

CORRESPONDENCE

Letter of response to Greenhawt et al. 'LEAPing Through the Looking Glass: Secondary Analysis of the Effect of Skin Test Size and Age of Introduction on Peanut Tolerance after Early Peanut Introduction'

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Dear Sir,

Greenhawt et al. performed a secondary analysis of the Learning Early About Peanut Allergy (LEAP) dataset and questioned the recent 'Addendum Guidelines for the Prevention of Peanut Allergy in the United States' (1–3). The Addendum recommends early introduction of peanut-containing foods, starting as early as 4–6 months for infants with severe eczema, egg allergy, or both. Their analysis, which we believe to be flawed, concludes that in the LEAP study, a successful oral food challenge (i.e., peanut allergy prevention) was significantly more likely with peanut introduction between 6 and 11 months as compared to 4–6 months of age.

Greenhawt et al. analyzed LEAP data, aggregating both study groups, and found a quadratic relationship between age of enrollment and peanut allergy at 60 months of age. This serves as the basis for their conclusion that peanut allergy prevention was more likely with introduction of peanut beginning at 6 months. However, when similarly analyzed, but separated by study group (Fig. 1, panel A), we see no evidence for an age effect in the peanut consumption group or a lessening of the treatment effect with younger

age. Furthermore, the quadratic relationship seen in the avoidance group appears to be driven primarily by a high proportion of subjects who became allergic among the small number of subjects enrolled at 4 months (Fig. 1, panel B). Greenhawt et al. do not consider an alternative interpretation that subjects 4–6 months at enrollment had characteristics putting them at greater risk for allergy, not that efficacy of dietary peanut was less.

The raw data are at odds with the Greenhawt et al. conclusion that introducing peanut prior to 6 months is less efficacious. In infants enrolled before 6 months, 26% of the avoidance group developed peanut allergy vs 5% of the consumption group—an 82% relative reduction in the rate of peanut allergy (OR = 7.06). Considering infants 6 months or older at enrollment, 15% of those in the avoidance group developed peanut allergy vs 3% of those in the consumption group, also an 82% relative reduction (OR = 6.33).

The LEAP study did not enroll a 4-month-old cohort and randomize to begin peanut consumption immediately vs after a delay in treatment, as would be necessary to draw definitive conclusions on the optimal time to introduce peanut. Hence,

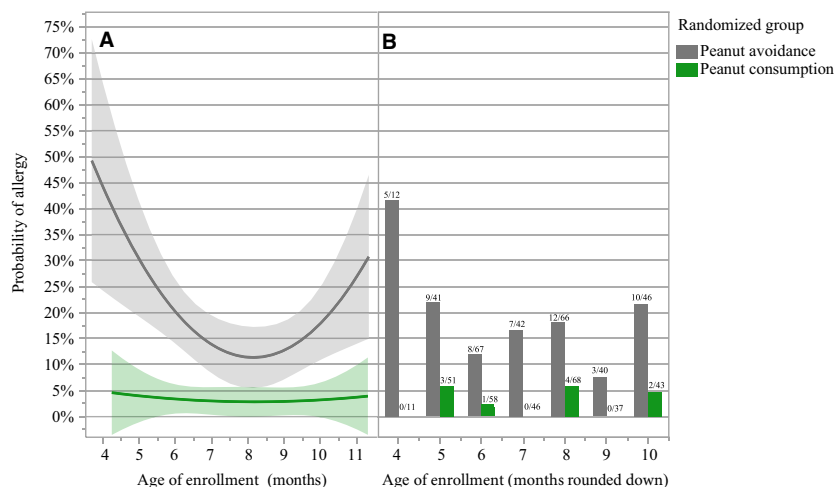


Figure 1 A logistic regression model using a quadratic effect for age is shown in panel (A) for each randomized group (top line, gray for peanut avoidance, bottom line, green for peanut consumption). The actual data are provided as bar charts in panel (B), and the fraction of allergic to total participants is annotated

above each bar (left bars, gray for peanut avoidance, right bars, green for peanut consumption). The y-axis displays predicted probabilities for the regression model and the proportion allergic for the bar charts.

the best available approach is to determine whether a treatment-by-age interaction (not presented by Greenhawt et al.) is detected within the LEAP dataset.

Accordingly, we fit an additional model: OFC outcome = Treatment + Age + Treatment*Age. The interaction term has a P -value = 0.8 indicating no evidence that the treatment effect differs by age, so that the conclusion of Greenhawt et al. is unsubstantiated. Apart from the lack of an interaction test, we have concerns about the statistical models presented in this publication. The standard for a logistic regression model requires there be ≥ 10 cases for each covariate. As there were 64 cases of peanut allergy in LEAP, the model of Greenhawt et al., which includes 11 variables, risks overfitting. Considering that several of these variables are correlated, this model is also subject to an elevated risk of false-positive results. Additionally, the authors did not transform the egg- and peanut-specific IgE (sIgE) values as would be appropriate. We ran the model with log-transformed sIgE values and found this substantially changes the results presented in Greenhawt's table 2a: Race, SCORAD, Egg sIgE (log10), Age, and Age*Age are no longer significant; Peanut sIgE (log10) is now significant (OR = 0.5, P = 0.001); and treatment and peanut wheal size remain significant.

Apart from these statistical concerns, the authors did not discuss the significance of progression of SPT sensitization with age. The LEAP screening data (4) (and unpublished analyses) show a positive correlation between age of enrollment and SPT diameter, arguing that beyond a certain age

the therapeutic window of opportunity may have already closed for some children. A further rationale for peanut introduction at 4–6 months for high-risk infants arises from the fact that well-child care visits occur in this interval, but less frequently later in infancy (5). Peanut introduction at this age proved feasible in LEAP and did not affect the duration of breast-feeding nor impact negatively on growth or nutrition (6).

In summary, the LEAP study did not find that peanut introduction between 6 and 11 months of age, as compared to 4–6 months, is more efficacious in preventing peanut allergy.

Conflicts of interest

The authors have no conflict of interest to disclose.

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Letter from Dr. Keet to the Editors to paper from Greenhawt et al.

I am writing in reference to Greenhawt et al. (1), which re-analyzes the LEAP study data (2) to assess the effect of age of peanut introduction on risk of developing peanut allergy. The optimal age to introduce peanut to maximally prevent peanut allergy is a critical unanswered question, with important implications for developing guidelines, and I commend the authors for using publically available data from the LEAP study to tackle it. However, my own analyses of the same publically available data do not support the conclusions of the authors.

The underlying question of interest is whether the effect of peanut introduction is modified by the age of introduction. Because this is a question about how treatment effect differs by age, the appropriate model should evaluate the interaction between age and treatment assignment on likelihood of developing peanut allergy. However, it appears that Greenhawt et al. did not evaluate an interaction term in their model or perform stratified analyses by age. Instead, based on a multi-variable adjusted model of age as a predictor of food allergy, they conclude that introduction of peanut between 6 and 10

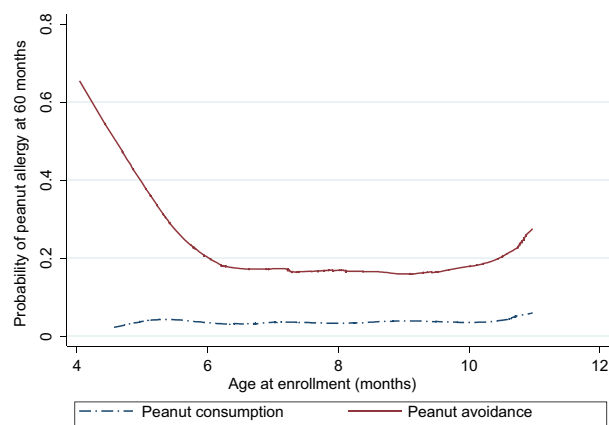


Figure 1 Relationship between age of entry into the LEAP study and development of peanut allergy at 60 months of age, stratified by treatment group (red = peanut avoidance, blue = peanut consumption), LOWESS graph, bandwidth 0.8. [Colour figure can be viewed at wileyonlinelibrary.com]

months of age was associated with less peanut allergy compared to younger ages. In my analyses, there is no difference overall in the protective effect of peanut introduction between infants less than 6 months of age (OR 0.14, 95% CI: 0.04–0.53) and 6 months and older (OR 0.16, 95% CI: 0.07–0.36). In a model that includes a treatment*age interaction, age does not appear to modify the treatment effect overall ($P = 0.89$ for the interaction when age is categorical, $P = 0.82$ when age is continuous, and $P = 0.46$ when an age squared term is included). Nor does age modify treatment when stratification by SPT positivity is performed (data not shown), although the data are sparse in certain categories, and moreover, stratifying or adjusting for SPT positivity in a model asking whether age modifies the protective effect of

introduction does not make sense because increasing peanut sensitization with age is a possible mechanism by which age could modify the effect of introduction. The lack of effect of age on the success of peanut introduction can be seen in an analysis of the raw data in a LOWESS graph (Fig. 1), which clearly shows that there is only a relationship between age at enrollment and probability of peanut allergy among those randomized to peanut avoidance ($P = 0.001$), with no relationship among those randomized to consumption ($P = 0.95$). Thus, data from the LEAP trial itself do not show evidence for an optimal age of peanut introduction.

However, any conclusions about the effect of age on peanut introduction need to take into account those subjects who already develop peanut allergy before peanut introduction. Du Toit et al. (3) reported that within the population screened for LEAP, older subjects were more likely to have large SPTs and thus be screened out of the intervention study, implying that catching infants before they develop peanut allergy is essential to optimally preventing allergy. This idea has not been tested, though, and it is possible that the implications of peanut SPT size for probability of peanut allergy may vary by age.

Overall, the decision about the optimal age to introduce peanut requires more data and a broader perspective on allergy prevention and overall childhood nutrition than any one study can provide. While the LEAP study was a very significant milestone in our field, more data on these questions are needed.

Thank you,

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Reply

We read with interest the correspondence from Dr. Keet to our manuscript ‘LEAPing Through the Looking Glass: Secondary Analysis of the Effect of Skin Test Size and Age of Introduction on Peanut Tolerance after Early Peanut Introduction,’ in which she has provided an alternative secondary analysis of the age effects for early peanut introduction on peanut tolerance that showed no difference in predicted

tolerance based on age of introduction in the trial. We appreciate and understand the approach of her modeling, but still favor our use of an age*age interaction term (to denote the specific effect of increasing age) in a multivariate logistic regression adjusted by a treatment arm factor variable (among multiple other variables), with marginal effects then determined across the age ranges of children in the trial. Her

approach does account for the interaction between age and early introduction, but we feel that our model is more comprehensive and included the effect of peanut skin test wheal, similarly investigating the interactions between skin test size and treatment arm. Despite our differing approaches and methodology, her findings with respect to timing of early introduction do fit within the confidence interval of our model.

We consider that our data show subtle but significant differences that favor a slightly higher predicted tolerance with peanut introduction commencing at 6 months or later rather than between 4 and 6 months. However, we do agree with Dr. Keet that there are no firm conclusions that can effectively be drawn from this data set on what that optimal 'early' introduction time may be, as applied to a larger population of infants outside this clinical trial at a policy level. Thus, the clinical significance of either of our arguments remains unproven, and it is hoped that it will be better understood in the coming years as early peanut introduction is implemented across many countries. This is clearly demonstrated in our conclusion where we question the urgency of introduction before 6 months, but we do not actually specify a precise time of introduction. 'Increasing peanut wheal size predicted peanut tolerance only in the avoidance arm. Peanut introduction between 6 and 11 months of age was associated with the highest rates of peanut tolerance, questioning the 'urgency' of introduction before 6 months.'

We also thank the LEAP team (Lawson et al) for their thoughtful response. Nowhere in our manuscript do we 'question the recent Addendum Guidelines for the Prevention of Peanut Allergy in the United States,' a document which we all co-authored and support, nor do we levy any criticism against the LEAP team or the Du Toit et al. study. The intent of our analysis was to focus on policy-relevant findings intended to complement and supplement the Du Toit et al. manuscript. Similar to our reply to Dr. Keet (a NIAID-funded investigator working on LEAP implementation, making the same argument), we respectfully agree to disagree on the statistical approach used. While we did consider the treatment effect interaction approach they discussed (with the point estimate they allude to representing an on-average effect for the interaction of age and treatment), we describe an alternative methodology of showing what happens within the early introduction group with respect to the timing of the age of introduction, using adjusted predictions of our model at representative age values stratified to just the early introduction group. Again, their findings do fit within our confidence interval, and in our manuscript, we explained the subtle nature of our findings, as well as detailing the exquisite model sensitivity of the argument we were making. In fact, in their figure they have the same issue regarding the width of the 95% confidence interval we demonstrate in the 4- and 5-month-olds relative to the 6- to 11-month-olds. Our choice of methodology was dictated by the very lack of power in this subgroup they discussed, a problem not solved by running an interaction. Our model was not over-specified due to power limitations in logistic regressions. Furthermore, we are justified in not log-transforming sIgE levels when they serve as an independent variable in a logistic model.

That is a preference, but one we disfavor because log transformation distorts differences in IgE levels while normalizing their distribution, which Lawson et al. actually demonstrate (relative to our model).

Lawson et al. suggest that 4–6 months of life is an 'optimal' time for peanut introduction. However, this argument was not made originally in 2015 publication. The LEAP study was not designed to assess this, nor do LEAP data actually demonstrate this. We are also concerned about the statement that these younger subjects were somehow at greater risk to have pre-existing peanut allergy. This also cannot be proven, nor can it be disproven that this was not the result of peanut introduction at a suboptimal 'early' age by a few months. The key is that this age subgroup was small in number, and requires further study in a separate trial powered to investigate the optimal age to introduce peanut within the 4- to 11-month window.

Of equal concern is the assertion that because SPT size progressed with age and was correlated with eczema, this inferred greater risk. This is completely untested. The LEAP study did not randomize the use of peanut skin testing to validate its necessity as a prescreening measure and actually demonstrate any increased risk. The protocol drew a line for a cutoff at 4 mm, which has not been validated or tested as oral food challenges were not carried out for SPT >4 mm. Our alternative hypothesis is that the skin test cutoff merely restricted a subset of children from the potential benefit of early introduction, inferred given the heterogeneity of treatment effect seen with respect to increasing skin test size (0 mm vs 1–4 mm) among those randomized to early introduction. There are no data to prove how many of infants with SPT >4 mm would not have reacted with early introduction, or that a so-called therapeutic window of opportunity had closed.

Therefore, the adequacy of the LEAP inclusion criteria (severe eczema, egg allergy, and a 4mm peanut skin test size cutoff) in determining high-risk infants cannot be presumed, given these have only been used in a single study and have not been compared to other possible criteria. Moreover, it has been noted these high-risk criteria would have missed 23% of cases of peanut allergy in the HealthNuts cohort and 26% of cases in the FAIR cohort (personal communication, Carina Venter), raising questions regarding how robustly these screening criteria may perform in real-life settings outside an randomized controlled trial where >100 individual contacts per patient in the intervention group were made (Michael Perkin, 2016 EAACI pro/con debate, Vienna, Austria).

Respectfully submitted,

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