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ORIGINAL ARTICLE

Follow-up to Adolescence after Early Peanut Introduction for Allergy Prevention

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Abstract

BACKGROUND A randomized trial demonstrated consumption of peanut from infancy to age 5 years prevented the development of peanut allergy. An extension of that trial demonstrated the effect persisted after 1 year of peanut avoidance. This follow-up trial examined the durability of peanut tolerance at age 144 months after years of ad libitum peanut consumption.

METHODS Participants from a randomized peanut consumption trial were assessed for peanut allergy following an extended period of eating or avoiding peanuts as desired. The primary end point was the rate of peanut allergy at age 144 months.

RESULTS We enrolled 508 of the original 640 participants (79.4%); 497 had complete primary end point data. At age 144 months, peanut allergy remained significantly more prevalent in participants in the original peanut avoidance group than in the original peanut consumption group (15.4% [38 of 246 participants] vs. 4.4% [11 of 251 participants]; P<0.001). Participants in both groups reported avoiding peanuts for prolonged periods of time between 72 and 144 months. Participants at 144 months in the peanut consumption group had levels of Ara h2-specific immunoglobulin E (a peanut allergen associated with anaphylaxis) of 0.03±3.42 kU/l and levels of peanut-specific immunoglobulin G4 of 535.5±4.98 μg/l, whereas participants in the peanut avoidance group had levels of Ara h2-specific immunoglobulin E of 0.06±11.21 kU/l and levels of peanut-specific immunoglobulin G4 of 209.3±3.84 μg/l. Adverse events were uncommon, and the majority were related to the food challenge.

CONCLUSIONS Peanut consumption, starting in infancy and continuing to age 5 years, provided lasting tolerance to peanut into adolescence irrespective of subsequent peanut consumption, demonstrating that long-term prevention and tolerance can be achieved in

Drs. Du Toit and Huffaker contributed equally to this article.

**A complete list of collaborators in the Immune Tolerance Network LEAP-Trio Trial Team is provided in the Supplementary Appendix, available at evidence.nejm.org.*

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food allergy. (Funded by the National Institute of Allergy and Infectious Diseases and others; ITN070AD, ClinicalTrials.gov number, NCT03546413.)

Introduction

With a prevalence of 1 to 2% in the Western world, peanut allergy exerts a significant burden on peanut-allergic individuals, their families, and society.[1-3] Peanut allergy is usually diagnosed in early childhood and is often life-long.[4-8] Thus, the prevention of peanut allergy is an important public health priority.

The LEAP (Learning Early About Peanut allergy) trial demonstrated that early consumption of peanut protected against peanut allergy development in infants at high risk of allergy when compared with peanut avoidance.[9] At 60 months of age, the prevalence of peanut allergy was 17.2% in the peanut avoidance group and 3.2% in the peanut consumption group (P<0.001), representing an 81% relative reduction.

The LEAP-On trial extended the LEAP trial, investigating whether 12 months of peanut avoidance would result in a loss of intervention efficacy.[10] After a year-long period of peanut avoidance, the prevalence of peanut allergy remained significantly higher in the peanut avoidance group compared with the peanut consumption group at 18.6% versus 4.8%, respectively (P<0.001).

We define tolerance as the choice to avoid or eat peanut at the frequency and quantity desired (ad libitum consumption) without risk of reaction, and we contrast this with the outcomes of oral immunotherapy. It is noteworthy that in one oral immunotherapy trial, 85 to 86% participants were desensitized to 4 g of peanut. However, upon reduction of peanut dose to 300 mg or discontinuation, there was a progressive loss of "tolerance" over the subsequent year with only 37% and 13% of participants, respectively, able to tolerate a 4-g peanut challenge 1 year later.[11] While the LEAP-On trial demonstrated protection from peanut allergy for 1 year after discontinuation of peanut, there is, as yet, no evidence that early introduction leads to durable long-term tolerance. In the original LEAP peanut consumption group, some participants were able to consume peanut at age 60 months despite large peanut skin-prick test wheals and elevated levels of peanut-specific and Ara h2-specific IgE.[9,10] This raised concern that they were not tolerant and would develop peanut allergy with further inconsistent exposure to peanut. In addition, a downward trend was observed in the peanut-specific IgG4 levels in the peanut consumption group between 30, 60, and 72 months (P<0.001).[9,10] The IgG4 responses to allergen are generally associated with protection, and decline in allergen-specific IgG4 upon withdrawal of immunotherapy correlates with loss of protection.[12-19] The decline in IgG4 levels in the sensitized LEAP peanut consumption group raised concern that the protection from peanut allergy seen with early peanut consumption may have only been temporary, as observed in many oral immunotherapy studies.

The LEAP trial findings informed changes to infant feeding guidelines in many countries.[20-22] It was therefore essential to understand the long-term clinical and immunologic sequelae of early peanut introduction.

We report here the long-term tolerance outcomes of the original LEAP participants in The Follow-up of LEAP Participants and Their Families: LEAP-Trio Trial.

Methods

TRIAL DESIGN AND OVERSIGHT

The LEAP-Trio trial was a long-term follow-up of the original LEAP participants. The designs of the LEAP and LEAP-On trials have been described previously.[9,10] After both groups underwent a 1-year period of peanut avoidance during LEAP-On, the nonallergic individuals were subsequently told to eat or not eat peanut as they wished. Those individuals found to be allergic at the end of LEAP-On were instructed to continue peanut avoidance, because this is the standard of care. In the LEAP-Trio trial, participants were assessed for peanut allergy at approximately 144 months (12 years) of age, following an extended period of ad libitum consumption. The trial was approved by the National Research Ethics Service Committee London–Fulham (REC reference 17/LO/1609). Written informed consent, assent, or both was obtained from all participants and/or their parent/legal guardian before enrollment. The protocol for the LEAP-Trio trial is available with the full text of this article in the supplementary materials available at evidence.nejm.org. The allergic status of the siblings and parents of the LEAP participants is not reported here.

ENROLLMENT

Enrollment took place from July 2018 to August 2022. Of the 640 LEAP trial participants, 630 were eligible to enroll in the LEAP-Trio trial; 10 had declined further contact. Additional eligibility criteria were age ≥114 months and willingness to participate in at least one trial data collection procedure. Participation in LEAP-On was not required.

OUTCOMES

The primary outcome was the proportion of participants with peanut allergy at 144 months of age. In most cases, this was determined by oral food challenge. Details of the oral food challenge procedure are provided in the Supplementary Methods in the Supplementary Appendix. If an oral food challenge was not possible, participants who reported consumption of at least 2 g of peanut protein without reaction on at least one occasion in the prior year were considered tolerant. The peanut allergy status for the remaining participants was determined using a prediction model developed for this trial using biomarker data.[23]

Secondary outcomes included the amount of peanut consumption, skin-prick test wheal sizes to peanut, and specific immunoglobulin (Ig) E measurements to peanut. Exploratory outcomes included concentration of environmental peanut protein in dust collected from the participants' homes. Adverse events related to trial procedures were collected during each trial visit and up to 30 days after each visit, or until the event was resolved, whichever came first.

Peanut consumption was assessed using questionnaires; details are provided in the Supplementary Methods.[9,10,24] Peanut protein levels were measured in bed dust as per previous studies.[9,10]

IMMUNE MARKERS

All participants were requested to undergo skin-prick testing to peanut and collection of serum for levels of peanut-specific IgE, IgG, and IgG4 and IgE and IgG4 to peanut-specific allergenic components, using the same methods reported in the LEAP and LEAP-On studies.[9,10] Details are provided in the Supplementary Methods.

STATISTICAL ANALYSIS

Sample size and power calculations are detailed in the Supplementary Methods. The intent-to-treat population included all LEAP trial participants who enrolled in LEAP-Trio and had at least one assessment completed. The per-protocol population included participants in the LEAP-Trio intent-to-treat population who were also in the LEAP trial per-protocol population (participants adherent to consumption or avoidance until at least 2 years of age).[9] The primary intent-to-treat analysis compared the rate of peanut allergy at 144 months between the LEAP-Trio participants in the original peanut consumption group and the participants in the original peanut avoidance group, using a logistic regression model with the LEAP treatment group as the fixed effect. The primary analysis was repeated in the LEAP-Trio participants in the original LEAP trial stratification groups (skin-prick test positive and negative at baseline) and in the per-protocol population. No multiplicity adjustments for the secondary and exploratory end points were defined. Therefore, only point estimates and 95% confidence intervals (CIs) are provided. The CIs have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects.

Methods for additional analyses are detailed in the Supplementary Methods.

Results

TRIAL POPULATION

We evaluated 508 of the 640 children who enrolled as infants into the primary LEAP trial (79.4%; 253 participants from the peanut avoidance group, 255 from the peanut consumption group) (Fig. S1). The mean age was 13.0 years of age (range, 10.5 to 16.3 years). Enrollment characteristics of LEAP-Trio participants compared with the LEAP trial participants who did not enroll in LEAP-Trio are shown in Table S1. Enrollment characteristics of LEAP trial participants compared with the general population of infants with atopic dermatitis are shown in Table S2.

DETERMINATION OF PEANUT ALLERGY STATUS

A total of 497 participants had sufficient data to determine the primary outcome of peanut allergy. Allergic status was determined by oral food challenge in 400 participants (80.5%). The allergy status for the remaining participants was determined as detailed in Figure S2 and Table S3. Two participants had indeterminate oral food challenges, one of which was deemed consistent with protocol-defined oral allergy syndrome. For the remaining participant with an indeterminate oral food challenge and the

95 participants for whom an oral food challenge was not done, 61 (12.3%) met the trial criteria for peanut tolerance by history of 2 g of peanut protein consumption on at least one occasion in the previous year without any symptoms. The allergic status of the remaining 35 participants (7.0%) was assessed using the previously developed prediction model. Internal validation within the LEAP-Trio population was performed comparing the results of the prediction model against food challenge outcome data and found the model correctly predicted 95.2% of the allergic participants as allergic, with only one incorrectly predicted as tolerant and 96.0% of the tolerant participants correctly as tolerant (Table S4).

PEANUT ALLERGY

In the intention-to-treat analysis, 15.4% (38 of 246) of participants in the peanut avoidance group and 4.4% (11 of 251) of participants in the peanut consumption group at 144 months had peanut allergy (P<0.001) (Fig. 1 and Fig. S4), representing a 71% reduction in the prevalence of peanut allergy at the LEAP-Trio time point. To account for potential bias due to differential rates of follow-up, sensitivity analyses were performed and yielded similar results to the primary analyses (Table S5).

Early peanut consumption had an impact on peanut allergy in the originally skin-prick test–negative participants, with 12.7% (26 of 205) manifesting peanut allergy at 144 months in the peanut avoidance group versus 2.8% (6 of 213) in the peanut consumption group. In the skin-prick test–positive participants, these figures were 29.3% (12 of 41) allergic in the avoidance group versus 13.2% (5 of 38) in the consumption group (Fig. 1). Subgroup analyses according to race or ethnic group showed the same trends (Table S6). Overall, early peanut consumption was associated with a 75% reduction in the prevalence of ever having had peanut allergy during the lifespan of the LEAP-Trio participants (Fig. S5).

Among the 470 children in the LEAP-Trio per-protocol analysis, peanut allergy was established in 15.1% (35 of the 232) of the participants in the peanut avoidance group and 0.8% (2 of the 238) of the participants in peanut consumption group. This represents a 14.2 percentage point difference between groups (95% CI, 9.5 to 19.0 percentage points), or a 95% relative reduction in peanut allergy (Fig. S6). The effect size was similar in the skin-prick test–negative and skin-prick test–positive groups: an 11.1% difference (95% CI, 6.3 to 15.9%) and 29.3% difference (95% CI, 15.3 to 43.2%) between peanut avoidance and peanut consumption groups.

Fourteen participants in the intention-to-treat analysis had a change in allergic status from 72 months to 144 months. New peanut allergy developed in one participant (0.5%) in the peanut consumption group and in two participants (0.9%) in the peanut avoidance group (Table S7). Nine participants from the peanut avoidance group and two participants from the peanut consumption group who were allergic at 72 months became tolerant to peanut by 144 months (Table S8).

PATTERNS OF PEANUT CONSUMPTION AMONG THOSE TOLERANT TO PEANUT

There was a wide range of average weekly peanut consumption in the 4 weeks before the 144-month assessment. The peanut consumption group participants ate 2.9 ± 12.0 g (geometric mean [geomean]±SD), and the peanut avoidance group participants ate 0.2 ± 20.6 g (geomean±SD) (ratio of geometric means, 12.2; 95% CI, 7.2 to 20.5) as part of the diet (Fig. 2). In the years following the last LEAP or LEAP-On visit, there was heterogeneity in the consumption and avoidance patterns of both the peanut consumption group and the peanut avoidance group participants (Fig. S7). Within each year interval, 26.8 to 33.1% of the participants from the peanut consumption group reported eating 50 g of peanut protein or less per year, and 13.3 to 15.1% completely avoided peanut for more than 6 months in a given year.

Concentrations of peanut protein, assayed through polyclonal enzyme-linked immunosorbent assay against whole peanut protein, in dust in the home, taken at the 144-month assessment similarly were 34.8 ± 7.0 μg/g (geomean±SD) in the peanut consumption group and 10.6 ± 4.4 μg/g (geomean±SD) in the peanut avoidance group (ratio of geometric means, 3.29; 95% CI, 2.00 to 5.40) (Fig. 2). Concentrations of peanut protein in dust increased in both the peanut avoidance and the peanut consumption group from 72 months to 144 months (Fig. S8).

A regression analysis of peanut-specific IgE and Ara h2 IgE against the variables of peanut consumption and peanut avoidance over the years since the last LEAP or LEAP-On visit showed no association (Table S9).

IMMUNOLOGIC ASSESSMENTS

The immunologic assessments for participants found to be peanut-allergic at 144 months are shown in Table S10.

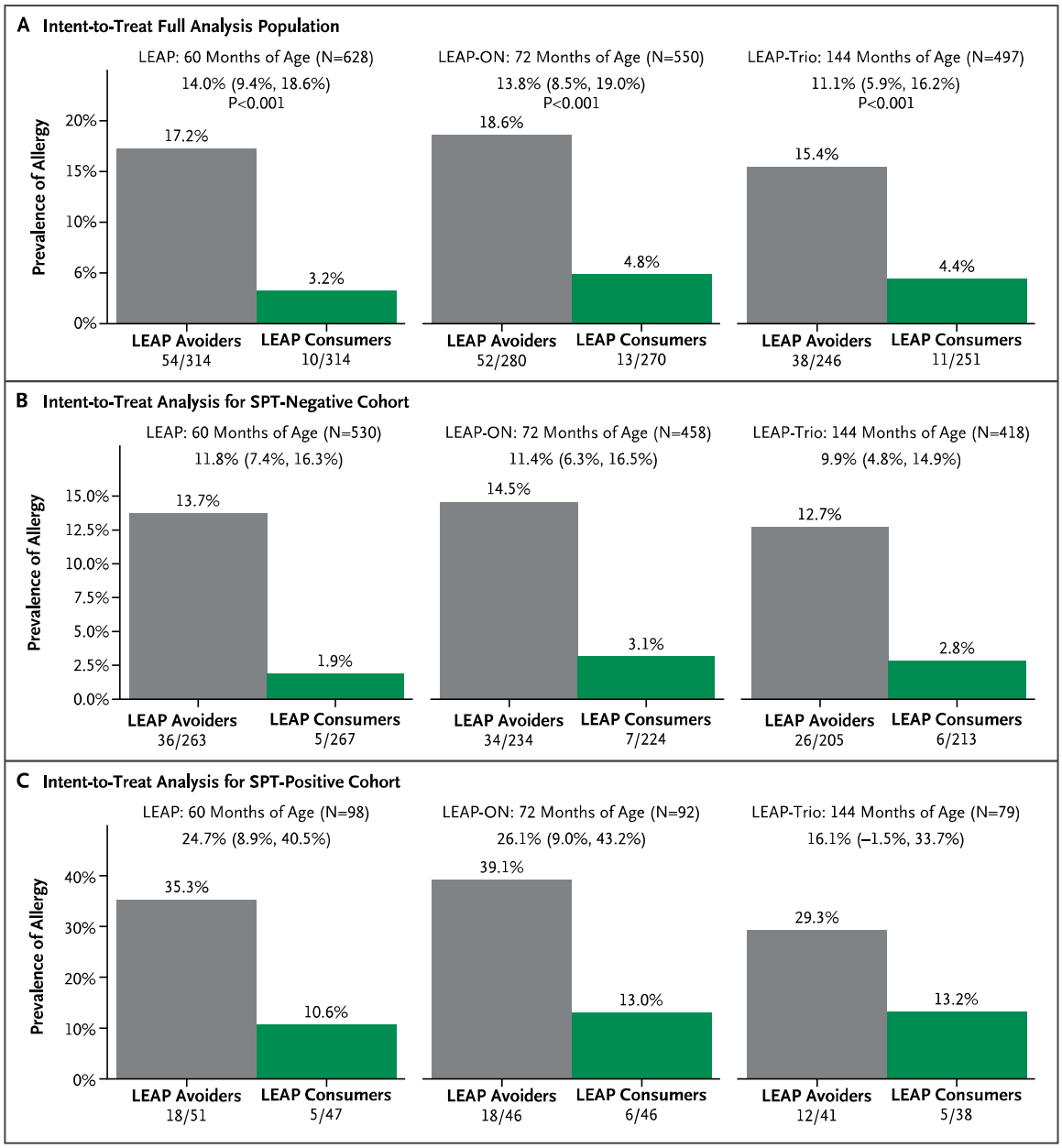

Figure 1. Primary Outcome at 60, 72, and 144 Months.

The prevalence of peanut allergy at 60, 72, and 144 months of age is shown in the intention-to-treat analysis for all trial participants (Panel A), among those who had a negative peanut-specific skin prick test result at baseline (Panel B), and among participants who had a positive peanut-specific skin prick test result at baseline (Panel C). The percentage differences and 95% confidence intervals for the differences between the percentage of allergic participants in the LEAP Avoider and LEAP Consumer treatment groups are shown. Confidence intervals were calculated using the unadjusted Wald method. The number of allergic participants and total number of participants within each treatment group are also presented. In the original LEAP trial, participants at high risk for allergy had been randomly assigned to consume peanut beginning in the first 11 months of life (peanut consumption group) or avoid peanut (peanut avoidance group) until 60 months. Between 60 and 72 months, all trial participants were asked to avoid peanut. Between 72 and 144 months, trial participants were eating peanut ad libitum. SPT denotes skin prick test.

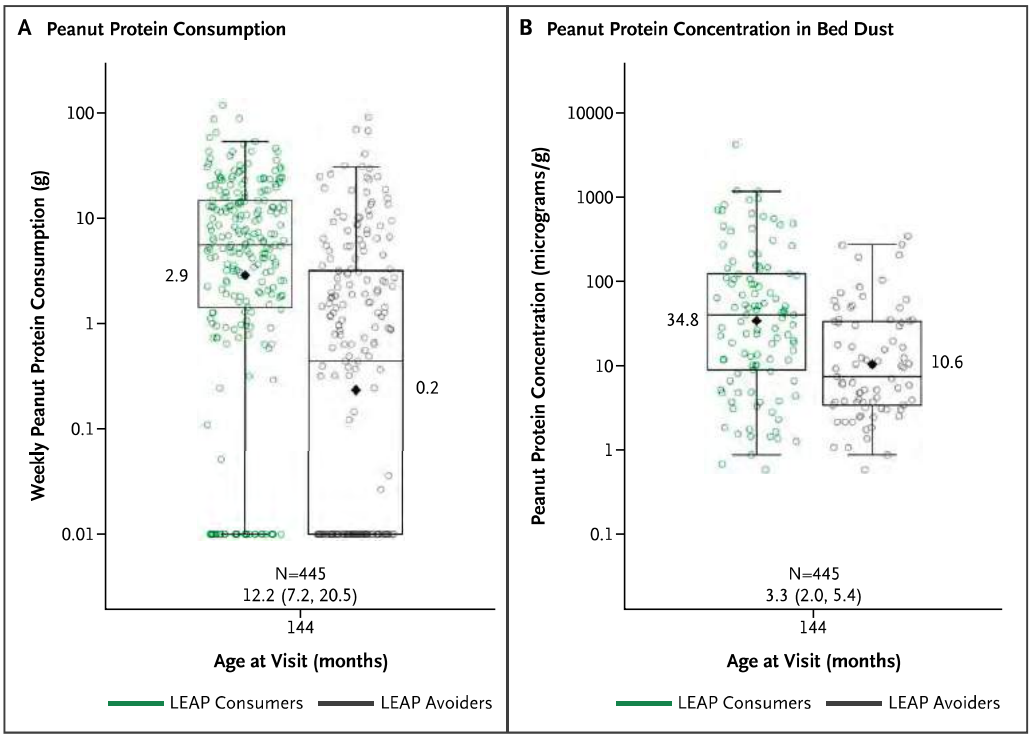

Figure 2. Peanut Consumption and Peanut Protein in Dust.

Panel A shows the average weekly peanut protein in grams consumed in the 4 weeks prior to the 144-month assessment for all tolerant participants in the intention-to-treat population. Panel B shows comparisons of peanut protein concentrations in bed dust of tolerant participants within the peanut avoidance and peanut consumption groups at 144 months. Dust samples from participants' beds at 144 months were obtained from 40.7% of participants in the peanut avoidance group and 48.6% in the peanut consumption group. Values are presented as micrograms of peanut protein per gram of collected dust. In both panels, gray circles represent peanut avoiders. Green circles represent peanut consumers. Horizontal bars indicate median values. Diamonds, as well as labels, indicate geometric mean values. The geometric mean ratios of LEAP Consumers:LEAP Avoiders, along with the 95% confidence intervals, are shown.

At 144 months, skin-prick test wheals were (mean±SD) 1.4±2.6 mm in the peanut consumption group and 2.8±4.7 mm in the peanut avoidance group, leading to a mean difference of −1.4 mm (95% CI, −2.1 to −0.7 mm) (Fig. 3 and Fig. S9). There was no change in Ara h2-specific IgE levels in the peanut consumption and peanut avoidance groups between 72 and 144 months (Fig. 3 and Fig. S10). At 144 months, the geometric mean (±SD) levels of Ara h2-specific IgE in the peanut consumption group were 0.03±3.42 μg/l and 0.06±11.2 μg/l in the peanut avoidance group (ratio of geometric mean, 0.4; 95% CI, 0.3 to 0.7) (Fig. S10). In this trial, the geometric mean (±SD) levels of Ara h6-specific peanut IgE, which was not measured in the prior studies, in the peanut consumption group were 0.03±3.04 μg/l and 0.06±10.75 μg/l in the peanut avoidance group (ratio of geometric mean, 0.4; 95% CI, 0.3 to 0.6) (Fig. S11). Peanut-specific IgE levels increased from 72 to 144 months in both groups and were not different between groups at 144 months (Fig. S12). The relative distributions of peanut-specific IgE and Ara h2-specific IgE in the peanut consumption and peanut avoidance groups at each of the study time points are shown in Figure 4.

At 144 months, the peanut-specific IgG4 geometric mean (±SD) levels were 535.5±5.0 μg/l in the peanut consumption group and 209.3±3.8 μg/l in the peanut avoidance group (ratio of geometric means, 2.6; 95% CI, 1.9 to 3.4) (Fig. S13). The peanut-specific IgG4 levels were similar in the peanut avoidance group between 72 months and 144 months.

IMMUNOLOGIC BIOMARKERS IN PARTICIPANTS WHOSE ALLERGY OUTCOME CHANGED

The two participants who became allergic between 72 and 144 months of age showed a rise in Ara h2-specific IgE and peanut-specific IgE and a decline in the peanut-specific

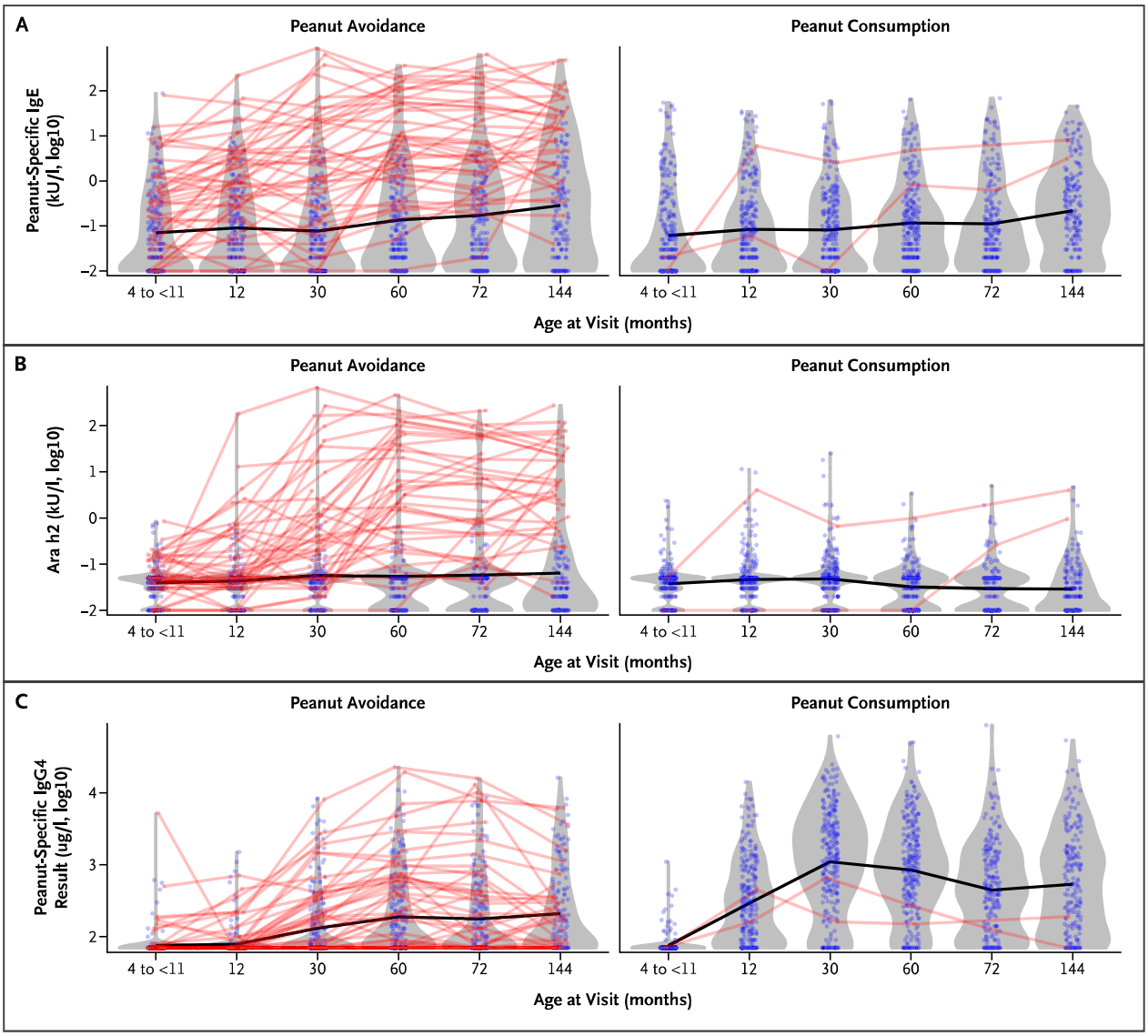

Figure 3. Immunologic Outcomes for the Peanut Avoidance and Peanut Consumption Groups at Baseline (4 to <11 Months of Age) and at 12, 30, 60, 72, and 144 Months of Age.

Data are shown for participants who met the per-protocol criteria for the primary trial. Panel A shows the $\log_{10}$-transformed levels of peanut-specific immunoglobulin (Ig) E in participants in the avoidance and consumption groups. Panel B shows the $\log_{10}$-transformed levels of Ara h2-specific IgE. Panel C shows the $\log_{10}$-transformed levels of peanut-specific IgG4. Panel D shows the $\log_{10}$-transformed peanut-specific IgG4:IgE ratio. Panel E shows wheal sizes after the peanut-specific skin-prick test. The solid black lines show the group mean at each assessment. Dots represent individual participants (blue indicates that the participant did not have peanut allergy, and red indicates allergy at 144 months). The red lines represent participants who were allergic at 144 months of age. The gray shading represents the density of the distribution of the participants. The $\log_{10}$ of the ratio of peanut-specific IgG4:IgE was calculated after peanut-specific IgG4 levels were converted from milligrams per liter to nanograms per milliliter and the 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]).

IgG4:IgE ratio (Fig. 5 and Table S7). The two participants from the consumption group that were allergic at 72 months and became tolerant by 144 months had Ara h2-specific IgE levels of 0.0 and 0.3 kU/l and peanut-specific IgE levels of 0.6 and 11.9 kU/l at 72 months; the nine participants from the avoidance group that were allergic at 72 months and became tolerant by 144 months had an Ara h2-specific IgE range of 0.0 to 2.3 kU/l and a peanut-specific IgE range of 0.2 to 23.7 kU/l (Fig. 5 and Table S8).

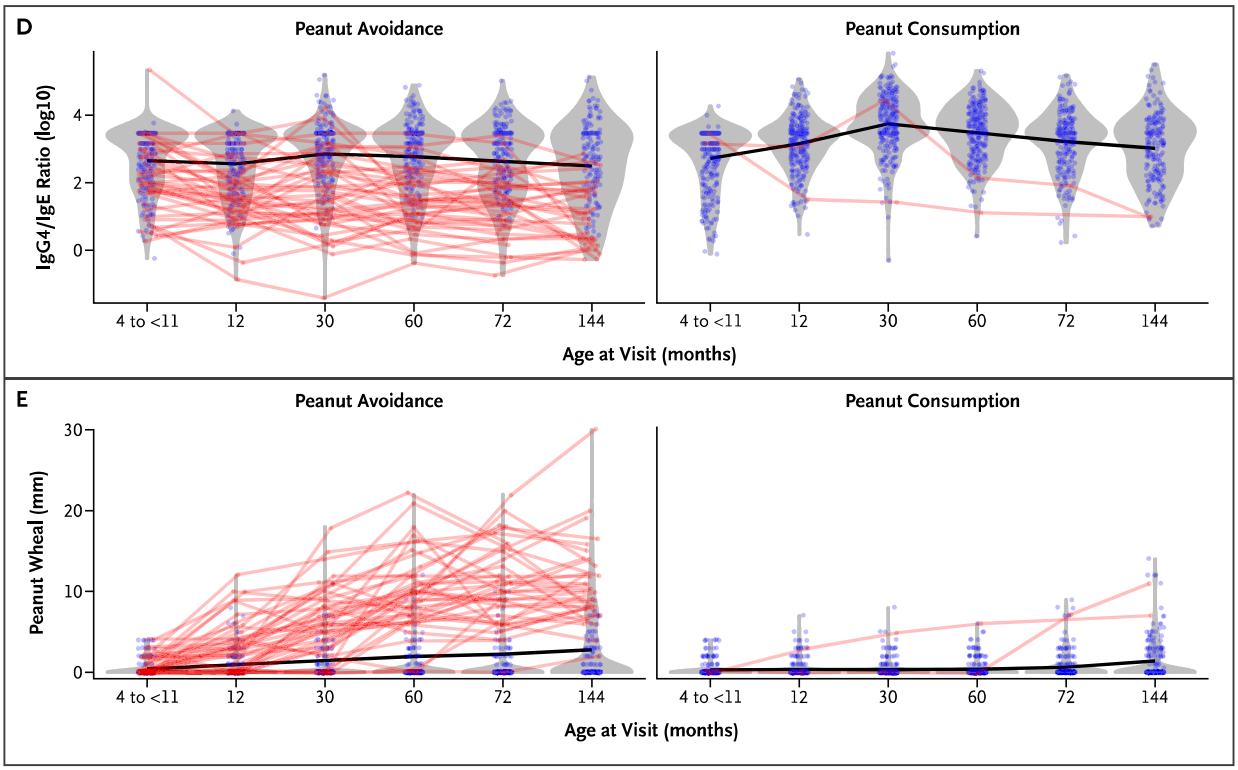

Figure 3. Continued.

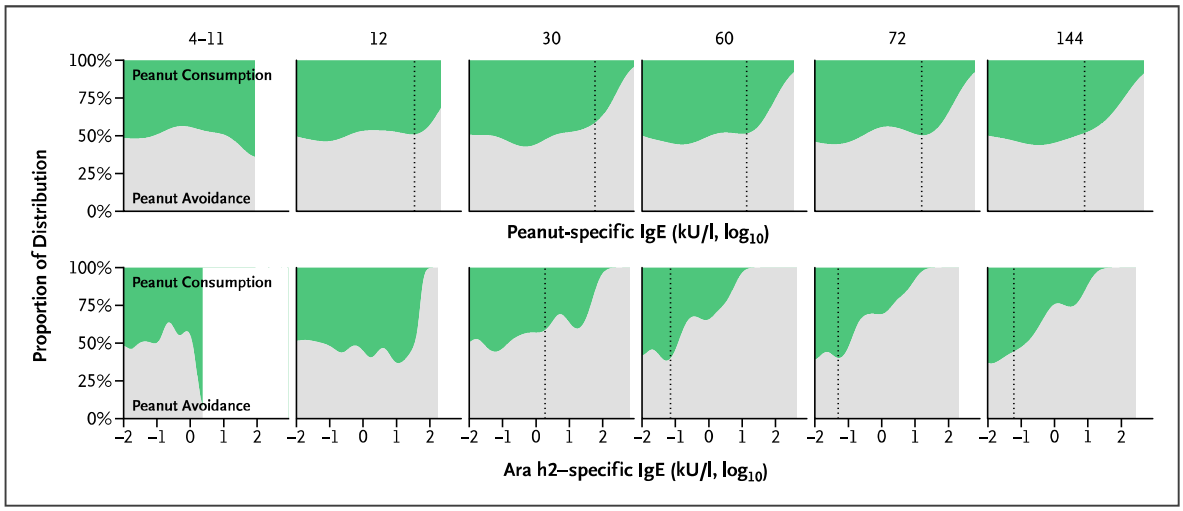

Figure 4. Proportion Density Plot for Peanut-Specific IgE and Ara h2-Specific IgE.

Shown are the relative distributions of peanut-specific immunoglobulin (Ig) E and Ara h2-specific IgE between the peanut consumption (shown in green) and avoidance (shown in gray) groups for participants who met the per-protocol criteria for the primary trial. The vertical reference lines indicate where the higher end of the distribution begins to differ at the 95% confidence level between the randomized groups using bootstrap sampling of 1000 replicates of the upper percentiles. Peanut-specific IgE and Ara h2-specific IgE values are $\log_{10}$-transformed.

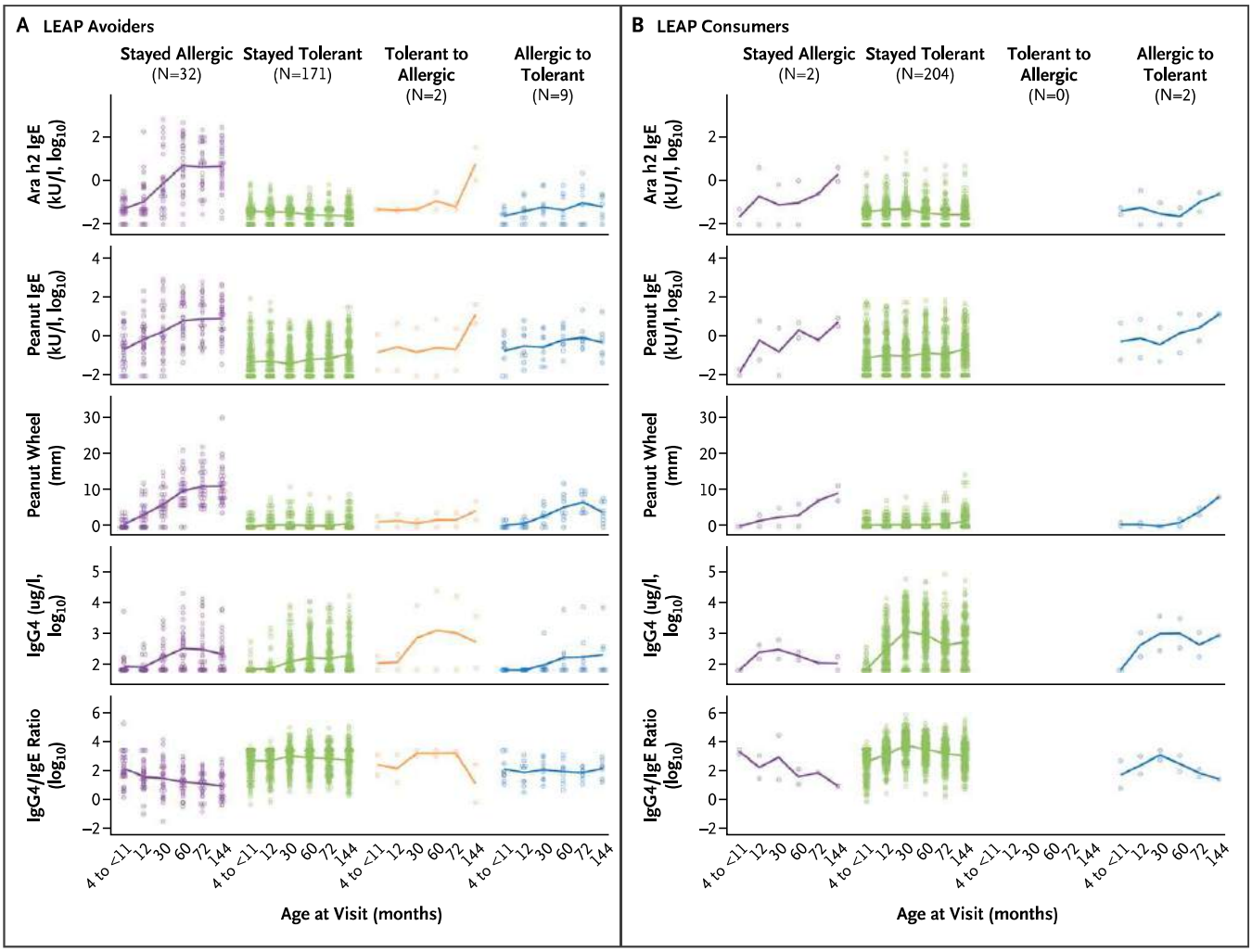

Figure 5. Immunologic Outcomes According to Allergy Status.

Participants were categorized as "stayed allergic," "stayed tolerant," "tolerant to allergic," or "allergic to tolerant." Shown are the $\log_{10}$-transformed Ara h2-specific immunoglobulin (Ig) E levels, $\log_{10}$-transformed peanut-specific IgE levels, wheal size on skin-prick testing for peanut, $\log_{10}$-transformed peanut-specific IgG4 level, and $\log_{10}$-transformed IgG4:IgE ratios at each assessment for the avoidance group (Panel A) and the consumption group (Panel B). Data are shown only for participants who met the per-protocol criteria in the primary trial and differ from the data reported at the end of LEAP-On, in which immunological outcomes are shown for participants who met the per-protocol criteria in both the primary trial and the follow-up trial. 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 ($\text{IgG4}/[\text{IgE} \times 2.4]$).

SAFETY

One participant was hospitalized overnight for prolonged vomiting. There were two instances of epinephrine administration during the oral food challenge (Table S10).

Discussion

In the LEAP-Trio trial, we demonstrated that regular early consumption of peanut achieved durable tolerance to peanut regardless of consumption in later childhood. The cumulative protective effect of early peanut introduction over time remained at a 75% reduction in peanut allergy in the intent-to-treat analysis. This reflects 10 children needing to introduce early peanut consumption to prevent one case of peanut allergy (95% CI, 6 to 17). Although LEAP-trial children were highly atopic as infants, tolerance to peanut was maintained across a whole spectrum of peanut consumption and various periods of avoidance. The LEAP-Trio trial extends the widely replicated

data from the original LEAP trial to show the efficacy of early introduction to an allergenic food persists into adolescence.[25,26] It should be noted that the protective effects of peanut consumption continued to age 13 years and that only one child of the 255 followed in LEAP-Trio from the 319 in the original LEAP consumption group developed peanut allergy between the ages of 6 and 13 years. Although the percent reduction in peanut allergy among peanut consumers at the end of LEAP-Trio was lower than at the end of LEAP, this is not because the protective effect waned with time, but rather because nine participants in the LEAP avoidance group became peanut-tolerant.

Children in LEAP-Trio who had originally been randomly assigned to the peanut consumption group had smaller peanut skin-prick test wheal sizes, lower Ara h2-specific IgE levels, higher peanut-specific IgG4 levels, and a higher IgG4:IgE ratio compared with the original peanut avoidance group. The differences between intervention groups became apparent very early in the LEAP studies, with high-level peanut-specific and Ara h2-specific IgE production suppressed as early as 30 months. Although cross-trial/study comparisons are fragile, this degree of peanut-specific and Ara h2-specific IgE suppression is greater than that reported in immunotherapy studies in adolescents.[11,27-29]

The decline in IgG4 seen in LEAP-On from 60 to 72 months of age raised concern that the protection gained from the first 5 years of consumption in the LEAP trial might be transient. Between LEAP-On at 72 months and LEAP-Trio at 144 months of age, nearly all of the peanut consumption group remained tolerant, and the difference in IgG4 levels between the peanut consumption and peanut avoidance groups remained relatively stable. One possible explanation for the continued difference between groups is that the participants originally randomly assigned to peanut consumption ate more peanut than those randomly assigned to avoidance. This is unlikely to be the only explanation, because most participants did not report consuming peanuts between 60 and 72 months of age, and most children in the peanut avoidance group were eating peanuts between 72 and 144 months of age. Instead, based on our findings, we speculate that early allergen exposure has a long-term influence on IgG4 levels, irrespective of consumption in the school-age years.

This trial had some limitations. The higher levels of ad libitum consumption seen in the original peanut consumption group in LEAP-Trio may have conferred ongoing protection through "ad hoc desensitization." This is unlikely because despite an appreciable proportion of children in the original LEAP consumption group eating very little or no peanut for variable periods of time, only one person developed peanut allergy. The effects of differing levels of ad libitum consumption or avoidance in the years after LEAP-On on the biomarkers of peanut allergy (peanut-specific IgE and Ara h2 IgE) were further assessed through regression analysis. No associations were found, supporting that the differences in outcome for the two groups of the trial at age 13 years were due to the original intervention of peanut consumption or avoidance during the first 5 years of life, irrespective of consumption patterns that ensued thereafter. Even if continued protection against peanut allergy was conferred to some degree by ongoing peanut consumption, which is unlikely given the above, these children were tolerant from a clinical perspective. The same is not true for peanut oral immunotherapy; peanut-allergic individuals can be desensitized to peanut, but discontinuation or reduction in daily therapy increases the likelihood of regaining clinical reactivity, and quotidian cofactors (such as exercise, hot baths or showers, or viral upper respiratory infections) increase the likelihood of reaction to the therapy itself.[11,27,30] In contrast, the LEAP-Trio trial showed that children, including 40% with detectable IgE to peanut at baseline,[31] randomly assigned to early peanut consumption remained tolerant to peanut after 1 year of avoidance and through 7 years of subsequent ad libitum consumption. During the period of ad libitum consumption, children in both groups ate little or no peanut for extended periods, consistent with the hypothesis that prevention through oral tolerance induction is inherently different from oral immunotherapy.

The peanut consumption findings during the intervening years between the LEAP-On and LEAP-Trio assessments may be subject to recall bias; however, such bias would likely affect both groups equally. Moreover, the reported peanut consumption by participants is consistent with the peanut protein levels measured in bed dust, an objective surrogate marker of peanut consumption.[32,33] Parental recall of peanut consumption has been shown to be reliable based on comparison of food frequency questionnaire data and a prospective food diary.[34,35] Recall of consumption beyond 1 to 2 years may have been less accurate in both groups. The fact that early consumers continued to eat more than early avoiders demonstrates prospectively that children fall into a consistent pattern of peanut consumption.

Our trial has several strengths. Nearly 80% of the original LEAP participants underwent the LEAP-Trio assessments,

and the 60- and 72-month outcomes for these participants were not different from those of the entire LEAP population. The primary outcome was robustly determined, with more than 80% of participants undergoing oral food challenge. Sensitivity analyses with imputation for missing outcomes confirmed the primary end point results. Finally, the period of ad libitum consumption represents over half the lived lifespan of most participants, further supporting the lasting impact of early introduction.

Our trial provides clinical evidence that induction of tolerance by early introduction of peanut led to a sustained tolerance to oral intake of peanut. The duration of protection, which persisted in the vast majority of participants in the LEAP trial, from at least age 6 to age 13 years, is consistent with the notion that true tolerance was achieved through this intervention.

Disclosures

Author disclosures and other supplementary materials are available at evidence.nejm.org.

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