l or greater) did not have a significant effect on the ability to consume milk, sesame or wheat at the 75% recommended dose threshold (Fig E6). No infant was sensitized (0.1 kU/l or greater) to fish at enrolment. For peanut and egg there was a delay in introduction in the key early introduction period in specific IgE sensitized infants compared with the non-sensitized infants. This resulted in a significant univariate association between enrollment IgE sensitization and food-specific nonadherence for egg and the relationship was of borderline significance for peanut (Fig 2). This was likely to be a consequence of the study design. A significant

proportion of specific IgE sensitized EIG infants were also skin prick test positive to the same food at enrollment, particularly for egg (Fig E6 - numbers in brackets). Any EIG infant who was enrollment skin prick test positive to an early introduction food came back for a supervised food challenge before being allowed to start consuming this food. They were issued with an amended early introduction regimen with the sensitized food being introduced last (so the scheduling of the challenge did not defer commencing consumption of the other early introduction foods). Inevitably this meant there was a delay before they could commence introducing the food into their diet, reflected in the figure.

Interestingly the difference was not apparent for milk despite there being 10 EIG milk IgE sensitized infants who were also skin prick test positive to milk. These specific families would appear to have been able to rapidly increment their infant's milk consumption once they were allowed to commence consumption such that in the week before turning six months of age these 10 infants were consuming 81% of the recommended weekly milk dose. In contrast, at the same point in time, the 6 peanut skin prick and specific IgE positive infants were consuming 50% of the peanut weekly dose and the 22 egg skin prick and specific IgE positive infants were consuming 62% of the egg weekly dose.

Post enrollment factors associated with nonadherence

Post enrollment - Parent early reported feeding difficulties

The strongest relationships with non per-protocol adherence in the EIG were observed between the questions that assessed the early emergence of parent reported feeding difficulties and food refusal at 4 months of age (Table E6). The reporting by parents of feeding difficulties at 4 months of age was associated with sustained lower levels of consumption of the six allergenic foods, significantly compromising the number of foods being consumed at the per-protocol level (Fig E4, left hand panel) and the ability to meet the overall per-protocol threshold (Fig E4, right hand panel).

Whilst the associations between food aversion behaviours and non per-protocol status were notable for the consistency of highly statistically significant relationships, there was no evidence that these behaviours were significantly associated with the development of food allergy in the EIG (Table E7).

Post enrollment - Parent suspected IgE or non-IgE-type symptoms with early food introduction in the EIG and the effect on food-specific and overall adherence

Rates of reporting food-specific symptoms during the early introduction period varied significantly by food (Table E8). Given that there were 652 infants in the EIG, absolute numbers of families reporting any symptoms ranged from very low, with 7 reports of any symptoms for fish (1.1% of the EIG cohort), to 68 for egg (10.4%). For egg, IgE-type symptoms predominated (52 versus 28 reporting non-IgE-type symptoms). Milk had a similar number of families reporting any symptoms (63), but the situation reversed with non-IgE-type symptoms predominating (46 versus 33). Compared to egg, peanut was perhaps surprisingly well tolerated, with only 27 reporting symptoms (22 IgE, 10 non-IgE). Any symptoms to one or more of the early introduction foods was reported by 149 families (22.9% of the whole EIG).

IgE-type food-specific symptoms were associated with nonadherence to the same food, with the exception of peanut which also influenced nonadherence to sesame, and for sesame which also influenced nonadherence to milk (Fig 3 & Table E6). For reported IgE-type symptoms with both peanut and sesame, the odds ratios for nonadherence to other foods were higher than those seen for IgE-type symptoms with egg and milk, suggesting that symptoms to peanut and sesame were more likely to make a family concerned about introducing the other early introduction foods.

IgE-type symptoms to one or more of the six early introduction foods was strongly associated with food-specific and overall nonadherence, whereas no statistically significant associations with adherence were seen for non-IgE-type symptoms to one or more of the early introduction foods.

Milk was the only food for which the reporting of non-IgE-type symptoms was associated with milk non per-protocol adherence (Table E6).

EIG families who were overall nonadherent were significantly more likely to have reported IgE-type symptoms in the key early introduction months than either EIG per-protocol infants or SIG infants (Fig E7). In fact, per-protocol EIG families and SIG families reported similar rates of IgE-type symptoms when allergenic foods were first introduced into the diet, but the former then showed particularly low rates of symptom reporting throughout the rest of the first year of life.

Parent suspected IgE or non-IgE-type symptoms with food introduction in the EIG and the effect on food allergy

Reporting of food-specific IgE-type symptoms was associated with food allergy to that food (Fig E8). Relationships were food-specific. Both IgE and non-IgE-type symptoms to any of the six foods were strongly associated with the primary outcome. When the two factors were included in a model with an interaction term, both remained statistically significant, suggesting that the association of both variables with the primary outcome was not explained by the strong correlation between the two. It is important to note that whilst there were strong food-specific correlations between the early reporting of symptoms and subsequent food allergy, the great majority of EIG infants in whom such symptoms were reported did not develop an allergy to that food. For example, 33 EIG families reported IgE-type symptoms to milk but only 2 EIG infants developed a milk allergy. One other EIG infant developed a milk allergy and they reported no IgE symptoms with milk in the early introduction period.

Discussion

Comparison with the Infant Feeding Survey 2010 findings

In the Infant Feeding Survey 2010 (IFS2010) there was also a very strong positive association between increasing maternal age and later introduction of solids (19% of mothers aged 35 or over had begun introducing solids by four months of age compared with 57% of mothers under 20).

Similarly, with ethnicity, nonwhite mothers introduced solids significantly later. Nearly eight in ten (77%) white mothers had introduced solids by the time their baby was five months old compared with around two-thirds of mothers from Asian, Black, Chinese backgrounds.

In the IFS2010 Asian, Black, and Chinese mothers were most likely to report having experienced difficulties introducing solid foods to their baby (16%, 14% and 18% respectively versus 10% in white mothers). Asian and Black mothers were also most likely to report their child as being a fussy or faddy eater (both 9% versus 4% in white mothers).⁹

If feeding difficulties explained the greatest proportion of EIG nonadherence, the question arises as to what was responsible for the feeding difficulties. Associations with sleep parameters suggest that other aspects of the infant such as their maturity might well be significant. However historical data would suggest that young infants are clearly able to introduce solids very early: the proportion of UK infants given solids by eight weeks of age being 49% in 1975.¹⁰

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. Sadeh A. A brief screening questionnaire for infant sleep problems: validation and findings for an Internet sample. *Pediatrics* 2004; 113(6):e570-e577.
3. 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.
4. 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.
5. 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.
6. 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.
7. 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.
8. Farahmand S, Tien L, Hui X, Maibach HI. Measuring transepidermal water loss: a comparative in vivo study of condenser-chamber, unventilated-chamber and open-chamber systems. *Skin Res Technol* 2009; 15(4):392-8.
9. McAndrew F, Thompson J, Fellows L, Large A, Speed M, Renfrew MJ. Infant Feeding Survey 2010. 2012. Health and Social Care Information Centre.
10. COMA working group on the weaning diet. Weaning and the weaning diet. 1994. London.

TABLE E1. Overall per-protocol adherence criteria in the EAT study

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

* Adherence status nonevaluable for 7% (45/651) of the SIG and 19% (123/652) of the EIG participants

TABLE E2. Univariate analysis of factors influencing EIG per-protocol status

		EIG Per-Protocol status						
		Per-Protocol (A) (N=223)	Non-Per- Protocol (B) (N=306)	P value (AvB)	Adherence Nonevaluable (C) (N=123)	P value (AvC)	Non-Per- Protocol or Adherence Nonevaluable (B+C) (N=429)	P value (Av(B+C))
Demography								
Sex (female) (%)		49.3	53.6	0.33	52.0	0.63	53.2	0.35
Ethnicity (%)	<i>White</i>	92.8	83.7	0.002	76.4‡	<0.001	81.6	<0.001
	<i>Mixed</i>	5.4	8.2		8.9		8.4	
	<i>Black/Asian/Chinese</i>	1.8	8.2		14.6		10.0	
Siblings (any) (%)		59.6	64.1	0.30	65.0	0.32	64.3	0.24
Pet ownership (any) (%)		45.7	39.5	0.15	33.6	0.03	37.9	0.05
Maternal education (%)	<i>>18 years</i>	83.4	82.7	0.80	78.1	0.008	81.4	0.22
	<i>17-18 years</i>	13.5	13.1		10.6		12.4	
	<i>16 years</i>	3.1	4.3		11.4		6.3	
Paternal education (%)	<i>>18 years</i>	69.5	71.2	0.86	65.6	0.16	69.6	0.62
	<i>17-18 years</i>	17.5	15.7		13.9		15.2	
	<i>16 years</i>	13.0	13.1		20.5		15.2	
Smoking								
Maternal smoking (%)		3.6	2.6	0.52	4.9	0.55	3.3	0.83
Paternal smoking (%)		11.2	10.5	0.78	10.7	0.88	10.5	0.79
Birth history								
Caesarean delivery (%)		24.7	29.1	0.26	29.3	0.35	29.1	0.23
Infant weight								
Birth to enrollment weight gain	<i>Lowest quartile</i>	29.2	24.5	0.55	22.1	0.56	23.8	0.44
	<i>2nd quartile</i>	25.1	23.9		26.2		24.5	
	<i>3rd quartile</i>	22.9	24.8		25.4		25.0	
	<i>Highest quartile</i>	22.9	26.8		26.2		26.6	
Enrollment weight	<i>Lowest quartile</i>	26.5	25.5	0.38	22.0	0.44	24.5	0.31
	<i>2nd quartile</i>	26.5	23.5		23.6		23.5	
	<i>3rd quartile</i>	27.4	24.8		27.6		25.6	
	<i>Highest quartile</i>	19.7	26.1		26.8		26.3	

EIG Per-Protocol status								
		Per-Protocol (A) (N=223)	Non-Per- Protocol (B) (N=306)	P value (AvB)	Adherence Nonevaluable (C) (N=123)	P value (AvC)	Non-Per- Protocol or Adherence Nonevaluable (B+C) (N=429)	P value (Av(B+C))
Enrollment skin barrier								
Visible eczema at 3m visit (%)	<i>None</i>	79.8	71.9	0.07	76.4	0.68	73.2	0.14
	<i>SCORAD 1-15</i>	16.6	20.9		20.3		20.8	
	<i>SCORAD >15</i>	3.6	7.2		3.3		6.1	
Raised TEWL		30.2	34.6	0.28	27.6	0.62	32.6	0.52
Enrollment sensitization								
Skin-prick positive at 3m visit (%)		4.0	5.2	0.52	6.5	0.31	5.6	0.39
Food-specific IgE (≥ 0.1 kU/l)		13.6	16.6	0.36	17.3	0.38	16.8	0.31
Food-specific IgE (≥ 0.35 kU/l)		2.9	6.5	0.07	9.1	0.02	7.2	0.03
Eczema natural history								
New onset eczema (4-6m) (%)		10.3	12.8	0.39	2.3	0.02	10.5	0.96
Enrollment eczema or new onset eczema (4-6m) (%)		30.5	40.9	0.02	27.9	0.66	38.0	0.06
Family atopy status								
Maternal atopy (%)		60.1	64.7	0.28	58.2	0.73	62.9	0.49
Paternal atopy (%)		51.1	51.0	0.98	48.4	0.62	50.2	0.83
Maternal factors								
Physical QOL	<i>Highest quartile</i>	26.9	17.1	0.04	20.4	0.24	18.0	0.04
	<i>2nd quartile</i>	19.6	26.9		26.2		26.7	
	<i>3rd quartile</i>	27.9	29.0		22.3		27.3	
	<i>Lowest quartile</i>	25.6	26.9		31.1		28.0	
Psychological QOL	<i>Highest quartile</i>	30.6	21.3	0.001	18.5	0.11	20.6	0.002
	<i>2nd quartile</i>	16.0	8.4		16.5		10.5	
	<i>3rd quartile</i>	27.4	39.2		30.1		36.8	
	<i>Lowest quartile</i>	26.0	31.1		35.0		32.1	
Social QOL	<i>Highest quartile</i>	25.1	20.0	0.31	14.6	0.10	18.5	0.17
	<i>2nd quartile</i>	14.6	16.1		11.7		14.9	
	<i>3rd quartile</i>	38.8	36.4		45.6		38.9	
	<i>Lowest quartile</i>	21.5	27.5		28.2		27.7	

EIG Per-Protocol status								
		Per-Protocol (A) (N=223)	Non-Per- Protocol (B) (N=306)	P value (AvB)	Adherence Nonevaluable (C) (N=123)	P value (AvC)	Non-Per- Protocol or Adherence Nonevaluable (B+C) (N=429)	P value (Av(B+C))
Environment QOL	<i>Highest quartile</i>	30.1	20.0	0.07	23.3	0.09	20.9	0.07
	<i>2nd quartile</i>	21.0	22.5		24.3		22.9	
	<i>3rd quartile</i>	27.9	33.3		20.4		29.9	
	<i>Lowest quartile</i>	21.0	24.2		32.0		26.3	
Maternal age (33+) (%)		52.0	63.1	0.01	56.9	0.38	61.3	0.02
Paternal factors								
Paternal age (35+) (%)		52.0	60.1	0.06	49.6	0.67	57.1	0.22
Childcare								
Nursery/childcare		2.2	2.6	0.79	0.8	0.33	2.1	0.91
Infant sleep at enrollment								
Where does baby sleep	<i>Cot in separate room</i>	23.3	17.8	0.06	13.6	0.01	16.7	0.01
	<i>Cot in parents' room</i>	66.2	67.8		66.0		67.4	
	<i>In parents' bed</i>	8.2	13.6		19.4		15.2	
	<i>Cot in sibling's room</i>	2.3	0.7		1.0		0.8	
How baby falls asleep	<i>While feeding</i>	35.2	43.9	0.26	47.6	0.25	44.9	0.14
	<i>Being rocked</i>	3.7	4.2		4.9		4.4	
	<i>Being held</i>	10.5	10.2		7.8		9.5	
	<i>In bed alone</i>	37.0	28.4		28.2		28.4	
	<i>In bed near parent</i>	13.7	13.3		11.7		12.9	
Night sleep duration	<i>Lowest quartile</i>	20.1	23.8	0.46	35.9 [†]	0.006	27.0	0.09
	<i>2nd quartile</i>	23.7	26.2		22.3		25.2	
	<i>3rd quartile</i>	27.9	27.3		27.2		27.3	
	<i>Highest quartile</i>	28.3	22.7		14.6		20.6	
Night wakings frequency (times per night)	<i>0</i>	19.6	13.6	0.33	12.6	0.49	13.4	0.23
	<i>1</i>	29.7	30.8		32.0		31.1	
	<i>2</i>	30.1	32.2		32.0		32.1	
	<i>3+</i>	20.6	23.4		23.3		23.4	

P-values for variables with multiple categories (e.g. maternal education) are comparing the overall distribution between the two relevant groups

TABLE E3. Food-specific versus overall EIG adherence status

			Overall EIG per-protocol adherence status					
			Adherence Evaluable (AE)		Adherence Unknown			
			Adhered (N=223)*	Nonadhered (N=306)†	Nonevaluable (N=123)‡	Total (N=652)		
						n	% (AE)	% (Total)
Food Specific EIG Adherence Status	Milk	Adhered	223	217	11	451	84.0	69.2
		Nonadhered	0	80	6	86	16.0	13.2
		Nonevaluable	0	9	106	115		17.6
	Egg	Adhered	188	41	5	234	42.5	35.9
		Nonadhered	35	262	20	317	57.5	48.6
		Nonevaluable	0	3	98	101		15.5
	Fish	Adhered	217	95	6	318	58.6	48.8
		Nonadhered	6	205	14	225	41.4	34.5
		Nonevaluable	0	6	103	109		16.7
	Sesame	Adhered	214	72	2	288	52.4	44.2
		Nonadhered	9	233	20	262	47.6	40.2
		Nonevaluable	0	1	101	102		15.6
	Peanut	Adhered	220	110	6	336	61.2	51.5
		Nonadhered	3	195	15	213	38.8	32.7
		Nonevaluable	0	1	102	103		15.8
	Wheat	Adhered	184	31	1	216	39.1	33.1
		Nonadhered	39	274	24	337	60.9	51.7
		Nonevaluable	0	1	98	99		15.2

* EIG overall adhered: 223/529 (42.2% of adherence evaluable EIG participants), 223/652 (34.2% of total EIG)

† EIG overall nonadhered: 306/529 (57.8% of adherence evaluable EIG participants), 306/652 (46.9% of total EIG)

‡ EIG overall adherence non-evaluable: 123/652 (18.9% of total EIG)

AE Adherence Evaluable

TABLE E4. Enrollment factors influencing likelihood of being overall and food-specific nonadherent in the EIG (univariate analysis)

		EIG Nonadherence						
		Unadjusted odds ratio for being nonadherent compared with adherent						
		Overall	Food-specific					Wheat
			Peanut	Egg	Milk	Sesame	Fish	
Demography								
Sex (female)		1.89	1.15	1.24	1.27	1.13	0.84	1.06
Ethnicity	White (baseline)	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	Mixed	1.70	1.52	1.44	1.34	1.34	1.90	1.39
	Black/Asian/Chinese	4.69†	3.90†	3.36†	2.16	3.34†	3.34†	3.01*
Siblings (any) (%)		1.22	1.11	1.26	1.47	1.27	1.37	1.10
Pet ownership (any)		0.78	0.75	0.76	0.70	0.83	0.63*	0.72
Maternal education	>18 years (baseline)	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	17-18 years	1.00	0.93	0.85	0.59	1.16	0.81	0.91
	16 years	1.39	1.25	1.22	1.39	1.13	0.72	1.06
Paternal education	>18 years	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	17-18 years	0.89	0.92	0.91	0.80	0.94	0.84	0.80
	16 years	0.97	0.79	0.90	0.99	1.25	0.86	1.01
Smoking								
Maternal smoking		0.73	0.79	0.74	0.73	0.65	1.80	1.01
Paternal smoking		0.91	1.11	0.62	0.73	1.15	0.91	0.96
Birth history								
Caesarean delivery		1.26	1.16	1.10	1.40	1.18	1.41	1.22
Enrollment growth status								
Birth to enrollment weight gain	Lowest quartile	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	2 nd quartile	1.13	1.90*	1.27	2.16*	1.16	1.65*	1.39
	3 rd quartile	1.27	1.58	1.45	1.83	1.18	1.94†	1.32
	Highest quartile	1.41	1.47	1.54	1.21	1.16	1.92†	1.23
Enrollment weight	Lowest quartile	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	2 nd quartile	0.88	1.03	1.35	1.09	1.05	1.24	1.25
	3 rd quartile	0.93	1.13	1.32	0.95	0.99	1.12	1.33
	Highest quartile	1.38	1.27	1.56	1.32	1.32	1.55	1.32

		EIG Nonadherence						
		Unadjusted odds ratio for being nonadherent compared with adherent						
		Food-specific						
		Overall	Peanut	Egg	Milk	Sesame	Fish	Wheat
Enrollment eczema								
Any visible eczema		1.47	1.30	1.68*	1.75*	1.58*	1.72*	1.04
SCORAD (continuous)		1.03*	1.03*	1.04*	1.03*	1.04*	1.04*	1.01
SCORAD severity at 3m visit	<i>None</i>	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	<i>SCORAD 1-15</i>	1.38	1.16	1.68*	1.77*	1.30	1.57*	0.93
	<i>SCORAD >15</i>	1.92	1.93	1.68	0.68	3.15†	2.44*	1.59
Raised TEWL		1.22	1.42	1.36	0.97	1.37	1.31	0.99
Enrollment sensitization								
Skin-prick positive	Any food	0.98	1.76	1.91	3.85†	1.86	1.82	1.12
	Specific food	-	8.09	1.76	8.53*	**	**	**
Specific IgE positive (≥0.1 kU/l)	Any food	1.16	1.22	1.40	1.30	1.09	1.65*	1.05
	Specific food	-	2.81*	2.58*	2.26	1.36	2.34	0.66
Family atopy status								
Maternal atopy		1.25	0.91	1.25	1.08	1.05	0.96	1.07
Paternal atopy		0.98	0.98	0.98	1.00	0.84	0.96	1.00
Maternal factors								
Physical QOL	<i>Highest quartile</i>	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	<i>2nd quartile</i>	2.20†	2.77‡	2.06†	2.75†	2.01†	1.79*	2.32†
	<i>3rd quartile</i>	1.67*	1.66	1.44	1.03	1.25	1.04	1.38
	<i>Lowest quartile</i>	1.62	1.81	1.36	1.45	1.17	1.22	1.27
Psychological QOL	<i>Highest quartile</i>	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	<i>2nd quartile</i>	0.77	0.70	0.92	0.70	1.14	1.06	0.59
	<i>3rd quartile</i>	2.07†	2.01†	1.72*	1.39	1.66*	1.63*	2.07†
	<i>Lowest quartile</i>	1.70*	1.53	1.30	1.10	1.22	1.22	1.37
Social QOL	<i>Highest quartile</i>	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	<i>2nd quartile</i>	1.41	1.25	1.66	1.19	1.22	0.98	0.99
	<i>3rd quartile</i>	1.19	1.64	1.37*	2.13*	1.26	1.07	1.01
	<i>Lowest quartile</i>	1.60	1.88*	1.98†	1.37	1.34	1.25	1.30
Environment QOL	<i>Highest quartile</i>	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	<i>2nd quartile</i>	1.61	1.30	1.21	1.39	1.82*	1.02	1.91*
	<i>3rd quartile</i>	1.84*	1.82*	1.23	1.67	1.85*	1.36	2.36‡
	<i>Lowest quartile</i>	1.72*	1.43	1.47	1.01	1.54	1.26	1.76*
Maternal age (33+)		1.59*	1.78†	2.27‡	1.72*	1.40	1.45*	1.21

		EIG Nonadherence						
		Unadjusted odds ratio for being nonadherent compared with adherent						
		Overall	Food-specific					
Peanut	Egg		Milk	Sesame	Fish	Wheat		
Paternal factors								
Paternal age (35+)		1.43*	1.40	1.53*	1.36	1.36	1.49*	1.16
Childcare								
Nursery/childcare		1.19	1.37	0.86	0.45	1.78	2.30	1.03
Infant sleep at enrollment								
Where does baby sleep	Cot in parents' room	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	Cot in separate room	0.74	0.68	0.71	0.89	0.90	0.79	0.84
	In parents' bed	1.59	2.40†	1.52	1.40	1.84*	1.95*	1.71
	Cot in sibling's room	0.30	0.28	0.29	1.00	0.48	0.61	0.52
How baby falls asleep	While feeding	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	Being rocked	0.94	1.05	0.81	0.52	0.56	0.92	1.07
	Being held	0.76	0.75	0.80	1.00	0.55	0.65	0.85
	In bed alone	0.62*	0.56†	0.73	0.62	0.59*	0.61*	0.63*
	In bed near parent	0.80	0.74	0.81	0.62	0.61	0.50*	0.91
Night sleep duration	Lowest quartile	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	2 nd quartile	0.95	0.96	0.94	0.86	0.86	0.64	0.82
	3 rd quartile	0.81	0.77	0.93	0.78	0.88	0.91	0.70
	Highest quartile	0.69	0.61	0.62	0.76	0.82	0.63	0.73
Night wakings frequency	0	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	1	1.53	2.08*	1.44	1.01	1.25	1.16	1.18
	2	1.54	2.26†	1.78*	1.06	1.50	1.22	1.56
	3+	1.66	1.89*	1.67	1.09	1.44	1.41	1.42
Parent reported sleep problem	No problem	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	Small problem	1.21	1.41	1.00	1.27	1.10	1.20	1.12
	Very serious problem	0.39	0.92	-	-	0.23	0.32	1.37

*p<0.05 †p<0.01 ‡p<0.001 **no infant sensitized in this category or predicts nonadherence perfectly and odds ratio can therefore not be calculated

TABLE E5. Association of ethnicity with demographic variables in the EAT study

	White (N=1104)	Mixed (N=119)	Asian, Black or Chinese (N=80)	Between race p value
Demographic				
Sex (male) (%)	50.5	47.9	48.8	0.84
Siblings (any) (%)	61.7	58.8	75.0	0.04
Maternal education (≤ 18 years) (%)	19.3	17.7	15.0	0.60
Smoking				
Maternal smoking (%)	3.2	5.9	0.0	0.07
Father smoking (%)	10.2	17.7	8.9	0.04
Birth history				
Birth weight (mean kg)	3.58	3.43	3.33	
<i>p value vs white</i>		0.005	<0.0005	
Caesarean delivery (%)	24.3	30.3	30.0	0.21
Participant enrollment atopy status				
Visible eczema at 3m visit (%)	22.6	30.3	39.2	0.001
Scorad at 3m visit (median)*	7.25	7.35	15.2	
<i>p value vs white</i>		0.40	<0.0005	
Any sensitisation at 3m visit (%)	3.6	4.2	23.4	<0.0005
Family atopy status				
Maternal asthma (%)	27.3	26.1	12.7	0.02
Maternal eczema (%)	34.9	38.7	22.8	0.06
Maternal atopy (%)	63.6	62.2	49.4	0.04
Paternal atopy (%)	54.3	51.3	39.2	0.03
Family history of food allergy				
Sibling (%)	16.8	17.7	29.1	0.02
Mother (%)	19.3	22.7	15.2	0.42
Father (%)	10.8	12.6	5.1	0.21
Maternal factors				
Maternal QOL at 3m mean (SD)				
Physical	16.6 (1.9)	16.1 (1.9)	15.4 (2.4)	
<i>p value vs white</i>		0.004	<0.0005	
Psychological	15.6 (2.0)	15.4 (1.7)	15.5 (2.5)	
<i>p value vs white</i>		0.22	0.58	
Social	15.7 (2.7)	15.0 (3.0)	15.0 (3.0)	
<i>p value vs white</i>		0.01	0.06	
Environment	16.5 (1.9)	15.7 (1.9)	15.3 (2.1)	
<i>p value vs white</i>		0.0001	<0.0005	
Maternal age (mean years)	33	34	33	
<i>p value vs white</i>		0.12	0.14	
Participation measures				
Number of IQ completed (median - max 17)	16	16	11.5	
<i>p value vs white</i>		<0.0005	<0.0005	
Breastfeeding data				
Duration of any breastfeeding (mean weeks)	50	52	52	
<i>p value vs white</i>		0.13	0.85	
Duration of exclusive breastfeeding (mean weeks)	18	21	18	
<i>p value vs white</i>		0.009	0.81	

TABLE E6. Post enrollment factors through to six months influencing likelihood of being overall and food-specific nonadherent in the EIG (univariate analysis)

			EIG Nonadherence						
			Unadjusted odds ratio for being nonadherent compared with adherent						
			Overall	Food-specific					
				Peanut	Egg	Milk	Sesame	Fish	Wheat
Eczema natural history									
New onset eczema (4-6m)			1.29	1.26	0.96	0.79	1.07	0.99	1.02
Parent reported symptoms with food consumption (4-6m)									
(A) IgE-type symptoms	(1) To one or more EI foods	2.26‡	1.39	3.23‡	1.56	2.32‡	1.49	1.67*	
	(2) To any other food	0.92	1.33	1.12	3.25	1.10	0.94	0.64	
	(1 or 2) To any food	2.14†	1.39	3.03‡	1.73*	2.22‡	1.43	1.46	
(B) Non-IgE-type symptoms	(1) To one or more EI foods	1.50	1.42	1.55	1.46	1.34	1.32	1.07	
	(2) To any other food	0.88	1.14	0.52	0.49	0.78	1.01	1.13	
	(1 or 2) To any food	1.28	1.30	1.44	1.39	1.25	1.20	0.99	
(A or B) Any food symptoms	(1) To one or more EI foods	2.01†	1.51*	2.58‡	1.42	1.95†	1.48*	1.46	
	(2) To any other food	1.02	1.20	0.73	1.31	0.90	0.94	0.96	
	(1 or 2) To any food	1.78†	1.40	2.38‡	1.48	1.80†	1.33	1.28	
Food-specific symptoms (4-6m)									
	IgE-type symptoms	-	5.40†	9.06‡	3.03†	5.11†	5.28	2.38	
	Non-IgE-type symptoms	-	1.30	1.85	3.03†	1.10	3.33	0.64	
	Any food symptoms	-	3.09†	4.76‡	2.52†	2.68*	3.16	1.39	
Feeding difficulties/aversion (4m)									
Any difficulty feeding baby what you want them to eat?	No difficulty (baseline)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
	Occasional difficulty	0.86	0.76	1.12	0.50	0.55*	0.76	0.68	
	Some difficulty	2.12†	2.09†	1.77*	2.10*	1.84*	2.05†	1.50	
	Great difficulty	17.69‡	5.19‡	5.53‡	9.41‡	7.00‡	7.30‡	9.10‡	
Refuses food?	Never (baseline)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
	Rarely	1.02	1.04	1.04	0.74	0.92	0.81	0.72	
	Sometimes	1.38	1.73*	1.41	0.76	1.19	1.47	1.11	
	Frequently	4.19*	4.01†	2.81*	3.86†	6.57†	5.04†	3.62*	
	Always	-	8.64†	-	15.5‡	13.14†	7.56*	6.51	

		EIG Nonadherence						
		Unadjusted odds ratio for being nonadherent compared with adherent						
		Overall	Food-specific					
			Peanut	Egg	Milk	Sesame	Fish	
Turns head away when offered food?	Never	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	Rarely	1.01	0.81	1.26	0.77	0.69	0.94	0.90
	Sometimes	1.90*	1.84*	1.61	1.08	1.88*	1.53	1.25
	Frequently	3.77†	4.17†	2.79*	4.53†	3.57†	5.32‡	3.80†
	Always	**	6.94	**	**	**	8.11	3.16
Spits food out?	Never	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	Rarely	0.64	0.55	0.82	0.77	0.68	0.49	0.51*
	Sometimes	1.21	0.84	1.67*	0.90	0.75	1.03	0.60
	Frequently	1.76	1.18	2.29†	2.39*	1.47	1.13	1.15
	Always	7.21*	2.85*	22.4†	8.18‡	4.63*	6.56†	3.23
Baby shuts mouth when offered food?	Never	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	Rarely	0.76	0.72	0.98	0.47	0.62*	0.71	0.68
	Sometimes	1.44	1.46	1.68*	1.00	0.95	1.12	1.36
	Frequently	1.87	1.98	1.83	2.39	1.41	1.79	1.53
	Always	**	5.27	**	17.20†	8.14	11.73*	**
*p<0.05 †p<0.01 ‡p<0.001		**These cells predict nonadherence perfectly hence no odds ratio can be calculated						

TABLE E7. Feeding difficulties and food refusal by EIG per-protocol status and primary outcome status - 4 months of age

		EIG Per-Protocol status				EIG Primary Outcome Positive (%)
		Per-Protocol	Non-Per-Protocol	Adherence Nonevaluable	Non-Per-Protocol or Adherence Nonevaluable	
		(A) (N=223)	(B) (N=306)	(C) (N=123)	(B+C) (N=429)	
Any difficulty feeding baby what you want them to eat?		(N=201)	(N=237)	(N=37)	(N=274)	
	<i>No difficulty</i>	41.8	34.2	37.8	34.7	6.2
	<i>Occasional difficulty</i>	38.3	26.2	32.4	27.0	4.6
	<i>Some difficulty</i>	18.9	28.3	21.6	27.4	6.2
	<i>Great difficulty</i>	1.0	11.4	8.1	11.0	6.3
	p value		(AvB) <0.0005	(AvC) 0.04	(Av(B+C)) <0.0005	0.93
Refuses food?		(N=200)	(N=232)	(N=37)	(N=269)	
	<i>Never</i>	47.5	42.2	54.1	43.9	4.7
	<i>Rarely</i>	35.5	30.6	24.3	29.7	6.0
	<i>Sometimes</i>	15.5	17.7	13.5	17.1	7.8
	<i>Frequently</i>	1.5	6.5	8.1	6.7	4.8
	<i>Always</i>	0.0	3.0	0.0	2.6	14.3
Turns head away when offered food?		(N=200)	(N=231)	(N=37)	(N=274)	
	<i>Never</i>	52.5	44.2	48.7	44.8	4.0
	<i>Rarely</i>	31.5	26.4	18.9	25.4	6.9
	<i>Sometimes</i>	13.0	19.5	29.7	20.9	8.5
	<i>Frequently</i>	3.0	8.7	2.7	7.8	3.7
	<i>Always</i>	0.0	1.3	0.0	1.1	33.3
			(AvB) 0.009	(AvC) 0.06	(Av(B+C)) 0.008	0.13

		EIG Per-Protocol status				EIG Primary Outcome Positive (%)
		Per-Protocol (A)	Non-Per-Protocol (B)	Adherence Nonevaluable (C)	Non-Per-Protocol or Adherence Nonevaluable (B+C)	
		(N=223)	(N=306)	(N=123)	(N=429)	
Spits food out?		(N=200)	(N=231)	(N=37)	(N=274)	
	<i>Never</i>	22.5	20.4	21.6	20.6	4.0
	<i>Rarely</i>	24.5	13.6	21.6	14.7	4.5
	<i>Sometimes</i>	34.5	35.3	32.4	34.9	5.5
	<i>Frequently</i>	17.5	25.5	24.3	25.4	8.7
	<i>Always</i>	1.0	5.1	0.0	4.4	7.1
	p value		(AvB)	(AvC)	(Av(B+C))	
			0.003	0.86	0.008	0.64
Baby shuts mouth when offered food?		(N=200)	(N=231)	(N=37)	(N=274)	
	<i>Never</i>	42.2	40.1	46.0	40.9	4.1
	<i>Rarely</i>	34.7	24.6	24.3	24.5	3.0
	<i>Sometimes</i>	18.6	24.6	27.0	24.9	11.5
	<i>Frequently</i>	4.5	8.6	2.7	7.8	10.0
	<i>Always</i>	0.0	2.2	0.0	1.9	0.0
	p value		(AvB)	(AvC)	(Av(B+C))	
			0.01	0.48	0.02	0.03

TABLE E8. Number of EIG families reporting food-specific non-IgE and IgE-type symptoms in the key early introduction period in the EIG

		Food-specific symptoms						Any food symptoms [†]
		Peanut	Egg	Milk	Sesame	Fish	Wheat	
4 months	<i>IgE-type</i>	3	3	10	2	0	0	15
	<i>Non-IgE-type</i>	4	5	20	3	1	0	27
	<i>IgE and/or non-IgE-type</i>	5	7	25	5	1	0*	36
5 months	<i>IgE-type</i>	8	39	21	12	3	5	63
	<i>Non-IgE-type</i>	3	22	28	7	2	6	52
	<i>IgE and/or non-IgE-type</i>	10	52	39	16	3	9	98
6 months	<i>IgE-type</i>	13	20	8	7	3	1	41
	<i>Non-IgE-type</i>	3	8	8	1	1	0	19
	<i>IgE and/or non-IgE-type</i>	14	26	16	7	3	1	55
4-6 months	<i>IgE-type</i>	22	52	33	18	6	6	99
	<i>Non-IgE-type</i>	10	28	46	11	4	6	82
	<i>IgE and/or non-IgE-type</i>	27	68	63	25	7	10	149

Symptoms were divided into IgE-type (urticaria, angioedema, acute rash, respiratory symptoms, acute vomiting) or non-IgE-type symptoms (diarrhoea, constipation, reflux, delayed vomiting, delayed rash, eczema)

*Wheat not introduced before 4 months of age in EIG

†Symptoms to one or more of the six early introduction allergenic foods

Supplementary Appendix Figure Legends

FIG E1. Likely true adherence status of the EIG adherence nonevaluable participants

For each of the six early introduction foods, in the left hand panels, the percentage of the weekly recommended dose of allergenic protein consumed from enrollment to 12 months of age is presented by *overall adherence status*. The EIG group is divided into those who were overall adherent (N=223; blue line), those who were overall nonadherent (N=306; red line), and those in whom overall adherence was nonevaluable (N=123; green line).

The middle panels show the percentage of the weekly recommended dose of allergenic protein consumed by *food-specific adherence status*. Food-specific adherence varied considerably by food and significantly exceeded overall adherence for a number of foods (Table E3). The number of EIG participants who were adherent (blue), nonadherent (red) and adherence nonevaluable (green) for each specific food is shown in the respective middle panel.

In the right hand panels, instead of looking at the weekly dose being consumed, as in the left and central panels, the percentage of EIG infants who were consuming a specific food at the per-protocol threshold (75% or more of the recommended dose) is presented.

FIG E2. The association between EIG overall adherence status and the weekly total number of allergenic foods being consumed at per-protocol level and weekly achievement of consumption of five or more foods at 75% or more of the recommended dose in the key early introduction period (to six months of age)

Panel A shows the number of foods being consumed at or above the per-protocol threshold at any particular time point by overall adherence status. Panel B shows the percentage of EIG participants who were meeting or exceeding the per-protocol definition of five or more foods being consumed at 75% or more of the recommended dose by overall adherence status. In Panel C, the interim questionnaire completion rate is shown for the 123 EIG participants whose overall adherence status was nonevaluable.

FIG E3. Order of introduction of the four randomised foods and overall and food-specific per-protocol adherence

The order of introduction of four of the six allergenic foods (peanut, egg, fish and sesame) was determined randomly. The effect of the position in the order in which each of these four foods was introduced on food-specific per-protocol compliance and overall per-protocol compliance is presented.

FIG E4. Effect of ethnicity, maternal age, eczema SCORAD severity group and parent reported feeding difficulties at 4 months of age on the weekly total number of allergenic foods being consumed at per-protocol level by the EIG and weekly achievement of consumption of five or more foods at 75% or more of the recommended dose.

The left hand panels show the number of foods being consumed at or above the per-protocol threshold at any particular time point by: Panel A Ethnicity; Panel B Maternal age; Panel C Enrollment eczema severity; and Panel D Family reported infant feeding difficulty at 4 months of age. The right hand panels show the percentage of EIG participants who were meeting or exceeding the per-protocol definition of five or more foods being consumed at 75% or more of the recommended dose. This figure excludes the seven enrollment challenge positive infants (1 wheat, 4 milk, 2 egg and 2 peanut) who were instructed to avoid consumption of that food completely.

FIG E5. EIG enrollment IgE sensitization and the development of food allergy

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 development of food allergy to specific foods, or to one or more of the six early introduction foods (primary outcome).

FIG E6. Consumption of each allergenic food by enrollment specific IgE sensitization status

Each panel shows the percentage of the recommended weekly dose of each allergenic food consumed, by enrollment specific IgE sensitization (0.1 kU/l or greater) to that food. Numbers of EIG participants nonsensitized are in blue and sensitized in red. In brackets are the number of EIG participants who were sensitized on skin prick testing to the specific food (wheal ≥ 1 mm). This figure excludes the seven enrollment challenge positive infants (1 wheat, 4 milk, 2 egg and 2 peanut) who were instructed to avoid consumption of that food completely.

FIG E7. Parent reporting of IgE and non-IgE type symptoms to early introduction foods, or any other food, by adherence status

The percentage of participants reporting any symptoms (left hand panels), IgE type symptoms (central panels) and non-IgE type symptoms (right hand panels) with food consumption is shown for each month from enrollment to 12 months of age. Top row is for symptoms with one or more of the six early introduction foods, middle row is for symptoms with any other food and bottom row is for symptoms with any food. Data are presented for the adherent SIG participants (blue line), adherent EIG participants (red line) and nonadherent EIG participants (green line).

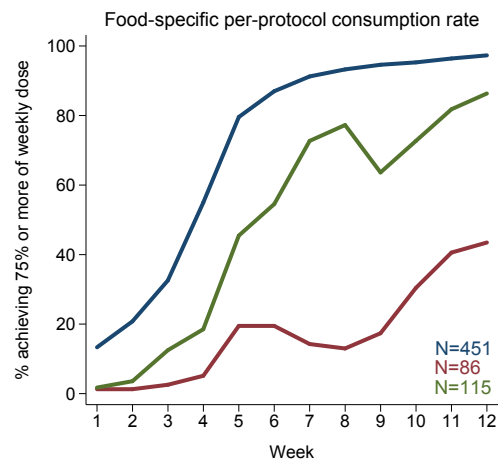
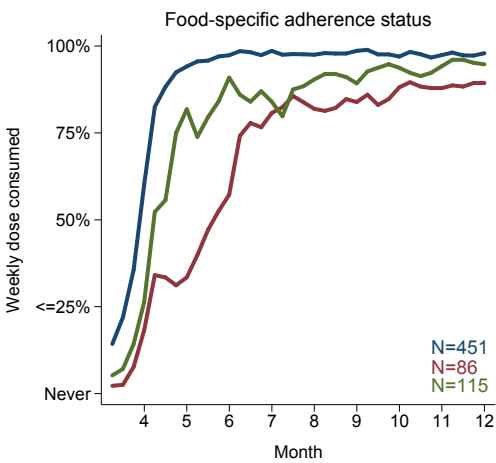
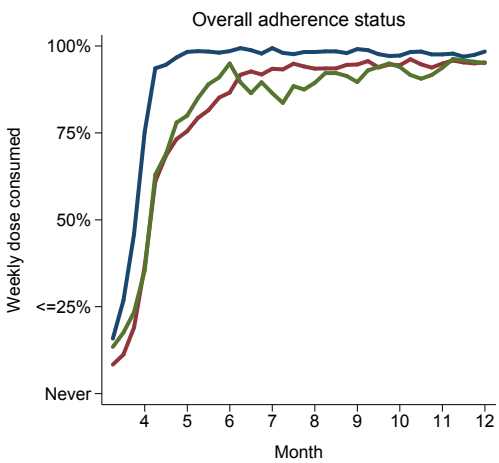
FIG E8. The reporting in the key early introduction period (up to six months) of IgE-type symptoms to specific foods, IgE or non-IgE-type symptoms to any of the early introduction foods, and the association with food-specific and overall food allergy

Penalized logistic regression of the association between parent reported symptoms with consumption of the six allergenic foods reported by 6 months of age and the development of food allergy to one or more foods (primary outcome), or to specific foods. 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.

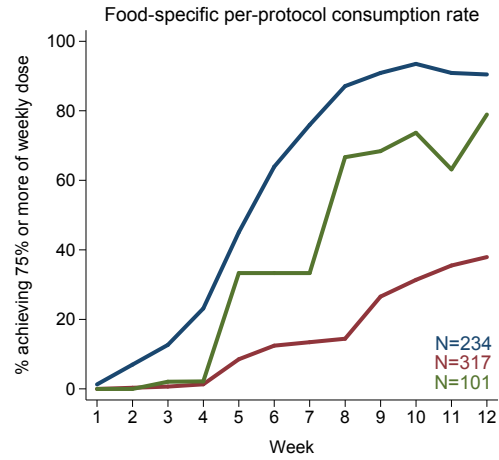
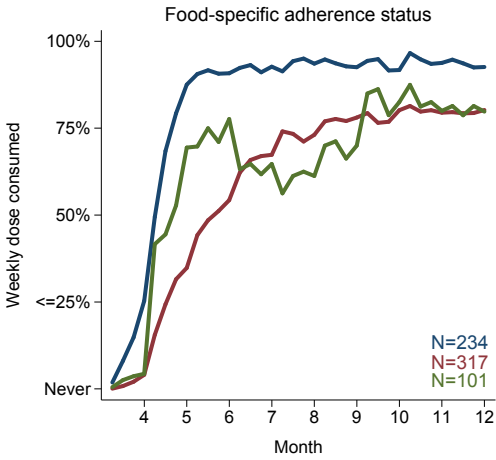
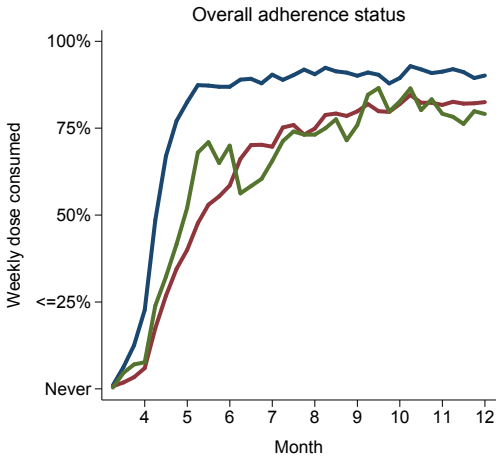
FIG E9. Interrelationship between ethnicity, enrollment IgE sensitization and enrollment visible eczema in both EAT study groups and their effects on per-protocol adherence and the development of food allergy

The Venn diagram examines how the combination of risk factors for allergy and per-protocol adherence are related. Rectangular areas represent the total number of participants in the respective ethnic group. All areas, rectangles and Venn diagrams, are to scale with regards to the number of participants. Within each region of the diagram, the sample size and percentage of the respective ethnic group is indicated on the top row. The second row displays the per-protocol adherence rate in the EIG and SIG participants respectively in the specific region. The third row displays the primary outcome of food allergy prevalence in the EIG and SIG participants respectively in the specific region.

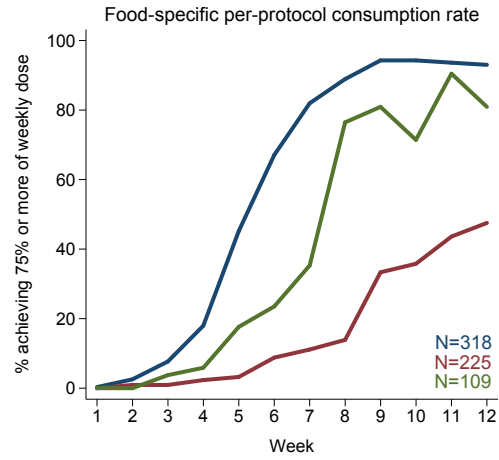
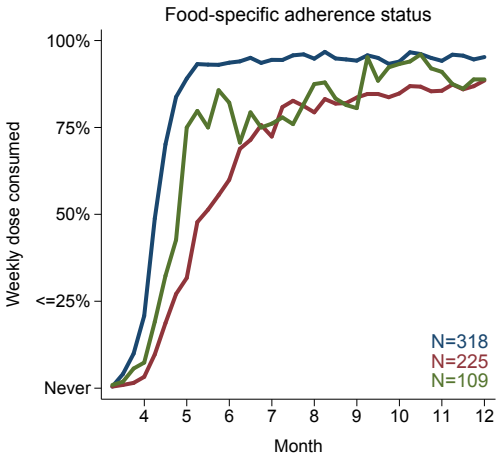
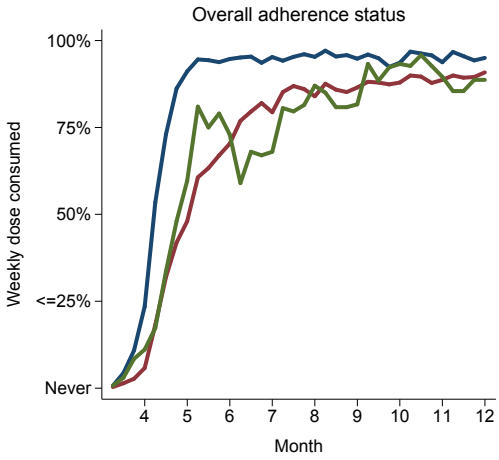
Milk



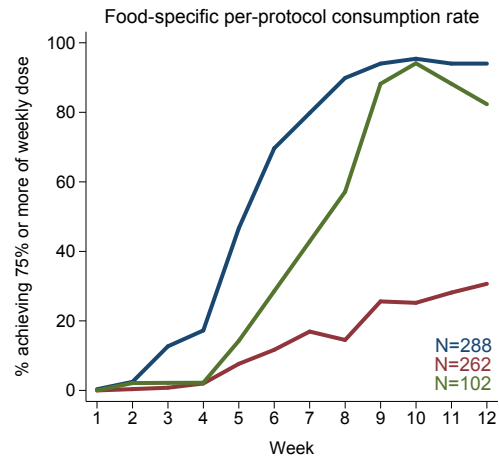
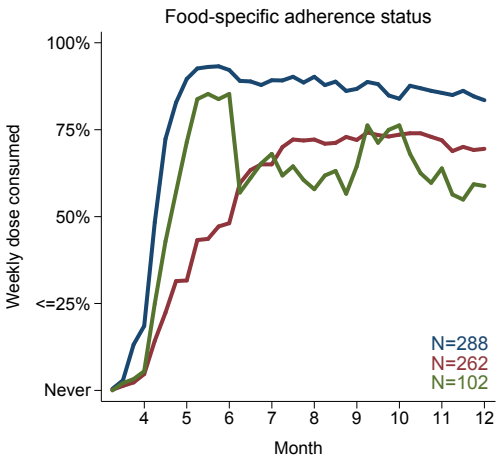
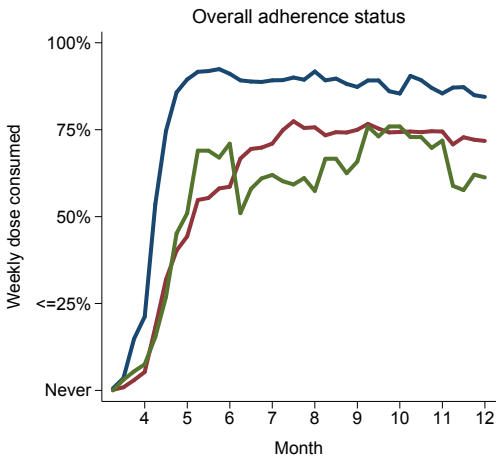
Egg



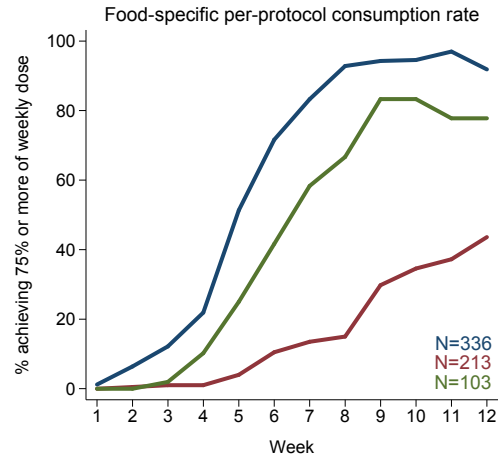
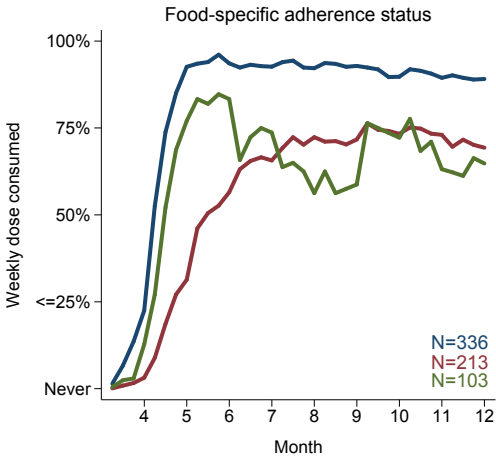
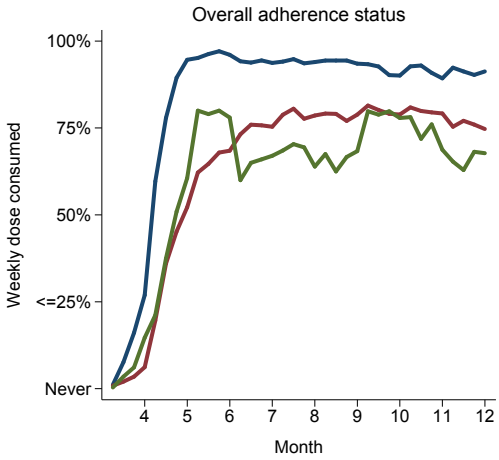
Fish



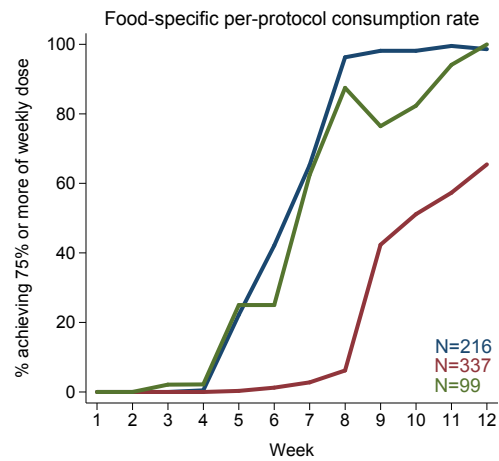
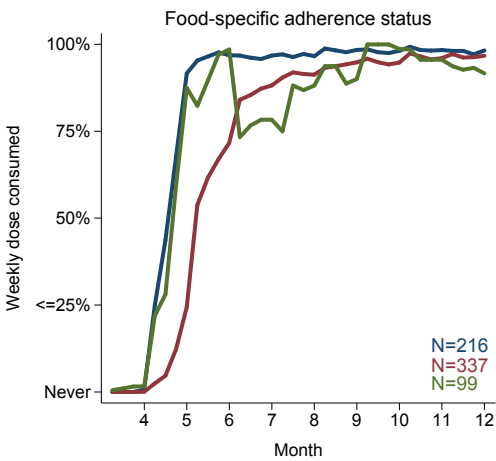
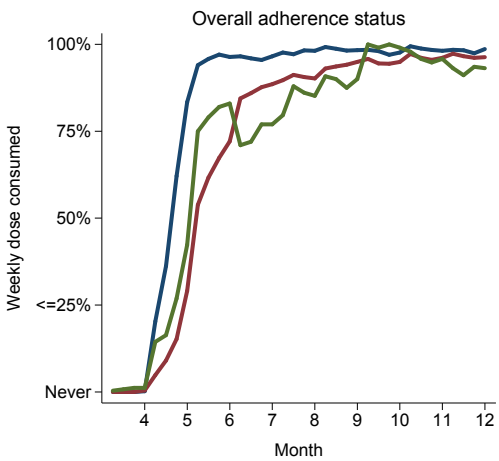
Sesame



Peanut



Wheat

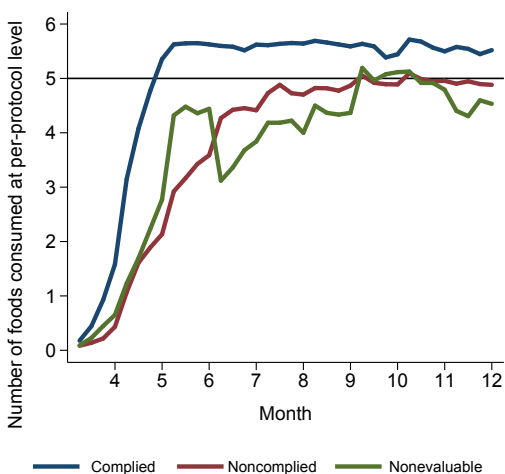


Complied

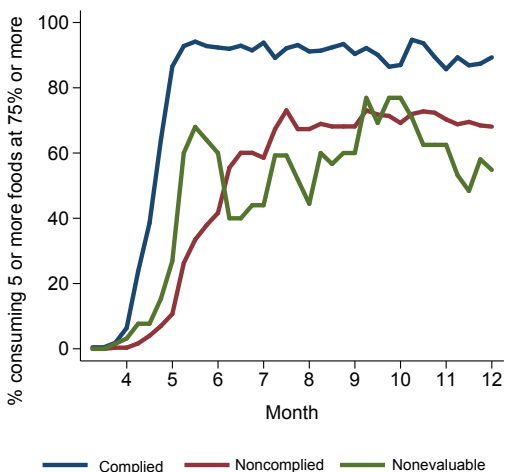
Noncomplied

Nonevaluable

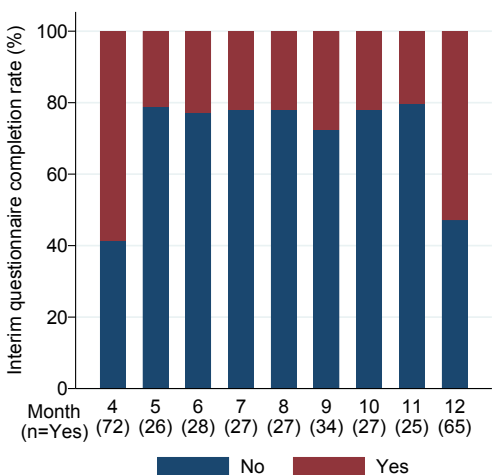
A. Number of foods

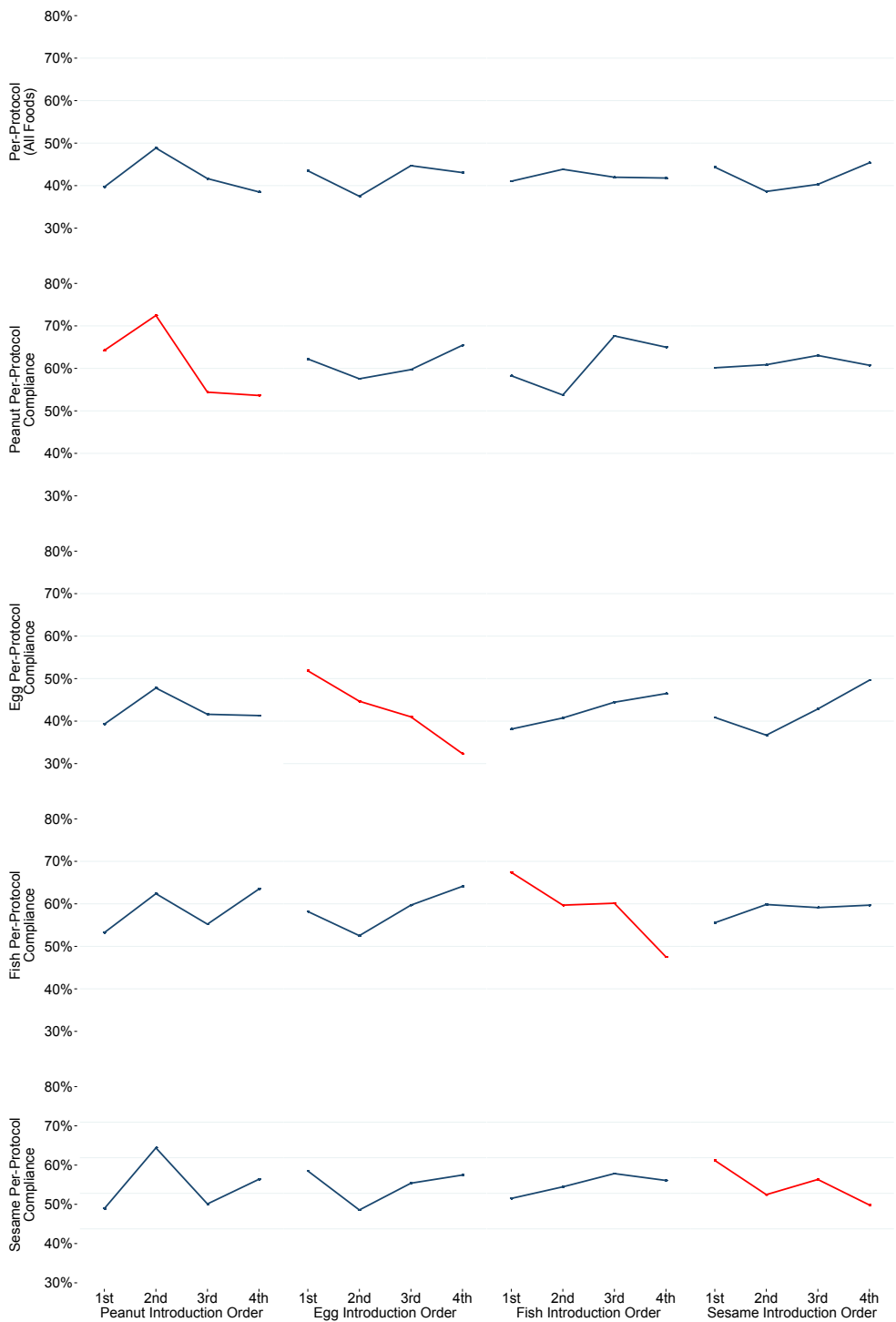


B. Percentage achieving 5 or more foods

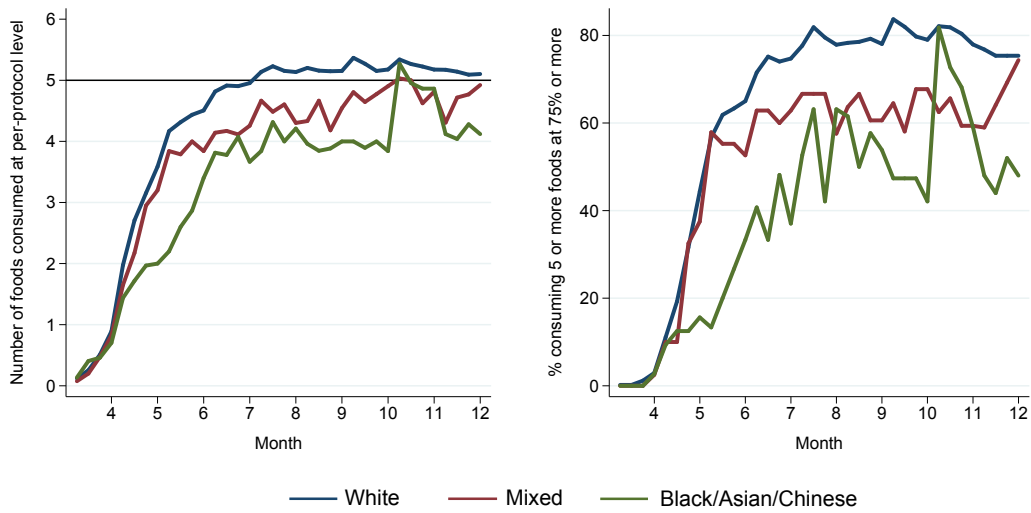


C. IQ completion by nonevaluable participants (N=123)

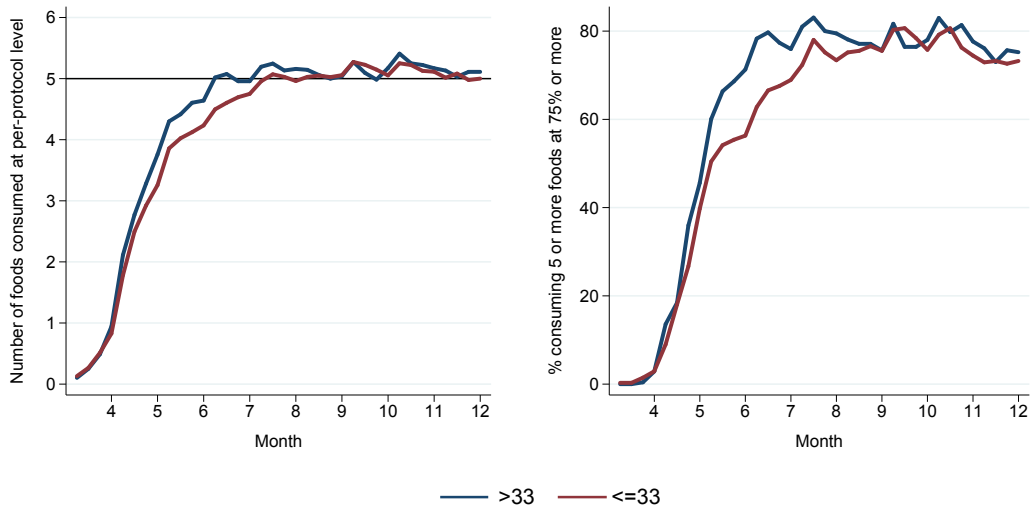




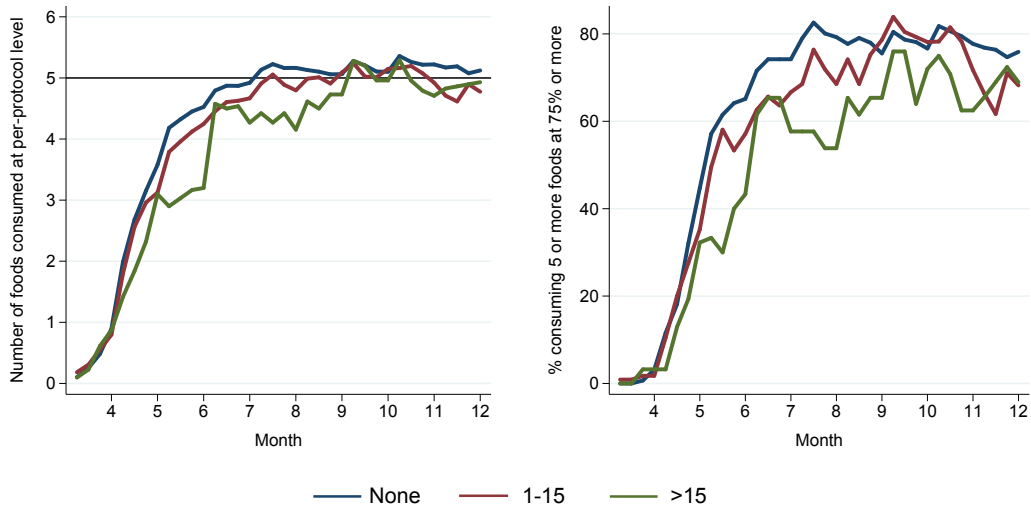
A: Ethnicity



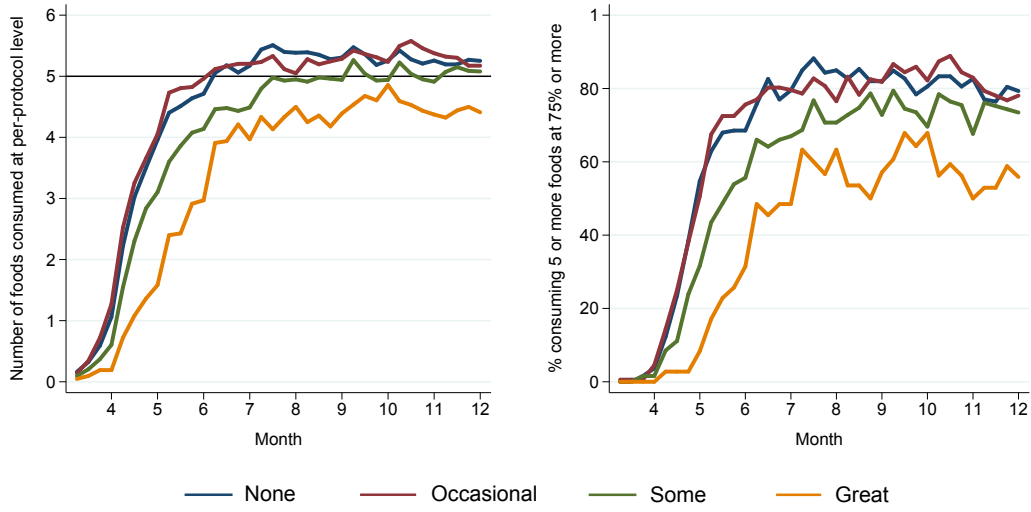
B: Maternal age



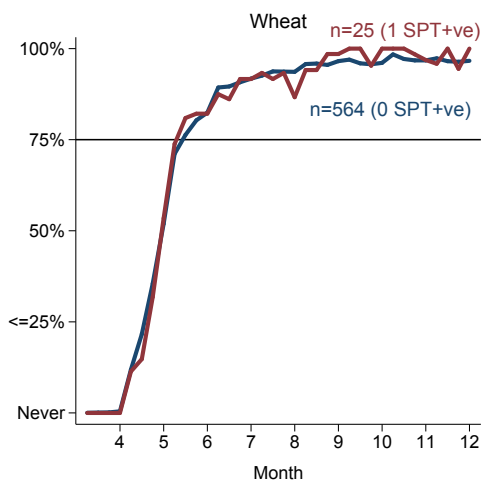
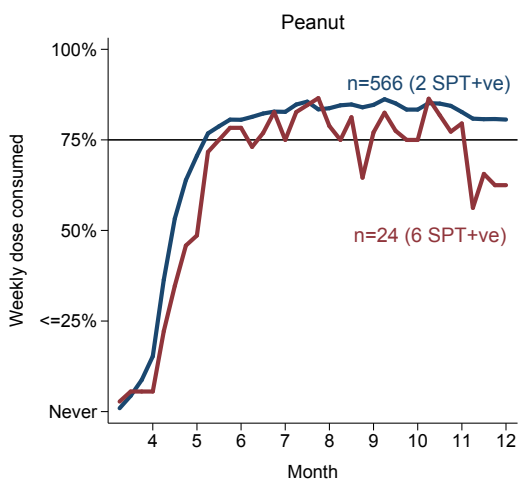
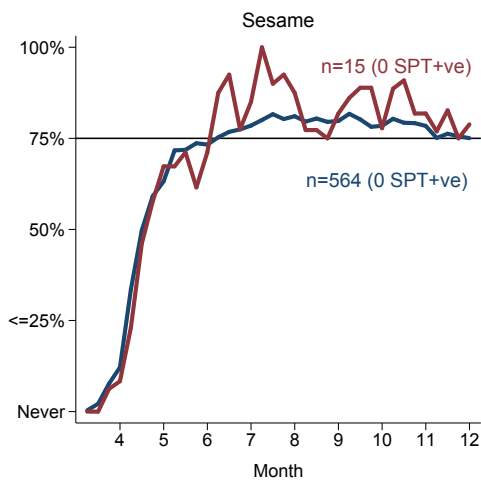
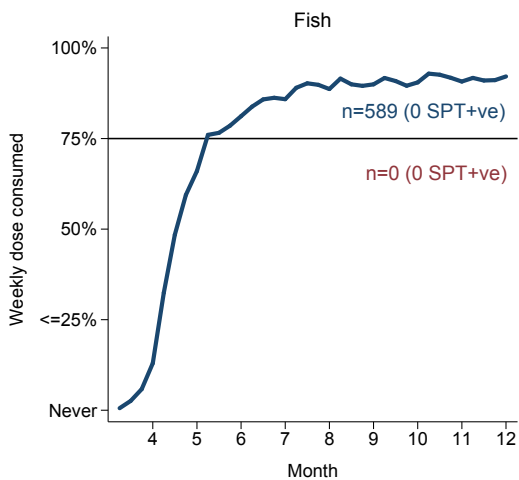
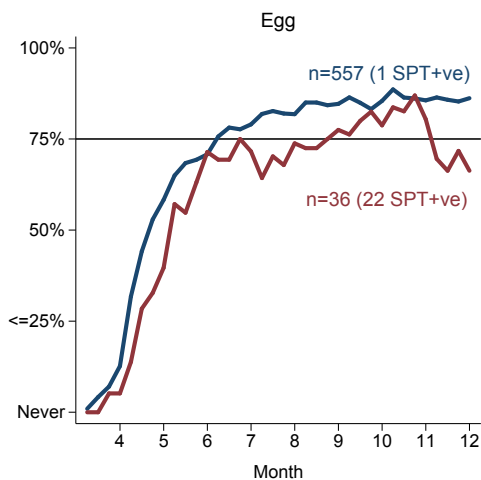
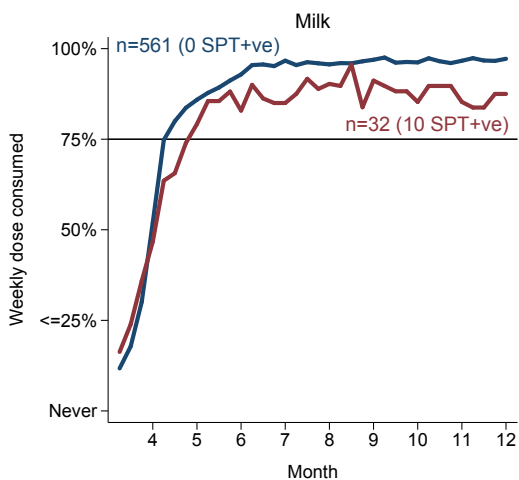
C: Eczema severity



D: Feeding difficulty 4m

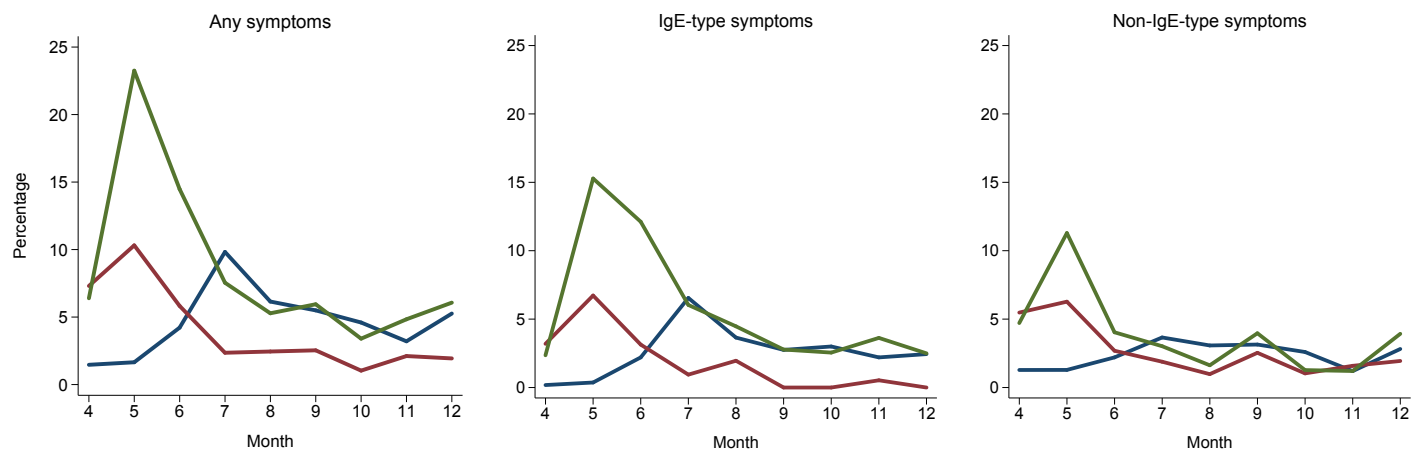


[illegible]

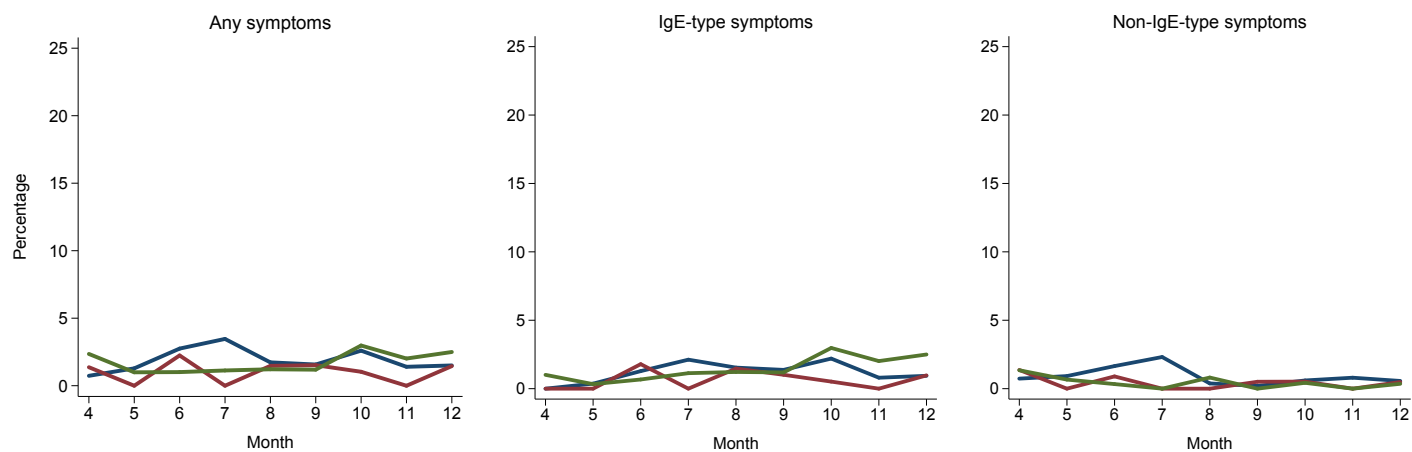


— Not sensitized — Sensitized (0.1 kU/l or greater)

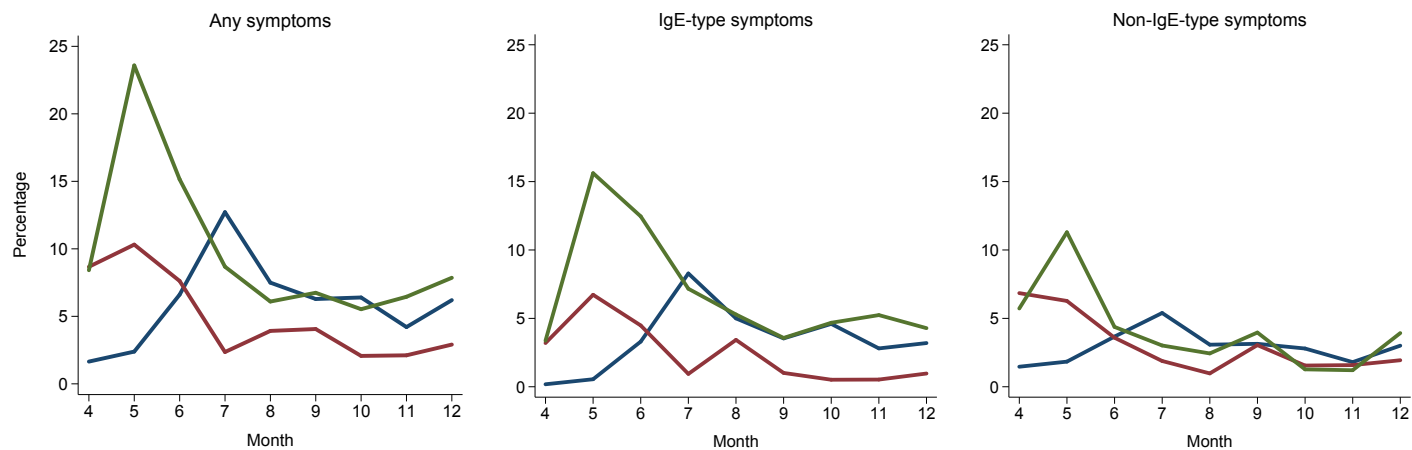
A. Symptoms with one or more of six early introduction foods



B. Symptoms with any other food



A. or B. Symptoms with any food

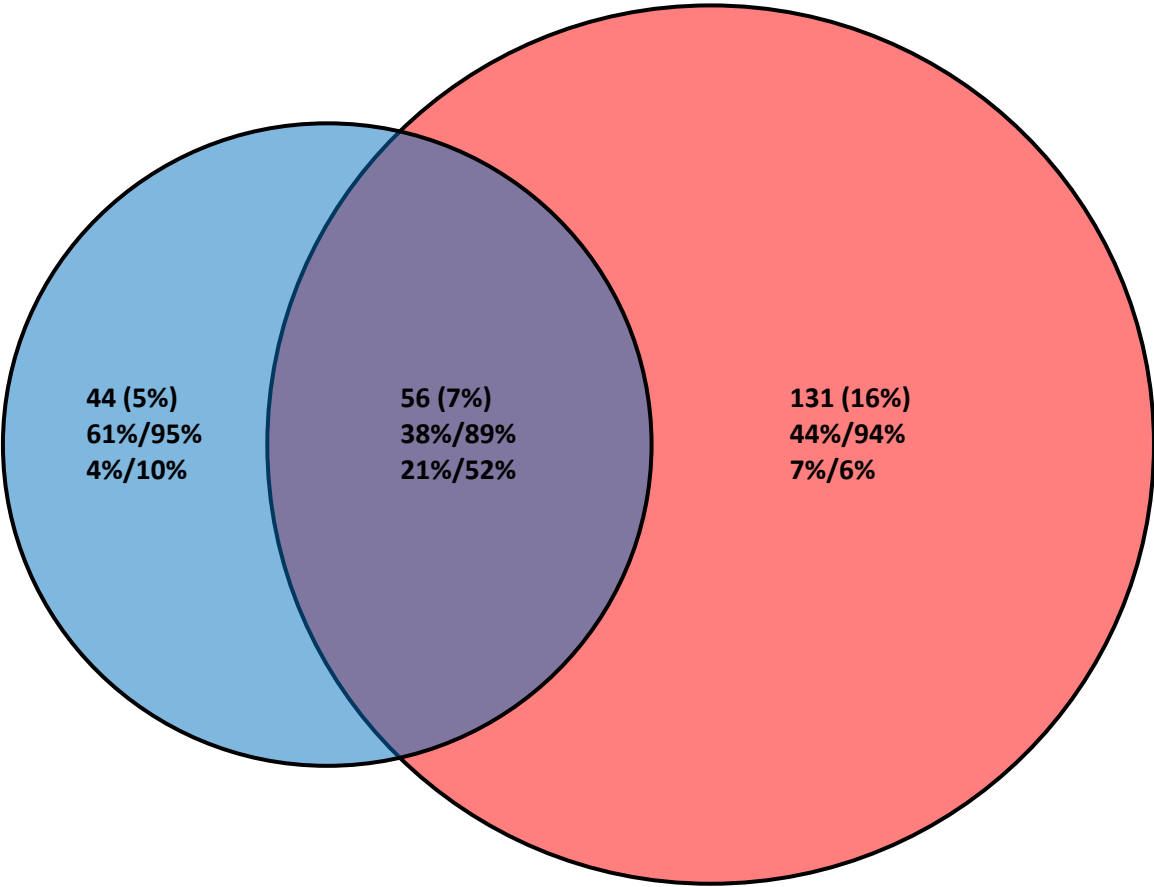


— SIG Complied
 — EIG complied
 — EIG noncomplied

EIG allergy to individual foods	Primary outcome Allergy to one or more foods (n=28)	1.25 (0.23-6.83) 0.80	7.34 (3.31-16.3) <0.001	5.09 (1.97-13.2) 0.001	1.48 (0.27-8.21) 0.65	1.80 (0.09-34.1) 0.70	4.55 (0.72-28.7) 0.11	7.01 (3.35-14.7) <0.001	6.71 (3.17-14.2) <0.001
	Wheat (n=1)	8.59 (0.34-217) 0.19	3.36 (0.14-83.7) 0.46	5.48 (0.22-137) 0.30	10.1 (0.40-257) 0.16	40.3 (1.44-1130) 0.03	27.8 (1.03-749) 0.05	1.60 (0.06-39.7) 0.77	2.23 (0.09-55.2) 0.63
	Fish (n=0)	8.61 (0.34-217) 0.19	3.37 (0.14-83.8) 0.46	5.49 (0.22-137) 0.30	10.1 (0.40-258) 0.16	40.4 (1.44-1131) 0.03	27.9 (1.04-750) 0.05	1.61 (0.06-39.7) 0.77	20.1 (0.81-498) 0.07
	Sesame (n=2)	3.68 (0.18-73.5) 0.39	1.44 (0.07-28.3) 0.81	2.34 (0.12-46.3) 0.58	4.33 (0.22-87.1) 0.34	17.3 (0.77-385) 0.07	11.9 (0.56-254) 0.11	0.69 (0.04-13.4) 0.80	4.00 (0.52-30.7) 0.18
	Milk (n=2)	3.65 (0.18-73.0) 0.40	1.49 (0.08-29.3) 0.79	30.1 (3.85-236) 0.001	19.2 (2.39-154) 0.005	17.1 (0.77-382) 0.07	11.8 (0.55-253) 0.11	8.4 (1.09-64.0) 0.04	4.03 (0.52-31.0) 0.18
	Egg (n=20)	2.00 (0.36-11.2) 0.43	15.7 (6.13-40.2) <0.001	4.95 (1.63-15.0) 0.005	0.71 (0.04-12.2) 0.81	2.83 (0.15-54.4) 0.49	7.29 (1.13-46.9) 0.04	15.9 (5.83-43.2) <0.001	7.57 (3.09-18.5) <0.001
	Peanut (n=7)	6.18 (0.99-38.6) 0.05	2.40 (0.40-14.5) 0.34	4.01 (0.65-24.6) 0.13	2.00 (0.11-36.4) 0.64	7.96 (0.39-161) 0.18	5.49 (0.28-107) 0.26	2.24 (0.49-10.1) 0.30	3.14 (0.69-14.3) 0.14
		Peanut (n=22)	Egg (n=52)	Milk (n=33)	Sesame (n=18)	Fish (n=6)	Wheat (n=6)	Any IgE- type symptoms (n=99)	Any non- IgE-type symptoms (n=82)
Food-specific IgE-type symptoms reported up to 6 months									

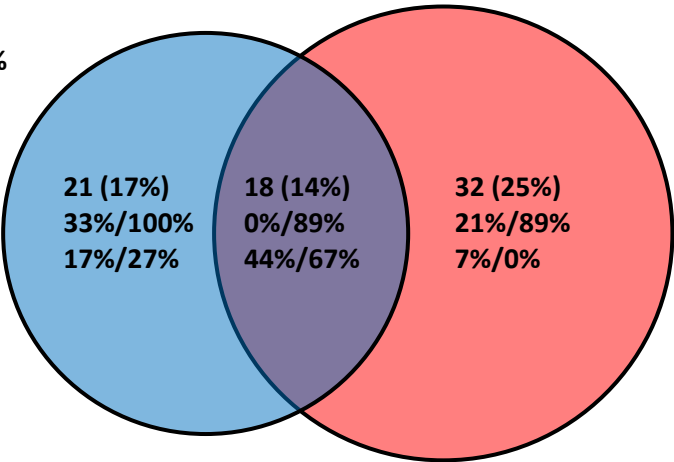
White (n=816)

No eczema or sensitization at enrollment
585 (72%)
46%/94%
1%/3%



Nonwhite (n=126)

No eczema or sensitization at enrollment
55 (44%)
36%/91%
0%/0%



Key

IgE sensitized (≥0.1kU/l) one or more foods

Visible eczema at enrollment

N (%) in each region
Probability of EIG/SIG per-protocol adherence
Probabilty of food allergy EIG/SIG