

ORIGINAL ARTICLE

Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants

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ABSTRACT

BACKGROUND

The age at which allergenic foods should be introduced into the diet of breast-fed infants is uncertain. We evaluated whether the early introduction of allergenic foods in the diet of breast-fed infants would protect against the development of food allergy.

METHODS

We recruited, from the general population, 1303 exclusively breast-fed infants who were 3 months of age and randomly assigned them to the early introduction of six allergenic foods (peanut, cooked egg, cow's milk, sesame, whitefish, and wheat; early-introduction group) or to the current practice recommended in the United Kingdom of exclusive breast-feeding to approximately 6 months of age (standard-introduction group). The primary outcome was food allergy to one or more of the six foods between 1 year and 3 years of age.

RESULTS

In the intention-to-treat analysis, food allergy to one or more of the six intervention foods developed in 7.1% of the participants in the standard-introduction group (42 of 595 participants) and in 5.6% of those in the early-introduction group (32 of 567) ($P=0.32$). In the per-protocol analysis, the prevalence of any food allergy was significantly lower in the early-introduction group than in the standard-introduction group (2.4% vs. 7.3%, $P=0.01$), as was the prevalence of peanut allergy (0% vs. 2.5%, $P=0.003$) and egg allergy (1.4% vs. 5.5%, $P=0.009$); there were no significant effects with respect to milk, sesame, fish, or wheat. The consumption of 2 g per week of peanut or egg-white protein was associated with a significantly lower prevalence of these respective allergies than was less consumption. The early introduction of all six foods was not easily achieved but was safe.

CONCLUSIONS

The trial did not show the efficacy of early introduction of allergenic foods in an intention-to-treat analysis. Further analysis raised the question of whether the prevention of food allergy by means of early introduction of multiple allergenic foods was dose-dependent. (Funded by the Food Standards Agency and others; EAT Current Controlled Trials number, ISRCTN14254740.)

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THE WORLD HEALTH ORGANIZATION recommends exclusive breast-feeding of infants for their first 6 months of life.¹ Two national guidelines that had previously recommended the delayed introduction of allergenic foods have been withdrawn (see the Introduction section in the Supplementary Appendix, available with the full text of this article at NEJM.org). In the 2010 United Kingdom Infant Feeding Survey, 45% of the mothers of infants 8 to 10 months of age reported avoiding giving their infant a particular food: 48% avoided nuts, 14% eggs, 10% dairy, and 6% fish.² Fear of allergy was the most common reason for avoiding foods, followed by a belief that the baby was too young.

Observational studies suggest that the early introduction of peanut,³ egg,⁴ or cow's milk⁵ may prevent the development of allergy to these foods. The randomized, controlled Learning Early about Peanut Allergy (LEAP) trial showed that the early consumption of peanut in high-risk infants with severe eczema, egg allergy, or both reduced the development of peanut allergy by 80% by 5 years of age.⁶ The Persistence of Oral Tolerance to Peanut (LEAP-On) study has now shown that the absence of reactivity is maintained in these infants.⁷ However, the LEAP trial did not investigate the efficacy of introduction of other allergenic foods, nor did it examine whether this approach could prevent peanut allergy in children in the general population. The Enquiring about Tolerance (EAT) trial was therefore conceived to determine whether the early introduction of common dietary allergens (peanut, cooked hen's egg, cow's milk, sesame, whitefish, and wheat) from 3 months of age in exclusively breast-fed infants in the general population would prevent food allergies, as compared with infants who were exclusively breast-fed for approximately 6 months.

METHODS

TRIAL DESIGN

This randomized, controlled trial was conducted at a single site in the United Kingdom. Ethics approval was provided by the St. Thomas' Hospital research ethics committee. Written informed consent was obtained from parents or guardians, and safety data were reviewed by an independent data and safety monitoring committee. The trial protocol is available at NEJM.org.

TRIAL PROCEDURES

Enrollment took place from November 2, 2009, to July 30, 2012. Details of the trial procedures have been published previously.⁸ Singleton infants who were 3 months of age and exclusively breast-fed were recruited from the general population in England and Wales. Participants were randomly assigned by an independent online service to the standard-introduction group or the early-introduction group (Fig. S1 in the Supplementary Appendix). Participants in the standard-introduction group were to be exclusively breast-fed to approximately 6 months of age. After 6 months of age, the consumption of allergenic foods was allowed according to parental discretion. After skin-prick testing in duplicate at baseline, participants in the early-introduction group had six allergenic foods introduced: cow's milk (yogurt) first, followed (in random order) by peanut, cooked (boiled) hen's egg, sesame, and whitefish; wheat was introduced last. The infants in the standard-introduction group did not undergo skin-prick testing at baseline because the results could have influenced the timing of the introduction of allergenic foods.

Infants in the early-introduction group who had a wheal of any size on skin-prick testing at baseline underwent an open-label incremental food challenge totaling 2 g of protein of that food. Families of infants in the early-introduction group who had negative results on skin-prick testing or who had positive results on skin-prick testing but negative results on the food challenge were asked to continue feeding their infants 2 g of the allergen protein twice weekly. Families of infants who had a positive result on the food challenge at baseline were instructed to avoid giving the infants that food but to continue feeding the infants the other foods.

All the families completed an online questionnaire each month to 1 year of age, and then every 3 months until the child reached 3 years of age. This questionnaire recorded the frequency of consumption of allergenic foods in the two groups. In addition, the parents of the participants in the early-introduction group kept a weekly diary to record the quantity of the six foods consumed.⁸

Peanut-protein levels were measured in dust collected from the participant's bed at 3 months of age (before the consumption of allergenic foods commenced in the early-introduction group) and at 12 months of age as an indepen-



A Quick Take is available at NEJM.org

dent measure of adherence to the dietary intervention.^{9,10} Participants had scheduled assessments at 1 year of age and 3 years of age and had unscheduled clinic visits for the investigation of parent-reported symptoms that were suggestive of food allergy. Additional details are provided in the Methods section and Tables S1, S2, and S3 and Figs. S2, S3, and S4 in the Supplementary Appendix.

OUTCOMES

The primary outcome was challenge-proven food allergy to one or more of the six early-introduction foods between 1 year and 3 years of age. In two exceptional circumstances, reactions to foods that occurred before 1 year of age were also included in the primary outcome. Categories of evidence for food allergy are presented in the Methods section in the Supplementary Appendix. Secondary outcomes were allergy to individual foods and positive results on skin-prick testing for individual foods.

STATISTICAL ANALYSIS

The statistical analysis followed a prespecified analysis plan. Post hoc analyses included a dominance analysis of factors contributing to having a positive result with respect to the primary outcome and to not adhering to the protocol in the two study groups. Dominance analysis discerns the relative importance of independent variables in an estimation model on the basis of the contribution of each variable to the fit statistics of the overall model (all post hoc analyses are listed in the Methods section in the Supplementary Appendix).

The intention-to-treat analysis for the primary outcome included all the participants who had data that could be evaluated. The analysis, which compared the proportion of participants in the two groups who had food allergy to one or more of the early-introduction foods, was performed with a chi-square test. For secondary analyses, comparisons were made with the chi-square test or Fisher's exact test, as appropriate. The trial had 80% power at the 5% significance level to detect a halving of the prevalence of food allergy, from 8% in the standard-introduction group to 4% in the early-introduction group.⁸

The per-protocol population included all participants who adhered adequately to the assigned regimen, which was defined as follows. In each group, breast-feeding was continued to

at least 5 months of age. In the standard-introduction group, there was no consumption of peanut, egg, sesame, fish, or wheat before 5 months of age and consumption of less than 300 ml per day of formula milk between 3 and 6 months of age. In the early-introduction group, there was consumption of at least five of the early-introduction foods, for at least 5 weeks between 3 and 6 months of age, of at least 75% of the recommended dose (i.e., 3 g per week of allergenic protein). The per-protocol population for food-specific allergy used the same consumption criterion — consumption for at least 5 weeks between 3 and 6 months of age of at least 75% of the recommended dose of that food (i.e., 3 g per week of allergenic protein). The data set will be made publicly available by August 2017.

RESULTS

PARTICIPANT POPULATION

The median age of the participants at enrollment was 3.4 months. The two groups were balanced, except for a significantly higher rate of birth by cesarean section in the early-introduction group than in the standard-introduction group (Table S4 in the Supplementary Appendix). A total of 91.3% of the participants attended the final clinic visit, 90.0% of whom attended within the visit window (by 4 years of age). A total of 94.0% of the participants' families completed the 3-year questionnaire.

FOOD ALLERGY

A food allergy developed in 74 participants. In 70 of these participants (39 in the standard-introduction group and 31 in the early-introduction group), diagnoses were made on the basis of double-blind, placebo-controlled food challenges (primary-outcome categories 1A and 1B), and in 4 (3 in the standard-introduction group and 1 in early-introduction group), diagnoses were made on the basis of an allergic reaction that resulted in a wheal size of 5 mm or more in diameter on skin-prick testing (primary-outcome category 3). A diagnosis of any food allergy was significantly associated with the presence of eczema at enrollment, nonwhite race, and having siblings. In the post hoc dominance analysis, these three factors accounted for 92.6% of the variation in the fit statistic of the overall logistic model (Table S5 in the Supplementary Appendix).

FOOD CONSUMPTION AND ALLERGY IN THE INTENTION-TO-TREAT ANALYSES

For the primary outcome, 595 of 651 enrolled participants (91.4%) in the standard-introduction group and 567 of 652 (87.0%) in the early-introduction group were included in the intention-to-treat analysis (Fig. S1 in the Supplementary Appendix). The rate of the primary outcome was nonsignificantly lower in the early-introduction group than in the standard-introduction group (5.6% [32 of 567 participants] and 7.1% [42 of 595], respectively), which represented a relative risk of 0.80 (95% confidence interval [CI], 0.51 to 1.25; $P=0.32$), with the point estimate representing a 20% lower prevalence in the early-introduction group (Fig. 1, and Table S6 in the Supplementary Appendix). The prevalence of allergy to more than one food was nonsignificantly lower in the early-introduction group than in the standard-introduction group ($P=0.17$) (Table S7 in the Supplementary Appendix).

Peanut allergy occurred in 1.2% of the participants in the early-introduction group and in 2.5% of those in the standard-introduction group, representing a nonsignificant 51% lower relative risk in the early-introduction group ($P=0.11$). Egg allergy occurred in 3.7% of the participants in the early-introduction group and in 5.4% of those in the standard-introduction group, representing a nonsignificant 31% lower relative risk in the early-introduction group ($P=0.17$) (Fig. 1).

For other early-introduction foods, the prevalence of food allergy was 0.7% or less in each group (Fig. S5 in the Supplementary Appendix). Non-IgE-mediated allergy-type symptoms are discussed in Tables S8 and S9 and the Results section in the Supplementary Appendix.

FOOD CONSUMPTION AND ALLERGY IN THE PER-PROTOCOL ANALYSIS

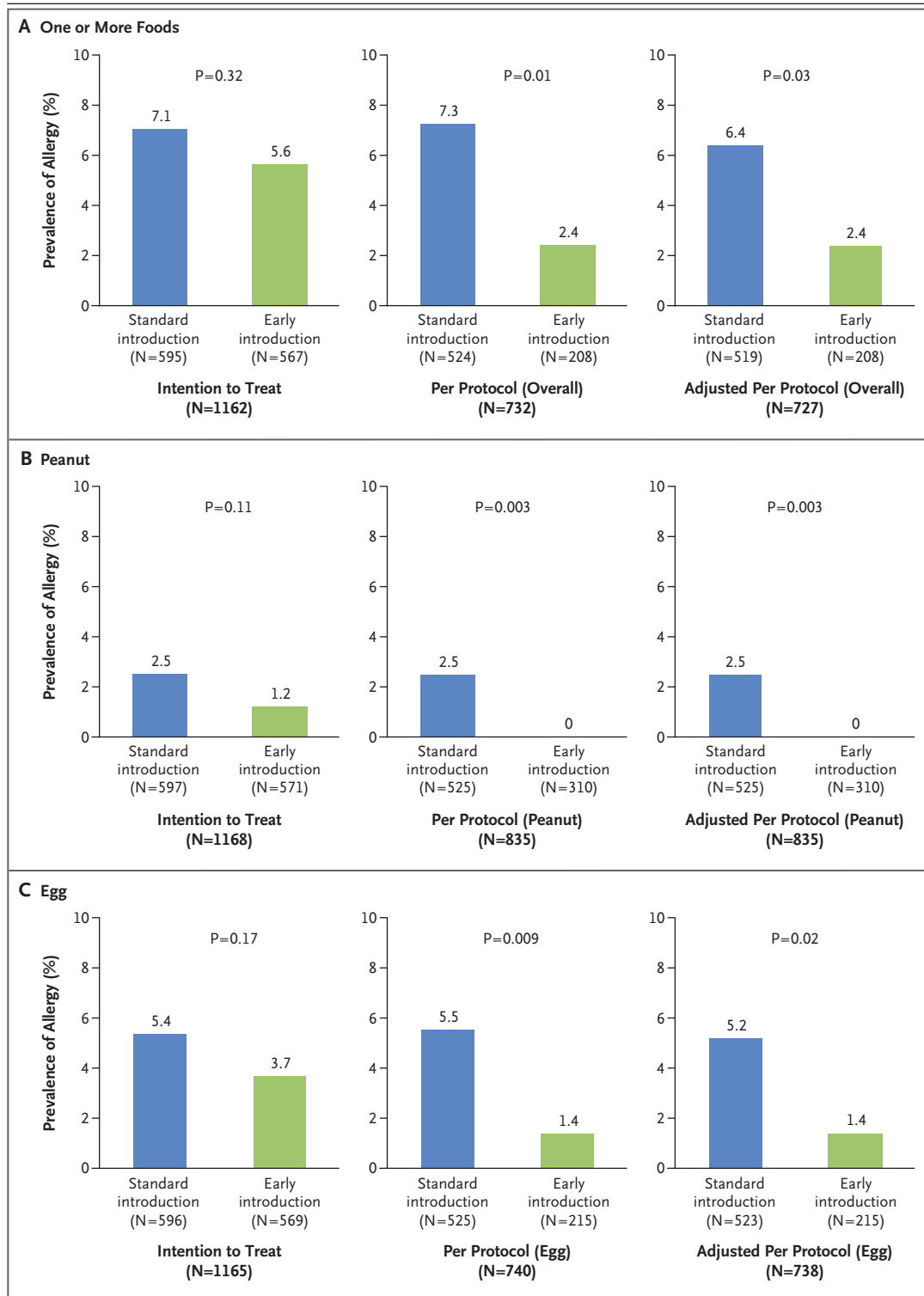
In the per-protocol analysis, the rate of the primary outcome was significantly lower in the early-introduction group than in the standard-introduction group (2.4% [5 of 208 participants] vs. 7.3% [38 of 524]). The relative risk in the early-introduction group was 0.33 (95% CI, 0.13 to 0.83; $P=0.01$), representing a prevalence that was 67% lower than that in the standard-introduction group (Fig. 1).

With regard to food-specific per-protocol consumption, the protective effects with respect to egg and peanut were larger in the early-intro-

Figure 1 (facing page). Primary Outcome of Allergy to One or More Foods and Secondary Outcomes of Allergy to Peanut and to Egg.

The prevalence of IgE-mediated food allergy is shown with respect to one or more of the six early-intervention foods (peanut, cooked egg, cow's milk, sesame, whitefish, and wheat; Panel A), to peanut (Panel B), and to egg (Panel C). The results regarding IgE-mediated food allergy to the other early-introduction foods are shown in Figure S5 in the Supplementary Appendix. The first column shows the intention-to-treat analysis, the second column the per-protocol analysis, and the third column an adjusted per-protocol analysis. The intention-to-treat analysis included all the participants who had data that could be evaluated; the per-protocol population included all participants who adhered adequately to the assigned regimen. The adjusted per-protocol analysis was a conservative per-protocol analysis that adjusted the prevalence of food allergy in the standard-introduction group by subtracting the number of participants in the early-introduction group who had a positive result on the challenge at enrollment and who completed the trial with a confirmed food allergy from both the numerator (the number of participants with allergy in the standard-introduction group) and the denominator (the number of participants in the standard-introduction group who adhered to the protocol). P values are based on chi-square analyses or Fisher's exact test, as appropriate. The relative risks with 95% confidence intervals are shown in Table S6 (intention-to-treat analysis) and Table S10A (per-protocol analysis) in the Supplementary Appendix.

duction group than in the standard-introduction group. In the per-protocol analysis of peanut consumption, there were no cases of peanut allergy among the 310 participants in the early-introduction group, as compared with 13 cases among 525 participants (2.5%) in the standard-introduction group ($P=0.003$) (Fig. 1). The prevalence of egg allergy among participants who adhered to the protocol with respect to egg consumption was 1.4% in the early-introduction group versus 5.5% in the standard-introduction group, representing a 75% lower relative risk ($P=0.009$) (Fig. 1). The rates of food allergy in the per-protocol analysis were lower, but not significantly so, in the early-introduction group than in the standard-introduction group for milk ($P=0.63$) and sesame ($P=0.56$). There were no cases of wheat allergy in either group in the per-protocol analysis. The rate of fish allergy was nonsignificantly higher in the early-introduction group than in the standard-introduction group ($P=1.00$) (Fig. S5 in the Supplementary Appendix).



Although adjustment for multiple testing was not part of the statistical analysis plan, if these six component food tests were adjusted for mul-

tiiple testing with the use of a Bonferroni correction, the critical value for statistical significance would be 0.0085 (i.e., $1-0.95^{1/6}$). Under this

constraint, in the per-protocol analysis the effect on peanut allergy would remain significant, and the results for egg would remain borderline significant (see the Discussion section in the Supplementary Appendix).

Protective effects with respect to the primary outcome and with respect to peanut allergy and egg allergy remained significant in the conservative adjusted per-protocol analysis. This analysis was not adjusted for multiple comparisons (Fig. 1, and the Results section in the Supplementary Appendix).

Participants in the two trial groups who did not adhere to the protocol or whose adherence could not be evaluated had rates of allergy that were similar to the rate among the participants in the standard-introduction group who adhered to the protocol. Statistical comparisons between the participants in the standard-introduction group who adhered to the protocol and the participants in the early-introduction group who did not adhere to the protocol or whose adherence could not be evaluated were all nonsignificant (Table S10B in the Supplementary Appendix).

RESULTS OF SKIN-PRICK TESTING

A similar pattern was seen for the results of skin-prick testing (Fig. 2). In the intention-to-treat analyses, the risk of a positive skin-prick test to any food was 22% lower in the early-introduction group than in the standard-introduction group at 12 months of age ($P=0.07$) and 12% lower at 36 months of age ($P=0.47$); both differences were nonsignificant. Positive skin-prick tests to wheat occurred significantly less frequently in the early-introduction group than in the standard-introduction group at 12 months (1.3% vs. 3.2%, $P=0.03$) and at 36 months of age (1.4% vs. 3.2%, $P=0.04$). The prevalence of positive skin-prick tests at 12 months and 36 months of age was nonsignificantly lower in the early-introduction group than in the standard-introduction group for every other food, with the exception of fish at 12 months of age, which had a higher prevalence in the early-introduction group (Fig. 2, and Fig. S6 and Table S11 in the Supplementary Appendix).

In the per-protocol analyses, the early-introduction group had a significant 42% lower rate of positive skin-prick tests to any food than the standard-introduction group at 12 months of age ($P=0.01$) and a significant 67% lower rate at 36

months of age ($P=0.002$). On food-specific testing, the relative risk of a positive result on skin-prick testing at 12 months of age was consistently lower, by approximately 50%, in the early-introduction group than in the standard-introduction group for every food with the exception of fish; the difference was significant with respect to egg ($P=0.009$) and peanut ($P=0.04$). At 36 months of age, the effect was greater; the relative risk of a positive result on skin-prick testing was 67% lower in the early-introduction group than in the standard-introduction group with respect to peanut ($P=0.007$), 48% lower with respect to egg ($P=0.10$), 88% lower with respect to milk ($P=0.02$), 100% lower with respect to both sesame ($P=0.04$) and fish ($P=0.17$), and 69% lower with respect to wheat ($P=0.12$). The rate of a positive skin-prick test to raw egg white was also lower in the early-introduction group than in the standard-introduction group at 36 months of age; the 49% lower relative risk ($P=0.07$) was similar to that observed with commercial egg extract (Fig. 2, and Table S11 in the Supplementary Appendix).

ADHERENCE TO THE PROTOCOL

A total of 92.9% of the participants in the standard-introduction group whose primary-outcome status could be determined (524 of 564 participants) adhered to the protocol (Fig. S1 in the Supplementary Appendix). In the dominance analysis, shorter duration of maternal education and maternal smoking accounted for the majority of the variation in the fit statistic of the overall model (Tables S12 and S13 in the Supplementary Appendix). A total of 85.6% of the participants in the standard-introduction group consumed no cow's milk formula before 6 months of age.

A total of 42.8% of the participants in the early-introduction group whose primary-outcome status could be determined (208 of 486 participants) adhered to the protocol (representing 31.9% of the total number of participants enrolled in the early-introduction group) (Fig. S1 in the Supplementary Appendix). Four factors accounted for 78% of the nonadherence in the dominance analysis: nonwhite race (odds ratio, 2.21; 95% CI, 1.18 to 4.14), parentally perceived symptoms in the child related to any of the early-introduction foods (odds ratio, 1.70; 95% CI, 1.02 to 2.86), reduced maternal quality of life

Figure 2. Secondary Outcome of Results on Skin-Prick Testing.

The prevalence of a positive skin-prick test (wheal of any size) is shown for one or more of the six early-intervention foods (Panel A), peanut (Panel B), egg (Panel C), and raw egg white (Panel D); this test was performed only at the 36-month visit). Results of skin-prick testing for the other early-introduction foods are shown in Figure S6 in the Supplementary Appendix. The first column shows the intention-to-treat analysis, and the second column the per-protocol analysis. P values are based on chi-square analyses. The group-specific denominators and relative risks with 95% confidence intervals are shown in Table S11 in the Supplementary Appendix.

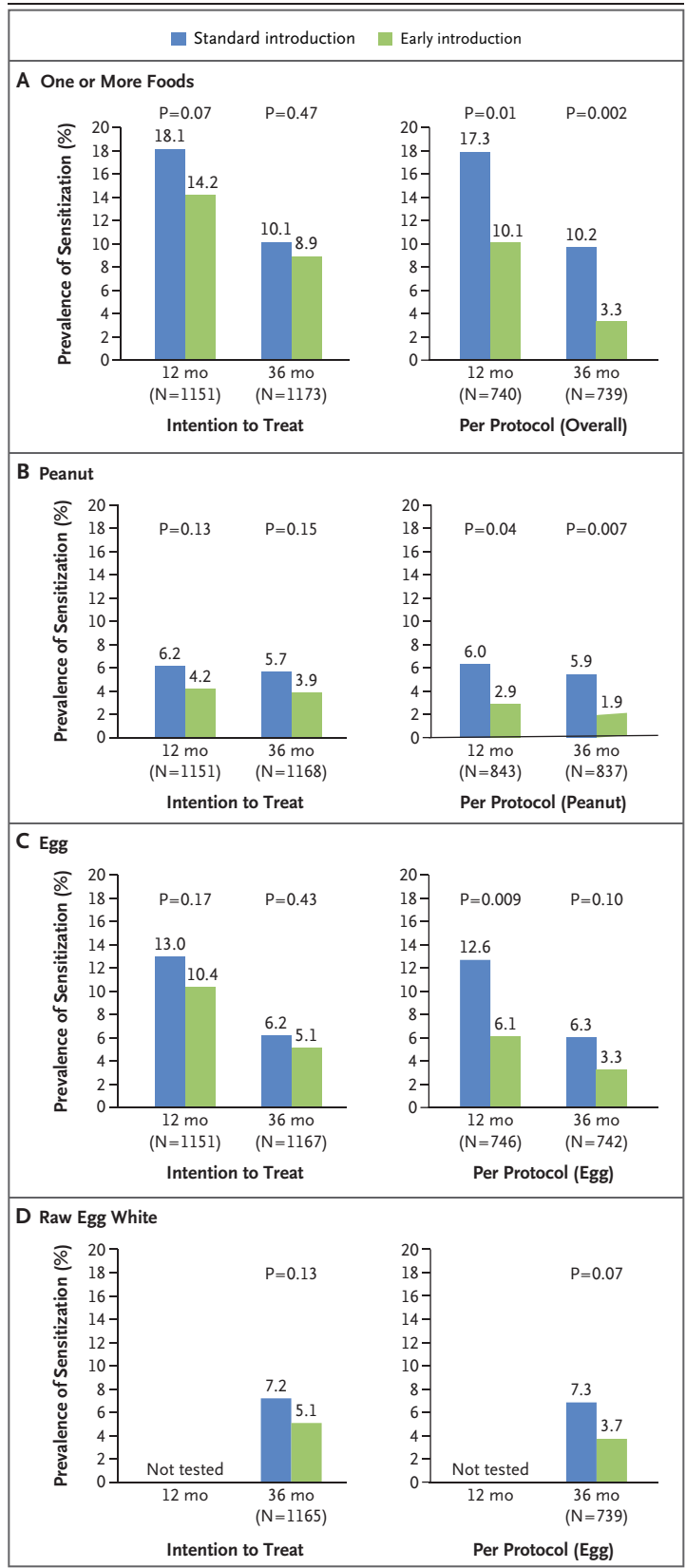
(psychological domain) (odds ratio, 0.69; 95% CI, 0.47 to 1.00), and the presence of eczema in the child at enrollment (odds ratio, 1.38; 95% CI, 0.87 to 2.19) (Tables S12 and S14 in the Supplementary Appendix).

The rate of adherence to the protocol with respect to individual foods in the early-introduction group varied. The rates were as follows: 43.1% for egg (215 of 499 participants), 50.7% for sesame (266 of 505), 60.0% for fish (297 of 495), 61.9% for peanut (310 of 501), and 85.2% for milk (415 of 487).

The levels of peanut protein in bed dust were similar at baseline in the early-introduction group and the standard-introduction group (median, 7.6 μg of peanut protein per gram of dust and 9.7 μg per gram, respectively). However, by 1 year of age, the levels were significantly higher in the early-introduction group than in the standard-introduction group (387.9 μg of peanut protein per gram of dust vs. 77.0 μg per gram, $P < 0.001$). At 1 year of age, participants in the early-introduction group who adhered to the protocol had higher levels of peanut protein in bed dust than did those in the same trial group who did not adhere to the protocol ($P = 0.04$) (Fig. S7 in the Supplementary Appendix). Further details on adherence to the protocol are provided in the Results section in the Supplementary Appendix.

DOSE—RESPONSE ANALYSIS

Variations in the number of foods consumed, the weekly dose of each food consumed, and the number of weeks during which this dose was consumed resulted in a rate of adherence in the early-introduction group that ranged from 6% to 81%. The prevalence of food allergy overall



and the prevalence of allergy to specific foods were reduced in concert with increases in any of these variables. At a consumption level of 2 g or more per week of allergenic protein for 4 or more weeks, peanut was consumed by 85.3% of the participants in the early-introduction group for whom adherence with peanut consumption could be determined (419 of 491 participants) and egg by 75.5% (370 of 490). The corresponding rates of allergy were 0.2% for peanut and 1.9% for egg. Details are provided in Tables S15A, S15B, and S16 in the Supplementary Appendix.

The mean weekly consumption of egg and peanut protein between enrollment and 6 months of age was calculated and divided into quartiles. The prevalence of allergy to peanut and egg and the prevalence of positive responses on skin-prick testing to peanut, egg, and raw egg white diminished with increasing quartile levels of consumption (Fig. S8 in the Supplementary Appendix). The mean weekly consumption data were used to generate predictive probability plots that were based on logistic modeling; analysis showed that higher consumption was associated with a lower prevalence of allergy and sensitization to that food (Fig. 3). The mean weekly consumption of 2 g of peanut protein and 4 g of egg protein (equivalent to 2 g of egg-white protein) was associated with the prevention of these two respective food allergies. The consumption of cooked egg was equally effective in inhibiting reactivity to raw egg-white protein and egg extract on skin-prick testing at 3 years of age.

SAFETY

No deaths occurred in the trial. There were three life-threatening events, all of which occurred in the standard-introduction group; none were related to allergic disease (heart-valve damage, prolonged febrile convulsion, and extensive burns). There were no significant between-group differences in the rates of hospitalization. There were no cases of anaphylaxis with the introduction of foods at home in the early-introduction group. The use of the epinephrine autoinjector is discussed in the Results section in the Supplementary Appendix.

The rate of visits to the emergency department was similar in the two groups. The early-introduction regimen did not affect the growth of the participants or the duration of breast-

feeding.⁸ Details on safety outcomes are provided in Tables S17 through S28 and Figures S9 through S19 in the Supplementary Appendix.

RESULTS ACCORDING TO SKIN-PRICK TESTING AND ALLERGY STATUS AT BASELINE

At enrollment, 33 of the 652 participants in the early-introduction group (5.1%) had a positive skin-prick test to an early-introduction food. All 33 participants were invited to undergo food challenges to the relevant foods: 7 participants had positive results (to one or more foods), 22 had negative results (to one or more foods), and 4 did not return for the challenges. Of the 7 participants who had a positive result on a challenge at baseline, 5 subsequently had a positive result with respect to the primary outcome, 1 had a negative result, and 1 withdrew from the trial. Of the 22 participants who had negative results on the challenge at baseline, 1 subsequently had a positive result with respect to the primary outcome, 3 could not be evaluated, and 18 had a negative result. Details are provided in Table S29A in the Supplementary Appendix.

All the reactions in the seven participants who had positive results on challenges at baseline were mild (Table S30 in the Supplementary Appendix). There were 10 positive challenges among these seven participants; 6 reactions required no treatment, and 4 were treated with antihistamines. There were no cases of anaphylaxis during the challenges, and no intramuscular epinephrine was administered.

DISCUSSION

This trial did not show efficacy of early introduction of allergenic foods versus standard introduction in an intention-to-treat analysis; there was a nonsignificant 20% lower relative risk of food allergy in the early-introduction group than in the standard-introduction group. In the per-protocol analysis, there was a significant 67% lower relative risk of food allergy overall in the early-introduction group. Unexpectedly, in the per-protocol analysis, significantly lower relative risks of peanut allergy and egg allergy were observed in the early-introduction group than in the standard-introduction group ($P=0.003$ and $P=0.009$, respectively). The rates of other food

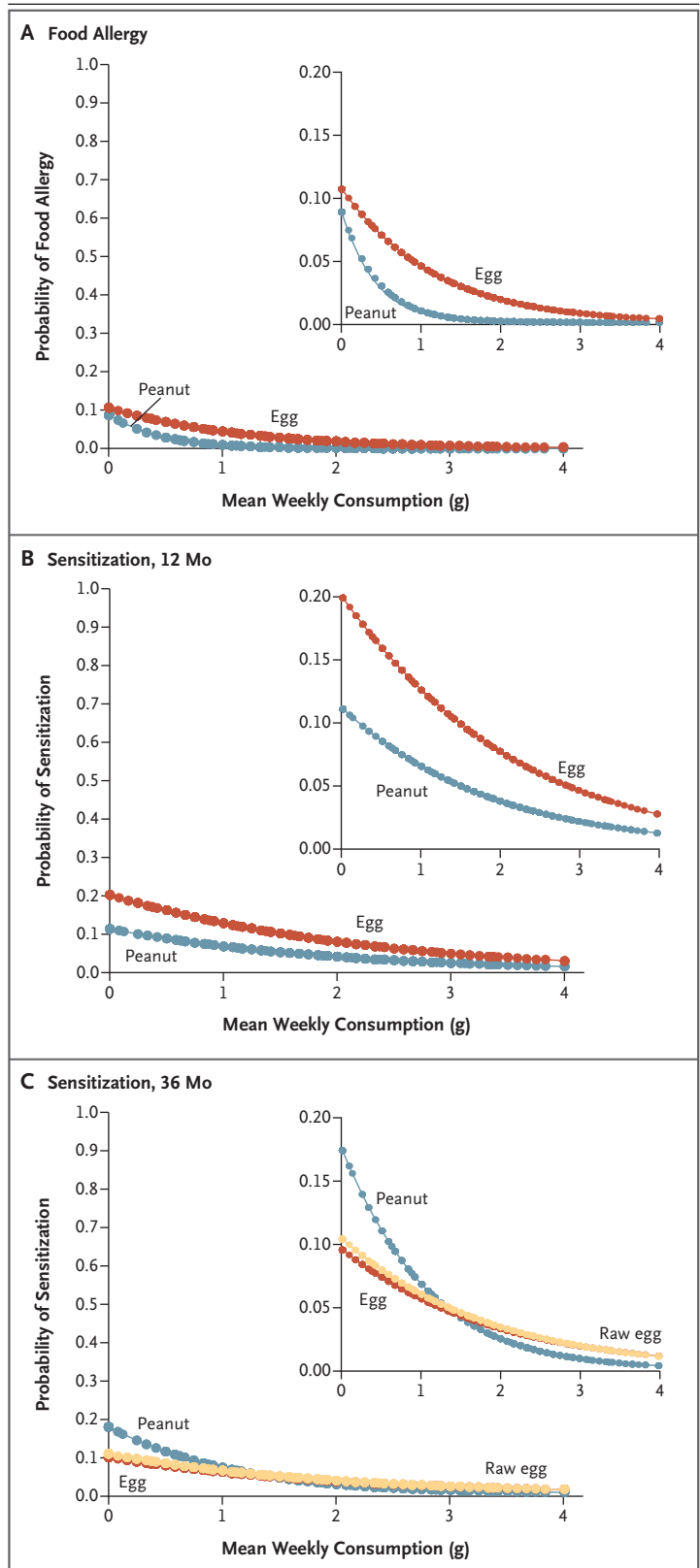
Figure 3. Dose–Response Analysis of the Relationship between Mean Weekly Dose of Peanut or Egg Protein Consumed and Allergy or Positive Result on Skin-Prick Testing to Peanut, Egg, and Raw Egg White.

Shown are the predictive probability plots that were generated from statistical models of the prevalence of peanut allergy and egg allergy (Panel A) and of a positive result on skin-prick testing to peanut and egg at 12 months (Panel B) and to peanut, egg, and raw egg white at 36 months (Panel C), according to the mean weekly consumption of peanut and egg protein between enrollment and 6 months of age. The prevalence of both food allergy and positive skin-prick test diminishes with increasing levels of mean weekly consumption. Insets show the same data on an enlarged y axis. Plots of the raw data and the probability plots are shown in Figure S8 in the Supplementary Appendix.

allergies were too low to show any effects. Nevertheless, at 36 months of age, the average relative risk of a positive skin-prick test to the six individual foods was 79% lower in the early-introduction group than in the standard-introduction group; findings were significant for peanut ($P=0.007$), milk ($P=0.02$), and sesame ($P=0.04$). The efficacy of the intervention was related to the duration of consumption of the specific food and the quantity of food consumed between 3 months and 6 months of age.

We found that the early introduction of allergenic foods was safe, with no cases of anaphylaxis during the initial introduction regimen and no adverse effects on breast-feeding or growth.⁸ Partial adherence among participants in the early-introduction group was not associated with any increase in the prevalence of allergy. Seven participants in the early-introduction group had positive results on food challenges at baseline, and hence complete adherence to the early-introduction protocol in this trial would not have prevented all cases of food allergy from occurring.

The per-protocol consumption of cooked egg resulted in a lower rate of a positive skin-prick test to raw egg white (by 49%) and to commercial egg extract, which suggests that the possible protective effect is not confined to the form in which the individual food is consumed. The Hen's Egg Allergy Prevention (HEAP) study, which enrolled patients from the general population,¹¹ and the Solids Timing for Allergy Research (STAR) study, which enrolled high-risk patients,¹² introduced raw-egg powder but showed significant



side effects. Our data suggest that the introduction of cooked egg is a safe strategy and may be effective for prevention.

The rates of food allergy were higher among nonwhite participants than among whites and higher among participants with eczema at enrollment than among those without eczema — findings that are consistent with those in the literature; however, adherence to the trial protocol was significantly lower among participants in the early-introduction group who were nonwhite and was lower (but not significantly) among those who had eczema than among the rest of the standard-introduction group.¹³⁻¹⁵ Adherence was also lower in cases in which parents perceived symptoms in their child with the early introduction of the foods and in cases in which mothers had a lower psychological quality of life at enrollment. These results raise the question of whether targeted clinical and dietetic support to these families at the earliest stages of food introduction could possibly augment adherence, and this concept requires further consideration if early introduction is to be considered as a policy to reduce the prevalence of food allergies.

The strengths of our trial included a high retention rate, the fact that nearly all cases of allergy were confirmed in a double-blind, placebo-controlled challenge, the enrollment of an unselected population of exclusively breast-fed infants, and the fact that all the children with a positive skin-prick test were invited to undergo a food challenge. The main weakness of the study was the low rate of per-protocol adherence in the early-introduction group, as discussed below.

There are a number of possible explanations for the finding of efficacy at the per-protocol level as opposed to the intention-to-treat level. The first is that the early introduction of allergenic foods prevented the development of food allergy. This explanation has some plausibility, given the food-specific findings and an apparent dose–response relationship for protection against peanut allergy and egg allergy. Reverse causality would provide a second explanation, reflecting the possibility that infants with nascent food allergy were less likely to successfully consume the foods because of aversive feeding behavior, which is the first sign of clinical food allergy. If this were the case, we would anticipate an excess of food allergy among the participants in the early-introduction group who did not adhere to

the protocol, but there was no evidence of this. Furthermore, the 3-month-old infants who were most at risk for nascent food allergy (positive skin-prick test at enrollment but negative result on the food challenge at baseline) did not have lower rates of adherence to the early-introduction protocol than those in this group who had a negative skin-prick test.

A third potential explanation is that of bias leading to a higher prevalence of atopy and food allergy among children outside the per-protocol analysis. This is an important consideration, given that only 31.9% of all the enrolled participants in the early-introduction group (208 of 652 participants) adhered to the protocol and had a primary outcome that could be evaluated, as compared with 80.5% in the standard-introduction group (524 of 651). Differential attrition between the two groups potentially introduces bias. An analysis for evidence of bias in the participants who were not in the group that adhered to the protocol does not provide an explanation for the apparent efficacy in the per-protocol analyses (Tables S12 and S31 in the Supplementary Appendix).

Finally, we eliminated the possibility that our findings were the result of an artifact of study design — the selective removal of participants who had food allergy at baseline exclusively from the early-introduction group. When the participants were 3 months of age, we evaluated food allergy only in the early-introduction group. Participants with confirmed food allergy at this point were unable to adhere to the protocol, which thus artificially lowered the rate of food allergy in this group. We therefore undertook an adjusted per-protocol analysis in which we subtracted the same number of participants with food allergy from the standard-introduction group. The results remained significant after the adjustment (Fig. 1). Nevertheless, we cannot be certain whether unmeasured sources of bias still exist.

Modeling determined that 2 g or more of peanut or egg-white protein per week may prevent these respective allergies. This level of consumption matches the median level of consumption observed in Israeli infants 8 to 14 months of age (7.1 g per month), who have a rate of peanut allergy that is 10 times lower than that among Jewish children in the United Kingdom, who consume very little peanut (0.17% vs. 1.85%).³ In the EAT trial, this level of peanut consump-

tion for at least 4 weeks also resulted in a rate of peanut allergy that was 10 times lower than that among the participants in the standard-introduction group (2.5% vs. 0.2%) — a finding that mirrors that of Du Toit et al.³ The results of our trial are complementary to those of the LEAP trial. Only 9 of the 1303 participants in our trial would have been considered to be at sufficiently high risk to enroll in the LEAP trial. It should be noted that 76% of the participants in the standard-introduction group did not have eczema at 3 months of age, and yet they accounted for 38% of the participants in the standard-introduction group with food allergy to one or more of the foods tested (Table S32 in the Supplementary Appendix; additional information regarding many of the findings discussed in this section is available in the Discussion section of the Supplementary Appendix).

This trial failed to show the efficacy of early introduction of allergenic foods as compared with standard introduction of those foods in an intention-to-treat analysis. Further analysis suggests that the possibility of preventing food allergy by means of the early introduction of multiple allergenic foods in normal breast-fed infants may depend on adherence and dose.

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REFERENCES

1. Global strategy for infant and young child feeding. Geneva: World Health Organization, 2003 (<http://apps.who.int/iris/bitstream/10665/42590/1/9241562218.pdf?ua=1&ua=1>).
2. McAndrew F, Thompson J, Fellows L, Large A, Speed M, Renfrew MJ. Infant feeding survey 2010. Leeds, United Kingdom: Health and Social Care Information Centre, 2012 (<http://www.hscic.gov.uk/article/3895/Infant-Feeding-Survey-2010>).
3. Du Toit G, Katz Y, Sasieni P, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* 2008;122:984-91.
4. Koplin JJ, Osborne NJ, Wake M, et al. Can early introduction of egg prevent egg allergy in infants? A population-based study. *J Allergy Clin Immunol* 2010;126:807-13.
5. Katz Y, Rajuan N, Goldberg MR, et al. Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. *J Allergy Clin Immunol* 2010;126(1):77-82.e1.
6. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015;372:803-13.
7. Du Toit G, Sayre PH, Roberts G, et al. Effect of avoidance on peanut allergy after early peanut consumption. *N Engl J Med* 2016;374:1435-43.
8. Perkin MR, Logan K, Marrs T, et al. Enquiring About Tolerance (EAT) study: feasibility of an early allergenic food introduction regimen. *J Allergy Clin Immunol* 2016 February 16 (Epub ahead of print).
9. Brough HA, Santos AF, Makinson K, et al. Peanut protein in household dust is related to household peanut consumption and is biologically active. *J Allergy Clin Immunol* 2013;132:630-8.
10. Brough HA, Makinson K, Penagos M, et al. Distribution of peanut protein in the home environment. *J Allergy Clin Immunol* 2013;132:623-9.
11. Bellach J, Schwarz V, Ahrens B, et al. Early introduction of hen's egg during weaning results in frequent allergic reactions: first results from a randomized placebo-controlled trial on hen's egg allergy prevention. EAACI Online Library, 2015. abstract (<http://eaaci.multilearning.com/eaaci/2015/barcelona/104806/>).
12. Palmer DJ, Metcalfe J, Makrides M, et al. Early regular egg exposure in infants with eczema: a randomized controlled trial. *J Allergy Clin Immunol* 2013;132(2):387-92.e1.
13. Du Toit G, Roberts G, Sayre PH, et al. Identifying infants at high risk of peanut allergy: the Learning Early About Peanut Allergy (LEAP) screening study. *J Allergy Clin Immunol* 2013;131(1):135-43.e1-12.
14. Liu AH, Jaramillo R, Sicherer SH, et al. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005-2006. *J Allergy Clin Immunol* 2010;126(4):798-806.e13.
15. Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics* 1998;101(3):E8.

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