Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

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Abstract

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BACKGROUND

The prevalence of peanut allergy among children in Western countries has doubled in the past 10 years, and peanut allergy is becoming apparent in Africa and Asia. We evaluated strategies of peanut consumption and avoidance to determine which strategy is most effective in preventing the development of peanut allergy in infants at high risk for the allergy.

METHODS

We randomly assigned 640 infants with severe eczema, egg allergy, or both to consume or avoid peanuts until 60 months of age. Participants, who were at least 4 months but younger than 11 months of age at randomization, were assigned to separate study cohorts on the basis of preexisting sensitivity to peanut extract, which was determined with the use of a skin-prick test — one consisting of participants with no measurable wheal after testing and the other consisting of those with a wheal measuring 1 to 4 mm in diameter. The primary outcome, which was assessed independently in each cohort, was the proportion of participants with peanut allergy at 60 months of age.

RESULTS

Among the 530 infants in the intention-to-treat population who initially had negative results on the skin-prick test, the prevalence of peanut allergy at 60 months of age was 13.7% in the avoidance group and 1.9% in the consumption group (P<0.001). Among the 98 participants in the intention-to-treat population who initially had positive test results, the prevalence of peanut allergy was 35.3% in the avoidance group and 10.6% in the consumption group (P=0.004). There was no significant between-group difference in the incidence of serious adverse events. Increases in levels of peanut-specific IgG4 antibody occurred predominantly in the consumption group; a greater percentage of participants in the avoidance group had elevated titers of peanut-specific IgE antibody. A larger wheal on the skin-prick test and a lower ratio of peanut-specific IgG4:IgE were associated with peanut allergy.

CONCLUSIONS

The early introduction of peanuts significantly decreased the frequency of the development of peanut allergy among children at high risk for this allergy and modulated immune responses to peanuts. (Funded by the National Institute of Allergy and Infectious Diseases and others; ClinicalTrials.gov number, NCT00329784.)

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The prevalence of peanut allergy among children in Western countries has doubled in the past 10 years, reaching rates of 1.4 to 3.0%.\textsuperscript{1-3} and peanut allergy is becoming apparent in Africa and Asia.\textsuperscript{4,5} This allergy is the leading cause of anaphylaxis and death due to food allergy and imposes substantial psychosocial and economic burdens on patients and their families.\textsuperscript{6}

Peanut allergy develops early in life and is rarely outgrown.\textsuperscript{7-9} Clinical practice guidelines from the United Kingdom in 1998\textsuperscript{10} and from the United States in 2000\textsuperscript{11} recommended the exclusion of allergenic foods from the diets of infants at high risk for allergy and from the diets of their mothers during pregnancy and lactation. However, studies in which food allergens have been eliminated from the diet have consistently failed to show that elimination from the diet prevented the development of IgE-mediated food allergy.\textsuperscript{12}

In 2008, recommendations for the avoidance of allergens were withdrawn. The question of whether early exposure or avoidance is the better strategy to prevent food allergies remains open.\textsuperscript{12,13}

Several years ago, we found that the risk of the development of peanut allergy was 10 times as high among Jewish children in the United Kingdom as it was in Israeli children of similar ancestry.\textsuperscript{14} This observation correlated with a striking difference in the time at which peanuts are introduced in the diet in these countries: in the United Kingdom infants typically do not consume peanut-based foods in the first year of life, whereas in Israel, peanut-based foods are usually introduced in the diet when infants are approximately 7 months of age, and their median monthly consumption of peanut protein is 7.1 g.\textsuperscript{14} This finding led us to hypothesize that the early introduction of peanuts to the diet may offer protection from the development of peanut allergy.

Oral tolerance is an incompletely understood immunologic phenomenon. In studies in animals, specific immune unresponsiveness has been achieved through the oral administration of antigens.\textsuperscript{15} In a single study in humans, researchers attempted to induce primary oral tolerance to egg in infants at high risk for allergy, but the study lacked the power to show efficacy.\textsuperscript{16} Several small studies have evaluated the use of oral immunotherapy with peanut and egg in older children with established food allergies; although the early results of these studies have been promising, the majority of children who initially showed a positive response to the therapy regained their allergic reactivity a few months after discontinuing the therapy.\textsuperscript{17-20}

The primary prevention of allergy targets nonsensitized persons, whereas secondary prevention targets those who are known to be sensitized on the basis of test results for allergen-specific IgE or reactions on skin-prick testing. The Learning Early about Peanut Allergy (LEAP) trial was conceived to determine whether the early introduction of dietary peanut could serve as an effective primary and secondary strategy for the prevention of peanut allergy. Here we report the primary findings of the LEAP trial.

METHODS

STUDY DESIGN AND OVERSIGHT

The LEAP study was a randomized, open-label, controlled trial conducted at a single site in the United Kingdom. An open-label design was chosen because participants and their parents were necessarily aware of their assigned group. The trial was approved by the institutional review board (the National Research Ethics Service Committee London–Fulham) and was overseen by the allergy and asthma data and safety monitoring board of the National Institute of Allergy and Infectious Diseases. Informed written consent was obtained for all participants from their parent or guardian. No manufacturer of peanut products contributed to the design of the study, the accrual or analysis of the data, or the preparation of the manuscript. The peanut snack used in the study, called Bamba, was purchased from Osem at a discounted rate. The protocol for the LEAP study is available with the full text of this article at NEJM.org.

ENROLLMENT AND STUDY PROCEDURES

Study enrollment took place from December 2006 to May 6, 2009. To be eligible for enrollment, infants had to be least 4 months and less than 11 months of age and had to have severe eczema, egg allergy, or both.\textsuperscript{21} Participants were stratified into two study cohorts on the basis of the results of a skin-prick test for peanut allergy (no measurable wheal after testing versus a wheal measuring 1 to 4 mm in diameter); participants in each study cohort were then randomly assigned to a group in which dietary peanut would be consumed or a group in which its consumption would be avoided (Fig. 1). Infants randomly assigned to consumption underwent a baseline, open-label food
challenge in which those who had had negative results on the skin-prick test were given 2 g of peanut protein in a single dose and those who had positive test results were given incremental doses up to a total of 3.9 g. Participants who had a reaction to the baseline challenge were instructed to avoid peanuts. These participants were included in the intention-to-treat analysis but not in the per-protocol analysis.

Participants randomly assigned to consumption who did not have a reaction to the baseline challenge were fed at least 6 g of peanut protein per week, distributed in three or more meals per week, until they reached 60 months of age. The preferred peanut source was Bamba, a snack food manufactured from peanut butter and puffed maize; it was not possible to administer a placebo for Bamba because of financial and logistic constraints. Smooth peanut butter (the brands Sunpat or Duerr’s) was provided to infants who did not like Bamba. Participants assigned to avoidance were to avoid the consumption of peanut protein until they reached 60 months of age. Adherence was assessed with the use of a validated food-frequency questionnaire, as detailed in the schedule of events in Table S1 in the Supplementary Appendix, available at NEJM.org. Some families agreed to have peanut protein levels measured in dust collected from the participant’s bed 2 to 4 weeks before the final visit.

Clinical assessments were undertaken at baseline (when participants were between 4 months and 11 months of age) and at the ages of 12, 30, and 60 months; between-visit scheduled telephone consultations were conducted weekly until participants reached 12 months of age, every 2 weeks from 12 months to 30 months of age, and monthly thereafter. Additional clinic visits were scheduled to evaluate aversion to peanut or refusal to eat peanut (Bamba or peanut butter) or suspected peanut allergy.

OUTCOMES
The primary outcome was the proportion of participants with peanut allergy at 60 months of age and was determined in 617 participants by means of an oral food challenge. Participants in whom peanut allergy was unlikely (no wheal after a skin-prick test at months 30 and 60, no history of allergic symptoms after ingestion of peanut, no diagnosis or suspicion of allergies to sesame or tree nut, and no history of anaphylaxis in response to any food) received 5 g of peanut protein in a single dose. A double-blind, placebo-controlled food challenge was conducted for other participants (with a total of 9.4 g of peanut protein administered in increments) in accordance with standard dose-escalation procedures (see the study protocol). Among 11 study participants for whom data from the oral food challenge were either inconclusive or not available, a diagnostic algorithm based on clinical history, the results of a skin-prick test, and the values for peanut-specific IgE were used to determine whether or not a participant should be considered to have peanut allergy (Fig. S1 in the Supplementary Appendix).

IMMUNE MARKERS
At baseline and at all study visits, skin-prick tests for peanut allergy were performed in duplicate with the use of a lyophilized peanut extract (manufactured by ALK-Abello), and the average of the diameter of the two widest wheals was recorded. Mean diameters were rounded off to the nearest millimeter, with the lowest positive value being 1 mm; positive values of 1 mm and 2 mm (which are associated with peanut-specific IgE production) were considered to be indicative of early sensitization, even though these values are lower than the traditional cut-off of 3 mm. Serum levels of peanut-specific IgE, IgG, and IgG4 antibodies were measured at each visit, since these are known biomarkers of allergic responses, antigen exposure, and potential immune modulation, respectively. The peanut-specific IgG4:IgE ratio was calculated, since it has been reported that this ratio may additionally reflect immune modulation. Immunoglobulin measurements were made with the use of the ImmunoCAP 100 and 250 assays (Thermo Fisher Scientific).

STATISTICAL ANALYSIS
Primary statistical analyses were performed in each cohort independently on an intention-to-treat basis with data from all participants who could be assessed for the primary outcome. The analyses compared the proportion of participants with peanut allergy in the peanut-avoidance group with the proportion with peanut allergy in the peanut-consumption group at month 60 with the use of a two-tailed chi-square test. Analyses of the data from the two cohorts were independently powered. In the cohort with negative results on the initial skin-prick test, the power to detect a difference in risk of 7 percentage points (9.0% in the avoidance group vs. 2.0% in the consumption group) was
834 Participants were screened for LEAP study

640 Underwent randomization

194 Were excluded

118 Did not have severe eczema

76 Had SPT > 4 mm

5 Had missing data on outcomes

2 Withdrew voluntarily

1 Was lost to follow-up

2 Had other reasons

7 Had missing data on outcomes

4 Withdrew voluntarily

1 Was lost to follow-up

118 Did not have severe eczema

5 Had missing data on outcomes

4 Withdrew voluntarily

2 Could not be evaluated by means of diagnostic algorithm

1 Had other reason

18 Were excluded owing to inadequate adherence to treatment

542 Were in the SPT-negative cohort

98 Were in the SPT-positive cohort

270 Were assigned to peanut avoidance

272 Were assigned to peanut consumption

51 Were assigned to peanut avoidance

47 Were assigned to peanut consumption

41 Consumed peanut protein

41 Were included in the ITT analysis

6 Had a positive baseline peanut challenge, did not consume peanut, and were included in the ITT analysis

1 Was excluded owing to inadequate adherence to treatment

2 Were included in the per-protocol analysis

271 Consumed peanut protein

266 Were included in the ITT analysis

1 Had a positive baseline peanut challenge, did not consume peanut, and was included in the ITT analysis

2 Were excluded owing to inadequate adherence to treatment

50 Were included in the per-protocol analysis

1 Was excluded owing to inadequate adherence to treatment

2 Were included in the per-protocol analysis

41 Consumed peanut protein

39 Were included in the per-protocol analysis

51 Were included in the ITT analysis

1 Was excluded owing to inadequate adherence to treatment

2 Were included in the per-protocol analysis
RESULTS

STUDY POPULATION

At screening, the median age of participants was 7.8 months (interquartile range, 6.3 to 9.1): the mean (±SD) age was 7.8±1.7 months. More male infants were randomly assigned to avoidance (64.8% of the avoidance group vs. 55.2% of the consumption group) were male infants. The groups were otherwise evenly balanced. Additional information on the baseline characteristics of the participants is presented in Table S2 in the Supplementary Appendix. The study had a 98.4% retention rate; 10 participants were withdrawn voluntarily by a parent or guardian or were lost to follow-up (Fig. 1).

PEANUT CONSUMPTION AND ALLERGY IN HIGH-RISK CHILDREN

Among the 542 infants in the group with a negative initial skin-prick test, 530 (97.8%) could be evaluated for the primary outcome and were included in the intention-to-treat analysis (Fig. 1). At 60 months of age, 13.7% of the avoidance group and 1.9% of the consumption group were allergic to peanuts; the absolute difference in risk of 11.8 percentage points (95% confidence interval [CI], 3.4 to 20.3; P<0.001) represents an 86.1% relative reduction in the prevalence of peanut allergy (Fig. 2).

All 98 children in the group with positive results on the initial skin-prick test were evaluated and were included in the intention-to-treat analysis. At 60 months of age, 35.3% of the avoidance group and 10.6% of the consumption group were allergic to peanuts; the absolute difference in risk of 24.7 percentage points (95% CI, 4.9 to 43.3; P=0.004) represents a 70.0% relative reduction in the prevalence of peanut allergy (Fig. 2).

The per-protocol analysis included 500 infants from the group with negative results on the initial skin-prick test (94.3% of the 530 who could be evaluated) and 89 infants from the group with positive results on the test (90.8% of the 98 who could be evaluated) (Fig. 1). The results in the per-protocol population were similar to those observed in the intention-to-treat population (Fig. 2). The results of a worst-case imputation analysis in the intention-to-treat population were also consistent with the results of the main intention-to-treat analysis (Fig. 2).

Primary prevention targets persons who are not sensitized to peanuts and secondary prevention targets those who are sensitized. In this study, the intervention was effective in reducing the prevalence of peanut allergy in terms of both primary prevention (prevalence of 6.0% in the avoidance group vs. 1.0% in the consumption group, P=0.008) and secondary prevention (33.1% vs. 6.8%, P<0.001) (Table S3 in the Supplementary Appendix). (Results of subgroup analyses according to race or ethnic group are provided in Table S12 in the Supplementary Appendix.)
The median weekly consumption of peanut protein in the first 2 years of life in the avoidance group was 0 g, whereas the median in the consumption group was 7.7 g (interquartile range, 6.7 to 8.8). The results with respect to adher-

**Figure 2. Primary Outcome.**

The prevalence of peanut allergy at 60 months of age is shown among participants who had a negative result on the skin-prick test at baseline, among those who had a positive result at baseline, and in both groups combined, in the intention-to-treat analysis (Panel A) and the per-protocol analysis (Panel B). Among the 640 participants who underwent randomization, peanut-allergy status was determined by means of an oral food challenge in 617 (96.4%) and by means of a diagnostic algorithm in 11 (1.7%). Peanut allergy could not be evaluated with the use of the diagnostic algorithm in 2 participants (0.3%). A total of 10 participants (1.6%) voluntarily withdrew or were lost to follow-up. The worst-case imputation analysis (Panel C) assumes that participants with missing data in the peanut-consumption group would have been allergic to peanuts and that participants with missing data in the peanut-avoidance group would have been nonallergic. P values are based on chi-square analyses.

**ADHERENCE**

The median weekly consumption of peanut protein in the first 2 years of life in the avoidance group was 0 g, whereas the median in the consumption group was 7.7 g (interquartile range, 6.7 to 8.8). The results with respect to adher-
Peanut Consumption in Infants at Risk for Peanut Allergy

**SAFETY**

No deaths occurred in the study. There were no significant differences in rates of hospitalization or serious adverse events between the avoidance group and the consumption group (Tables S6 and S7 in the Supplementary Appendix). Considering all adverse events, 99% of participants in each group reported at least one event, with more events recorded in the consumption group than in the avoidance group (4527 vs. 4287, P = 0.02), according to a Poisson regression analysis (Table S8 in the Supplementary Appendix). With respect to adverse events for which frequencies differed between the two groups, we identified five categories of interest in which the frequencies were higher in the consumption group: upper respiratory tract infection, viral skin infection, gastroenteritis, urticaria, and conjunctivitis. Events in these categories were generally mild or moderate and did not differ significantly in severity between groups. The severity of the events was also similar in a comparison of participants with a peanut-specific IgE level below 0.1 kU per liter and those with a level of 0.1 kU per liter or higher (Table S9 in the Supplementary Appendix).

**RESPONSE TO ORAL FOOD CHALLENGE**

Seven participants who were randomly assigned to the consumption group had a positive response to the oral food challenge at baseline and did not consume peanuts. At month 60, four of these participants had a positive response to an oral food challenge and three had a negative response.

Nine participants who were randomly assigned to peanut consumption subsequently discontinued consumption (Table S10 and the Results section in the Supplementary Appendix). At month 60, six of these participants had a positive response to the oral food challenge and three had a negative response.

The 7 participants randomly assigned to consumption who had a positive response to the oral food challenge at baseline had symptoms that were predominantly cutaneous during the challenge. Six were treated with an antihistamine and 1 was treated with an oral glucocorticoid. Among the 57 participants (9 randomly assigned to consumption and 48 to avoidance) who had a positive response to the oral food challenge at 60 months, 14 had respiratory or cardiovascular signs and 9 received intramuscular epinephrine owing to concerns about the severity of the allergic reaction (Table S11 in the Supplementary Appendix).

**IMMUNOLOGIC ASSESSMENTS**

Peanut-specific immunoglobulins were measured in serum samples at baseline (at which time participants were between 4 months and 11 months of age) and when the children were 12, 30, and 60 months of age. Figure 3A shows wheal size and level of peanut-specific IgE in participants who met the per-protocol criteria. A significant increase from baseline in wheal size was seen only in the peanut-avoidance group. Participants who were allergic to peanuts at month 60 showed a more pronounced increase in wheal size over time. These participants also had higher peanut-specific IgE levels. Although peanut-specific IgE levels increased over time in both the peanut-avoidance and peanut-consumption groups, there were fewer participants in the consumption group with very high IgE levels at 12, 30, and 60 months (Fig. S4 in the Supplementary Appendix).

Figure 3B shows the levels of peanut-specific IgG and IgG4 and the IgG4:IgE ratio. The levels of peanut-specific IgG and IgG4 were higher in the consumption group than in the avoidance group. Peanut-specific IgG4 levels increased over...
time in both groups, but these changes were significantly larger in the consumption group ($P<0.001$). The ratio of peanut-specific IgG4 to IgE increased up to 30 months of age in the consumption group but was relatively constant in the avoidance group. At month 60, the IgG4:IgE ratio in nearly all the participants with peanut allergy in the avoidance group fell below the mean ratio for the group.

Some participants in the per-protocol analysis who were allergic at month 60 had elevated levels of peanut-specific IgE as early as 12 months of age. At month 60, all the participants in the peanut-avoidance group who had peanut-specific IgE levels of more than 10.0 kU per liter were allergic to peanuts, regardless of their level of peanut-specific IgG4. All other allergic participants had levels of peanut-specific IgE between 0.1 and 10 kU per liter and levels of IgG4 that were less than 1000.0 µg per liter. (Fig. S5 in the Supplementary Appendix shows contour diagrams of the distribution of peanut-specific IgE in relation to peanut-specific IgG4 over time in participants who met the per-protocol criteria. Fig. S5 also shows that levels of peanut-specific IgE did not exceed 100.0 kU per liter in the peanut-consumption group. Peanut-specific IgG4 levels in this
Among infants with high-risk atopic disease, sustained peanut consumption beginning in the first 11 months of life, as compared with peanut avoidance, resulted in a significantly smaller proportion of children with peanut allergy at the age of 60 months. This intervention was safe, tolerated, and highly efficacious. In the intention-to-treat analysis, peanut consumption was associated with an 86% reduction in peanut allergy at 60 months of age among participants who had had negative results on a peanut-based skin-prick test at study entry and with a 70% reduction among those who had positive test results at study entry.

The overall rate of adherence to the two assigned interventions was 92.0%. Among the 319 participants randomly assigned to consumption, 7 were instructed not to consume peanuts because they had a positive result at baseline to the oral food challenge, and 9 terminated consumption largely because they began to have allergic symptoms to peanuts. This indicates that peanut consumption may not be possible in some children who meet the LEAP eligibility criteria. In addition, the LEAP study design excluded 9.1% of the infants who were screened (76 of 834) because large wheals (greater than 4 mm in diameter) developed after the skin-prick test that were probably associated with peanut allergy; the safety and effectiveness of early peanut consumption in that population remain unknown.

Almost all the participants (98.4%) were available for assessment at 60 months of age, with 617 (96.4%) assessed by means of an oral food challenge, the most stringent determination of food allergy. Adherence was monitored with the use of food-frequency questionnaires during the study and was corroborated at the end of the study through the measurement of peanut in bed dust, an objective and previously validated surrogate for consumption.23,24

The main weakness of the study was the lack of a placebo regimen, a problem that was partially mitigated by the use of objective peanut challenges as the primary outcome. In addition, the study did not include low-risk infants and those who had large wheals (>4 mm in diameter) after the skin-prick test. A further limitation was the failure to collect dust samples to validate consumption at earlier time points in the study.

At 60 months, the mean diameter of wheals and the number of participants with markedly elevated levels of peanut-specific IgE titers were higher in the peanut-avoidance group than in the consumption group. In contrast, the peanut-consumption group showed a significantly greater and earlier increase in levels of peanut-specific IgG and IgG4 (Fig. 3B); this effect mirrors the immunologic changes seen in successful allergen immunotherapy.29 Furthermore, in the avoidance group, unless peanut-specific IgE levels were very high, elevated IgG4 levels were associated with the absence of an allergic reaction to peanuts (Fig. S5 in the Supplementary Appendix). Both observations indicate that IgG4 is associated with a protective role against the development of allergy; although peanut-specific IgG4 has recently been shown to inhibit basophil activation in vitro in response to peanut,30 our data do not establish causality at the clinical level.

In this study, very early sensitization was observed in infants with no history of peanut consumption. As we have proposed in our dual allergen hypothesis, early environmental exposure (through the skin) to peanut may account for early sensitization,31 whereas early oral exposure may lead to immune tolerance. The LEAP study showed that early oral introduction of peanuts could prevent allergy in high-risk, sensitized infants and in nonsensitized infants (Table S3 in the Supplementary Appendix).

The question of whether the participants who consumed peanut would continue to remain protected against the development of peanut allergy even after prolonged cessation of peanut consumption requires further study and is under investigation in the LEAP-On study (Persistence of Oral Tolerance to Peanut; ClinicalTrials.gov number, NCT01366846). Our findings showed that early, sustained consumption of peanut products was associated with a substantial and significant decrease in the development of peanut allergy in high-risk infants. Conversely, peanut avoidance was associated with a greater frequency of clinical peanut allergy than was peanut consumption, which raises questions about the usefulness of deliberate avoidance of peanuts as a strategy to prevent allergy.
The content of this article is the sole responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Dr. Brough reports receiving grant support from Action Medical Research and study materials from Stallergenes, Thermo Scientific, and Meridian Foods. Dr. Lack reports holding stock and stock options in DBV Technologies. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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