ORIGINAL ARTICLE

Effect of Avoidance on Peanut Allergy after Early Peanut Consumption

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ABSTRACT

BACKGROUND

In a randomized trial, the early introduction of peanuts in infants at high risk for allergy was shown to prevent peanut allergy. In this follow-up study, we investigated whether the rate of peanut allergy remained low after 12 months of peanut avoidance among participants who had consumed peanuts during the primary trial (peanut-consumption group), as compared with those who had avoided peanuts (peanut-avoidance group).

METHODS

At the end of the primary trial, we instructed all the participants to avoid peanuts for 12 months. The primary outcome was the percentage of participants with peanut allergy at the end of the 12-month period, when the participants were 72 months of age.

RESULTS

We enrolled 556 of 628 eligible participants (88.5%) from the primary trial; 550 participants (98.9%) had complete primary-outcome data. The rate of adherence to avoidance in the follow-up study was high (90.4% in the peanut-avoidance group and 69.3% in the peanut-consumption group). Peanut allergy at 72 months was significantly more prevalent among participants in the peanut-avoidance group than among those in the peanut-consumption group (18.6% [52 of 280 participants] vs. 4.8% [13 of 270], P<0.001). Three new cases of allergy developed in each group, but after 12 months of avoidance there was no significant increase in the prevalence of allergy among participants in the consumption group (3.6% [10 of 274 participants] at 60 months and 4.8% [13 of 270] at 72 months, P=0.25). Fewer participants in the peanut-consumption group than in the peanut-avoidance group had high levels of Ara h2 (a component of peanut protein)–specific IgE and peanut-specific IgE; in addition, participants in the peanut-consumption group continued to have a higher level of peanut-specific IgG4 and a higher peanut-specific IgG4:IgE ratio.

CONCLUSIONS

Among children at high risk for allergy in whom peanuts had been introduced in the first year of life and continued until 5 years of age, a 12-month period of peanut avoidance was not associated with an increase in the prevalence of peanut allergy. Longer-term effects are not known. (Funded by the National Institute of Allergy and Infectious Diseases and others; LEAP-On ClinicalTrials.gov number, NCT01366846.)

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Peanut allergy is a common and potentially life-threatening food allergy for which prevention and treatment strategies are required.[1-5] The Learning Early about Peanut Allergy (LEAP) trial showed that among infants at high risk for allergy, the sustained consumption of peanut, beginning in the first 11 months of life, resulted in an 81% lower rate of peanut allergy at 60 months of age than the rate among children who avoided peanuts.[6,7] In a study of oral immunotherapy to hen's egg white, although children achieved unresponsiveness to an oral food challenge with egg, the majority had a reversion to egg allergy 1 month after the cessation of consumption.[8] Similar results have been seen with oral immunotherapy with peanuts.[9] However, there may be different mechanisms operating in those interventions than in the intervention used in the LEAP trial, and the LEAP trial intervention may result in unresponsiveness that lasts for at least 1 year — a duration of unresponsiveness that is longer than has been observed in other studies.

Here we report the results of the Persistence of Oral Tolerance to Peanut (LEAP-On) study, which was a 12-month extension of the LEAP trial. We investigated whether participants who had consumed peanut in the primary trial would remain protected against peanut allergy after cessation of peanut consumption for 12 months. The study design represented an opportunity to investigate the mechanisms of loss of protection from allergic responses, with potential implications for other food allergies and immune-mediated diseases.

Methods

Study Design and Oversight

This follow-up study was a two-group comparison that involved all the eligible participants in the two groups of the primary trial at 72 months of age. The study was conducted at a single site in the United Kingdom. In brief, in the primary trial, 640 infants at high risk for allergy were stratified into two groups on the basis of the results of a skin-prick test with the use of peanut extract (no measurable wheal vs. wheal measuring 1 to 4 mm in diameter). The participants were then randomly assigned to peanut avoidance or consumption until 60 months of age, at which time peanut allergy was assessed by means of an oral peanut challenge.[6]

The follow-up study was approved by an institutional review board (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. Written informed consent was obtained for each participant from a parent or guardian. Details of the inclusion and exclusion criteria for this follow-up study are provided in the study protocol, available with the full text of this article at NEJM.org.

Study Procedures

All the participants in the primary trial who were in the intention-to-treat population (which included all participants who could be assessed for the primary outcome) were eligible for inclusion in the follow-up study. All the participants in the follow-up study were asked to avoid dietary consumption of peanut for 12 months.

Study Outcomes

The primary outcome in the follow-up trial was the percentage of participants with peanut allergy after 12 months of peanut avoidance. Allergy was determined by means of an oral peanut challenge at 72 months (see the protocol). Among study participants for whom the results of the oral peanut challenge were inconclusive or not available, allergic status at 72 months was determined as discussed in the Determination of Allergy section in the Supplementary Appendix, available at NEJM.org. Safety outcomes were assessed according to the reports of adverse events in each group.

Immune Markers

Immune assessments included skin-prick testing and measurements of peanut-specific IgE and IgG4 levels. Information regarding testing methods and skin-prick testing materials has been published previously[6] and is included in the Supplementary Appendix. In addition, we assessed the specific IgE responses to peanut protein Ara h2 (IgE responses to this protein are pathognomonic of peanut allergy) by means of the ImmunoCAP Assay (Thermo Fisher Scientific) at all time points in participants who had a peanut-specific IgE level of 0.1 kU per liter or more at at least one time point.

ASSESSMENT OF ADHERENCE

Adherence to peanut avoidance was assessed with the use of a validated peanut-frequency questionnaire[10] at regular intervals (see the protocol). Peanut-protein levels in dust that was collected from the participants' beds were used as an independent marker of peanut consumption.[6,11,12]

STATISTICAL ANALYSIS

The intention-to-treat analysis included all the enrolled participants in the follow-up study who had a peanut-allergy outcome that could be evaluated. In the follow-up study, the per-protocol population included participants who adequately adhered to avoidance of peanut protein over a period of 12 months. Adherence was defined as fulfilling all three of the following criteria: consumption of 2 g or less of peanut on no more than 6 occasions (maximum of once per month); consumption of 1 g of peanut or less on no more than 12 occasions (maximum of twice per month); and a cumulative ingestion of no more than 18 g of peanut. For analyses that required participants to meet the per-protocol criteria of both the primary trial and the follow-up study, the per-protocol population in the primary trial included participants who had adequate adherence to their randomized assignment to consume or avoid peanuts.[6]

The primary analysis was a between-group comparison of the percentage of participants in the intention-to-treat population who had peanut allergy at 72 months; the analysis was performed with the use of a two-tailed chi-square test at the 0.05 level of significance. In a secondary analysis, a paired comparison was made with the use of McNemar's test at the 0.05 level of significance between the percentages of participants in the peanut-consumption group who had peanut allergy at 60 months and at 72 months. Worst-case imputation was performed, which assumed that all participants with missing outcomes in the peanut-consumption group had peanut allergy and all participants with missing outcomes in the peanut-avoidance group did not have peanut allergy. A subgroup analysis was also performed that included only participants who had their primary outcome assessed by means of an oral peanut challenge at 72 months of age (i.e., excluding participants for whom the results of the oral peanut challenge were not available). Data sets for these analyses are accessible through TrialShare, a public website managed by the Immune Tolerance Network (www.itntrialshare.org/LEAPOn.url).

RESULTS

ENROLLMENT AND CHARACTERISTICS OF THE PARTICIPANTS

A total of 628 participants completed the primary trial (314 participants in the peanut-avoidance group and 314 in the peanut-consumption group) and had peanut-allergy outcomes that could be evaluated; these participants were eligible to enroll in the follow-up study. From May 26, 2011, to May 29, 2014, we enrolled 556 of these participants (88.5%; 282 participants in the peanut-avoidance group and 274 in the peanut-consumption group) in the follow-up study. Of these, 550 participants (280 in the peanut-avoidance group and 270 in the peanut-consumption group) had a peanut-allergy outcome that could be evaluated in the follow-up study and were included in the intention-to-treat analysis (Fig. S1 in the Supplementary Appendix).

The mean age of the participants at enrollment was 61.3 months. Of the 64 participants in the primary trial who had peanut allergy, 63 enrolled in the follow-up study. Additional characteristics of the participants in the primary trial who enrolled in the follow-up study and those who did not enroll are provided in Table S1A and S1B in the Supplementary Appendix.

DETERMINATION OF PEANUT ALLERGY

Among the 550 participants in the intention-to-treat population, determination of peanut allergy was made by means of an oral peanut challenge in 515 (93.6%). Among the 41 participants who did not undergo an oral challenge, we determined on the basis of a diagnostic algorithm that 28 participants had a peanut allergy and 7 were tolerant (Fig. S2 in the Supplementary Appendix). A determination could not be made for 6 participants. Further details regarding these participants who did not have primary-outcome data (and were not included in the intention-to-treat population) are shown in Table S2A and S2B in the Supplementary Appendix.

ADHERENCE

A total of 223 of 282 participants who had been assigned to the peanut-avoidance group in the

primary trial (79.1%) and 127 of 274 who had been assigned to the peanut-consumption group in the primary trial (46.4%) reported complete peanut avoidance during the follow-up period (Table S3 in the Supplementary Appendix). A total of 32 participants in the peanut-avoidance group (11.3%) and 63 in the peanut-consumption group (23.0%) reported consuming some peanut but still met the per-protocol definition; 8 participants in the peanut-avoidance group (2.8%) and 65 in the peanut-consumption group (23.7%) consumed too much peanut to meet the per-protocol definition.

Dust samples from participants' beds were obtained at month 72 from 180 of 282 participants (63.8%) in the peanut-avoidance group and from 171 of 274 (62.4%) in the peanut-consumption group. In the peanut-avoidance group as a whole (those who met the per-protocol criteria for the follow-up study and those who did not), the median concentration of peanut protein in bed dust was 4.1 μg per gram at 60 months, as compared with 4.6 μg per gram at 72 months (Fig. S3 in the Supplementary Appendix). In the peanut-consumption group as a whole, the median concentration declined from 95.2 μg per gram at 60 months to 10.5 μg per gram at 72 months (Fig. S3 in the Supplementary Appendix). Participants in the peanut-consumption group who met the per-protocol criteria for the follow-up study had a greater decline in the concentration than did those in the peanut-consumption group as a whole and also a greater decline than those participants in the peanut-consumption group who did not meet the per-protocol criteria — from 75.9 μg per gram to 6.3 μg per gram, which is a level similar to the concentration in the peanut-avoidance group at 60 months.

EVIDENCE FOR UNRESPONSIVENESS TO PEANUT

At 72 months, among the 550 participants in the intention-to-treat population, 18.6% of the participants in the peanut-avoidance group (52 of 280 participants) and 4.8% of those in the peanut-consumption group (13 of 270) had peanut allergy (P<0.001) (Fig. 1). The findings remained significant in analyses that used worst-case imputation or that excluded participants who did not undergo an oral challenge (P<0.001) (Fig. S4 in the Supplementary Appendix). In the peanut-consumption group, the percentage of participants with peanut allergy was 3.6% (10 of 274 participants) at 60 months and 4.8% (13 of 270) at 72 months (P=0.25).

A total of 445 participants met the per-protocol criteria in both the primary trial and the follow-up study. At 72 months, 19.2% of the participants in the peanut-avoidance group had peanut allergy and 2.1% of those in the peanut-consumption group had peanut allergy (P<0.001) (Fig. 1).

We also assessed the percentage of participants with peanut allergy according to the degree of peanut consumption during the follow-up study among participants who met the per-protocol criteria in the primary trial (Table S3 in the Supplementary Appendix). Among participants who reported no peanut consumption during the follow-up study, the percentage of those with allergy was 21.5% (48 of 223 participants) in the peanut-avoidance group and 2.4% (3 of 127) in the peanut-consumption group (P<0.001).

SAFETY

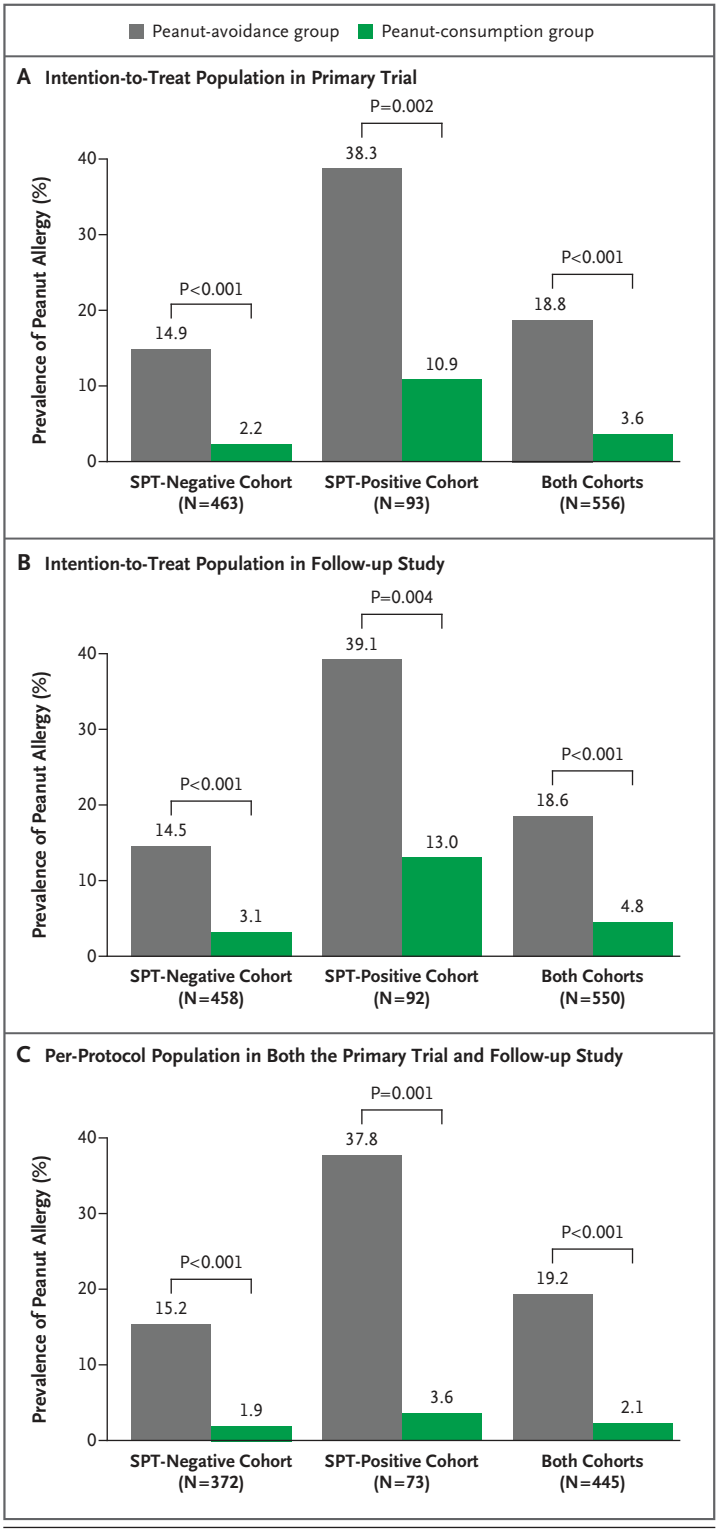
Overall, more participants in the peanut-avoidance group than in the peanut-consumption group reported adverse events during the follow-up study (252 of 282 participants [89.4%] vs. 221 of 274 [80.7%]). Eczema, lower respiratory tract infection, myopia, and gastroenteritis were reported more frequently among participants in the peanut-avoidance group than among those in the peanut-consumption group (Table S4 in the Supplementary Appendix).

IMMUNOLOGIC ASSESSMENTS

As expected, participants with peanut allergy at 72 months had higher levels of Ara h2–specific IgE and peanut-specific IgE and larger wheal size on skin-prick testing with peanut extract than participants who did not have peanut allergy (Fig. 2A; and Fig. S5A, S5B, and S5D in the Supplementary Appendix). The mean levels of Ara h2–specific IgE declined significantly in the peanut-consumption group from 30 months to 60 months during the primary trial (P<0.001) (Fig. 2A, and Fig. S5A in the Supplementary Appendix) and remained low at 72 months in the follow-up study. In contrast, the mean levels of Ara h2–specific IgE in the peanut-avoidance group in the primary trial were stable over time and were significantly higher than the levels in the peanut-consumption group at 60 months and at 72 months (P<0.001) (Fig. 2A, and Fig. S5A

Figure 1. Primary Outcome.

The prevalence of peanut allergy at 72 months of age is shown among participants who had a negative result on the skin-prick test (SPT) at the baseline visit in the primary trial, among those who had a positive result at the baseline visit, and in both groups combined. In the primary trial, participants at high risk for allergy had been randomly assigned to consume peanuts beginning in the first 11 months of life (peanut-consumption group) or avoid peanuts (peanut-avoidance group). Panel A shows the prevalence of peanut allergy at 60 months of age among only the participants in the primary trial who enrolled in the follow-up study. Panel B shows the prevalence of peanut allergy at 72 months of age among participants in the follow-up study who were included in the intention-to-treat analysis (i.e., all enrolled participants in the follow-up study who had a peanut-allergy outcome that could be evaluated). Panel C shows the prevalence of peanut allergy at 72 months of age among participants who met the per-protocol criteria in both the primary trial and the follow-up study. The main per-protocol criterion in the primary trial was adequate adherence to the randomized assignment to consume or avoid peanuts; the main per-protocol criterion in the follow-up study was adequate adherence to avoidance of peanut protein over a period of 12 months.



in the Supplementary Appendix). The mean wheal size on skin-prick testing remained smaller in the peanut-consumption group than in the peanut-avoidance group at month 72 (P<0.001) (Fig. 2A, and Fig. S5B in the Supplementary Appendix).

After the yearlong period of peanut avoidance, the peanut-specific IgG4 levels continued to be higher in the peanut-consumption group than in the peanut-avoidance group (P<0.001) (Fig. 2B, and Fig. S5C in the Supplementary Appendix), despite a decline that started before the participants in the peanut-consumption group stopped eating peanuts. The ratio of peanut-specific IgG4:IgE also continued to be significantly higher in participants in the peanut-consumption group than in those in the peanut-avoidance group (Fig. 2B).

IMMUNOLOGIC CHANGES IN PARTICIPANTS WHOSE ALLERGY OUTCOME CHANGED

New allergy developed in three participants in the peanut-consumption group (1.1%) and in three in the peanut-avoidance group (1.1%) between month 60 and month 72 (Fig. 3). The ratio of peanut-specific IgG4:IgE declined between month 60 and month 72 in all six participants (Table S6A in the Supplementary Appendix).

In addition, four participants in the peanut-avoidance group who had peanut allergy at month 60 did not have an allergic status by

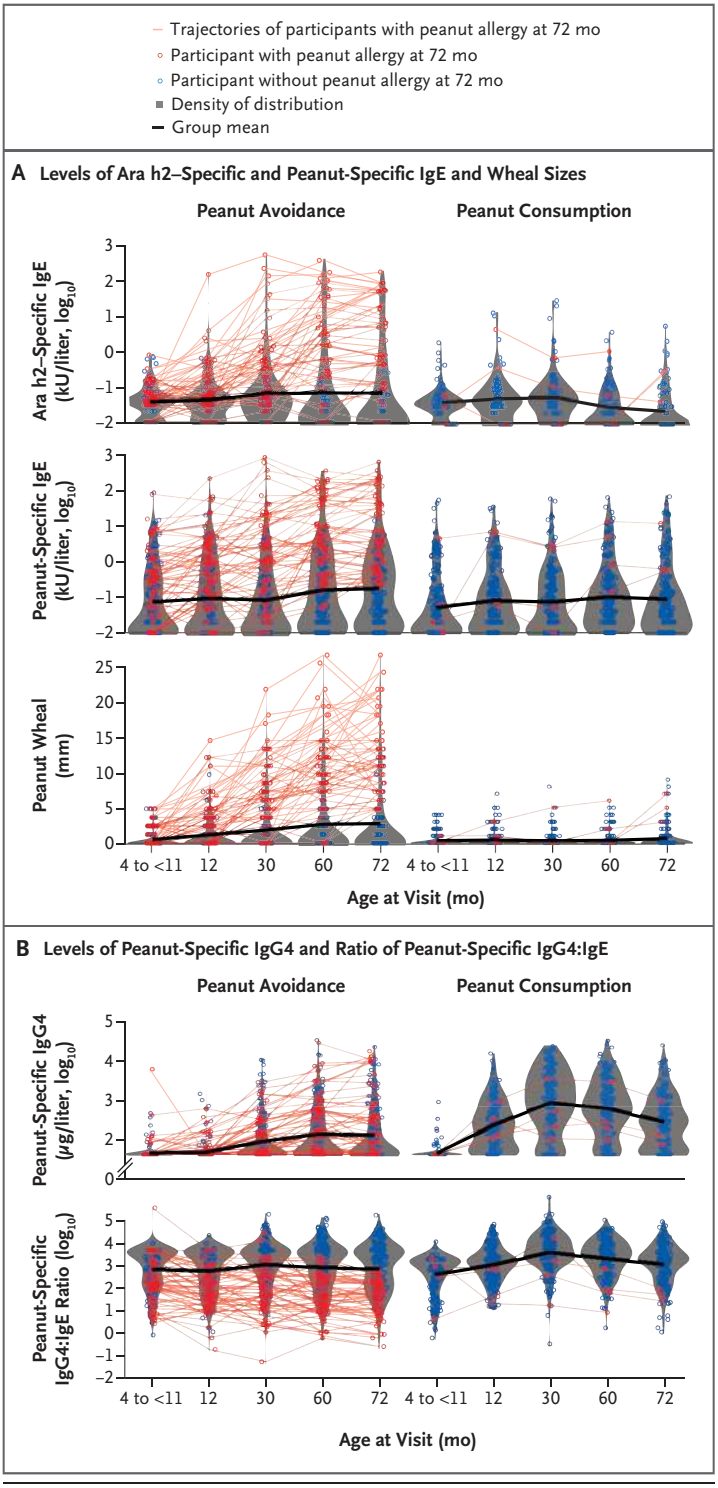


Figure 2. Immunologic Outcomes in the Peanut-Avoidance and Peanut-Consumption Groups, from Baseline to 72 Months of Age.

Data are shown for participants who met the per-protocol criteria for both the primary trial and the follow-up study. Panel A shows the Ara h2–specific and peanut-specific IgE titers and wheal sizes on skin-prick testing for peanut. (Ara h2 is a component of peanut protein.) The level of Ara h2–specific IgE was assessed in all available participants who had a peanut-specific IgE level that was greater than or equal to 0.1 kU per liter at any visit (approximately 60% of the participants). Panel B shows peanut-specific IgG4 levels and IgG4:IgE ratios. The solid black lines show the group mean over the course of the study period. The thin red lines represent the trajectory among participants who had a peanut allergy at 72 months of age. Dots represent individual participants (blue indicates that the participant did not have peanut allergy, and red indicates allergy at 72 months). The gray shading represents the density of the distribution of the dots for participants who met the per-protocol criteria for both the primary trial and the follow-up study. The density of the distribution facilitates visual comparisons over time and between groups, which is not easily achievable with display of the individual dots alone, owing to a large amount of overplotting. The $\log_{10}$ of the ratio of peanut-specific IgG4:IgE was calculated after peanut-specific IgE levels were converted from kilo unit per liter to nanograms per milliliter with the use of the formula ($\text{IgG4} \div [\text{IgE} \times 2.4]$).

month 72. Their wheal size on skin-prick testing declined, although other immunologic variables remained stable (Fig. 3, and Table S6B in the Supplementary Appendix).

DISCUSSION

This follow-up study showed that the reduction in the prevalence of peanut allergy that was associated with the early introduction and consumption of peanuts until 60 months of age persisted at 72 months of age after 12 months of not eating peanuts. Overall, after the introduction of peanuts in the first year of life, peanut consumption for the following 4 years, and a year of abstinence from peanuts, the peanut-consumption group had a prevalence of peanut allergy that was 74% lower than the prevalence in the peanut-avoidance group, a finding that shows unresponsiveness to peanut after a long period (12 months) of peanut avoidance.

Among participants in the peanut-consumption group who had not been assessed as having peanut allergy, the small wheal size on skin-prick testing, low levels of Ara h2–specific IgE, and high ratios of peanut-specific IgG4:IgE that were observed at month 60 were maintained

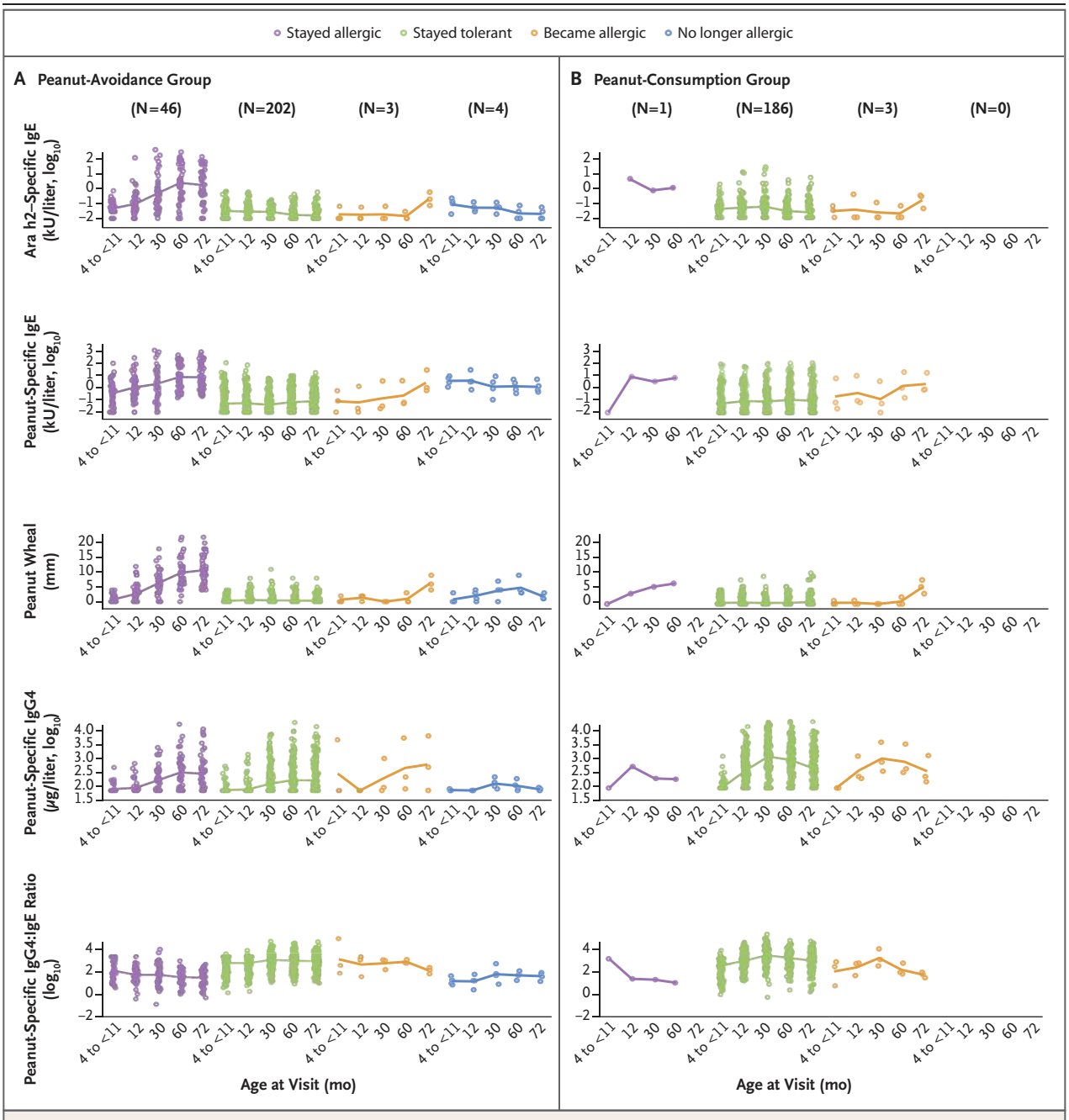


Figure 3. Immunologic Outcomes According to Differing or Stable Allergy Status between Months 60 and 72.

Participants were categorized as "stayed allergic," "stayed tolerant," "became allergic," or "no longer allergic." Shown are the Ara h2–specific IgE antibody levels, peanut-specific IgE level, wheal size on skin-prick testing for peanut, peanut-specific IgG4 level, and IgG4:IgE ratios at the five assessments during the primary trial and the follow-up study. Data are shown only for participants who met the per-protocol criteria in both the primary trial and the follow-up study. At month 72, a total of 46 participants in the peanut-avoidance group and 1 in the peanut-consumption group were determined by the investigators to be still allergic, 202 in the peanut-avoidance group and 186 in the peanut-consumption group were still not allergic, 3 in the peanut-avoidance group and 3 in the peanut-consumption group became allergic, and 4 in the peanut-avoidance group and 0 in the peanut-consumption group no longer had allergy. Lines represent population means. The $\log_{10}$ of the ratio of peanut-specific IgG4:IgE was calculated after peanut-specific IgE levels were converted from kilo unit per liter to nanograms per milliliter with the use of the formula (IgG4 ÷ [IgE × 2.4]).

after 12 months of not eating peanuts. This observation suggests that their nonallergic status remained stable.

With respect to the immunologic changes associated with peanut consumption, the timing of the effects on IgG4 levels differed from the timing of the effects on IgE levels. Whereas participants in the peanut-consumption group had elevated peanut-specific IgG4 levels as early as month 12 (Fig. 2B, and Fig S5C in the Supplementary Appendix), a significant decrease in the mean levels of Ara h2–specific IgE had occurred by month 60 and continued to month 72 (Fig. 2B, and Fig. S5A in the Supplementary Appendix). The inhibition of IgE synthesis in the participants in the peanut-consumption group is further reflected by the fact that as compared with participants in the peanut-avoidance group, relatively few participants in the peanut-consumption group had high-level IgE to peanut and to Ara h2, beginning primarily at month 30 and continuing through months 60 and 72. Our data do not allow us to distinguish among potential cellular mechanisms, including clonal deletion, immune suppression, or the influence of regulatory cells, that could underlie these changes.

One of the possibilities we considered was that avoidance after the consumption of peanut might cause the development of new peanut allergy. However, the low incidence of new peanut allergy over the 12-month period of the follow-up study, which was similar in the peanut-avoidance group and the peanut-consumption group, showed that this was not the case. We cannot determine whether, among the few participants in the peanut-consumption group with new-onset allergy, the allergy developed as a result of loss of tolerance to peanut or acquisition of new allergy. The benefit of the intervention was evident even if participants ate some peanut, which shows that intermittent consumption did not lead to a break in tolerance to peanuts.

Together, these findings show that 4 years of consuming peanut was sufficient to induce stable unresponsiveness to peanut, independent of the level of subsequent consumption of peanut. Our study design did not allow us to determine the minimum duration of consumption that is required to induce such a state. Our findings suggest, however, that peanut consumption should be prolonged in order to reduce ongoing production of IgE specific for peanut and Ara h2. Our findings are also consistent with the observation that durable clinical benefit requires long-term immunotherapy, as has been shown with stinging-insect venom,[13] grass pollen,[14-16] and oral egg.[8]

A strength of the study is that the enrollment rates in the follow-up study were high, with 88.5% of the eligible participants from the primary trial enrolled. Children who enrolled in the follow-up study were more likely than those who did not enroll to have allergy or to be sensitized (Table S1A in the Supplementary Appendix). This finding reassures us that we were unlikely to have missed new cases of peanut allergy.

Overall adherence to the intervention of peanut avoidance in the follow-up study was also high, with 80.0% of the participants (445 of 556 participants) meeting the per-protocol criteria. However, the rates differed between the peanut-avoidance group and the peanut-consumption group (90.4% of participants [255 of 282 participants] vs. 69.3% [190 of 274]) (Table S3 in the Supplementary Appendix). Although this finding may be considered a weakness of the study, the per-protocol analysis was adequately powered. Furthermore, this finding enabled us to conclude that intermittent low-dose consumption of peanut during the follow-up study after either prolonged consumption or avoidance during the primary trial did not result in new-onset peanut allergy. Although the low rate of development of new peanut allergy among participants in the peanut-consumption group was reassuring, this result precluded the identification of predictive biomarkers for the acquisition of peanut allergy.

The LEAP trial and the LEAP-On study together showed that the early introduction of peanut induced unresponsiveness to peanut that persisted after 12 months of avoidance. The effectiveness and safety of this prevention strategy was maintained in children who avoided peanut altogether or who consumed peanut in lesser amounts after 60 months of age. It remains to be seen whether the effects of peanut consumption in early life are maintained if peanuts are consumed ad libitum over the course of many years.

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