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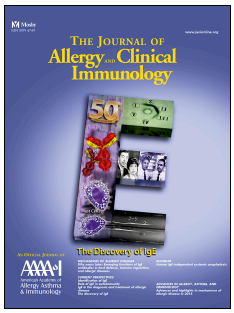

The allergen-specificity of early peanut consumption and the impact on the development of allergic disease in the LEAP Study Cohort

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PII: S0091-6749(17)31664-0

DOI: 10.1016/j.jaci.2017.09.034

Reference: YMAI 13085

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 22 May 2017

Revised Date: 31 August 2017

Accepted Date: 21 September 2017

Please cite this article as: du Toit G, Sayre PH, Roberts G, Lawson K, Sever ML, Bahnson HT, Fisher HR, Feeney M, Radulovic S, Basting M, Plaut M, Lack G, for the Immune Tolerance Network LEAP Study Team, The allergen-specificity of early peanut consumption and the impact on the development of allergic disease in the LEAP Study Cohort, *Journal of Allergy and Clinical Immunology* (2017), doi: 10.1016/j.jaci.2017.09.034.

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Abbreviations

CI - Confidence interval

ITT - Intention-to-treat

PAR – Perennial Allergic Rhinoconjunctivitis

PP – Per Protocol

SAR – Seasonal Allergic Rhinoconjunctivitis

SCORAD - SCORing Atopic Dermatitis

SPT - Skin Prick Test

LEAP Study - Learning Early About Peanut Allergy Study

LEAP-On Study - 12 month extension of LEAP Study: Persistence of Oral Tolerance to Peanut

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Abstract

Background: Early introduction of dietary peanut in high-risk infants with severe eczema and/or egg allergy prevented peanut allergy at 5 years of age in the LEAP Study; the protective effect persisted after 12 months of avoiding peanuts in the LEAP-On Study. It is unclear whether this benefit is allergen and allergic-disease specific.

Objective: To assess the impact of early introduction of peanut on the development of allergic disease, food sensitization and aeroallergen sensitization.

Methods: Asthma, eczema and rhinoconjunctivitis were diagnosed by clinical assessment. Reported allergic reactions and consumption of tree nuts and sesame were recorded by questionnaire. Sensitization to food and aeroallergens was determined by skin prick testing and specific IgE measurement.

Results: A high and increasing burden of food and aeroallergen sensitization and allergic disease was noted across study time points; 76% of LEAP participants had at least one allergic disease at 60 months of age. There were no differences in allergic disease between LEAP groups. There were small differences in sensitization and reported allergic reactions for select tree nuts; levels were higher in the LEAP consumption group. Significant resolution of eczema and sensitization to egg and milk occurred in LEAP participants; this was not affected by peanut consumption.

Conclusion: Early consumption of peanut in infants at high risk of peanut allergy is allergen-specific and does not prevent the development of other allergic disease, sensitization to other foods and aeroallergens, or reported allergic reactions to tree nuts and sesame. Furthermore, peanut consumption does not hasten the resolution of eczema or egg allergy.

Clinical Implications:

1. Prevention of peanut allergy through early peanut consumption is allergen-specific and allergic-disease specific.
2. The immune mechanisms underlying tolerance to peanut do not hasten the resolution of other allergic disease.

Capsule Summary:

The early consumption of peanut in high-risk infants is allergen-specific and protects against peanut allergy but does not prevent the development of sensitization to other allergens or allergic diseases.

10 Keywords:

Food Allergy; Peanut Allergy; Allergy prevention; Allergen-specific; Asthma. Eczema; Atopic Dermatitis; Rhinoconjunctivitis; Tolerance

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INTRODUCTION

Atopic diseases represent a public health concern, particularly in the developed world.(1-3) Atopic conditions rarely occur in isolation and children frequently suffer from multiple allergic diseases. For example, infants with eczema are at higher risk of developing food allergy and asthma, children with egg allergy are at increased risk of developing allergic respiratory diseases, and children with a single food allergy frequently develop additional food allergies.(3)

Early dietary allergen exposure has been shown to be a successful strategy for the prevention of peanut allergy (and possibly egg allergy), however, the specificity of the observed clinical and immunological benefits is not known.(4-10) Peanut, tree nuts and sesame contain seed storage proteins with highly conserved areas of shared identity and homology between their amino acid sequences.(11-13) This raises the important clinical question as to whether cross-sensitization to similar allergens accounts for the frequent co-occurrence of these allergies in allergic populations.

If the consumption of peanut during infancy protects against the development of peanut allergy, it may also protect against the development of related food allergies. Israeli children have a low prevalence of peanut, tree nut and sesame allergy when compared with age-matched UK children.(14) Israeli children consume high quantities of both peanut and sesame from an early age, which is likely to explain the difference in peanut and sesame allergy rates.(14, 15) However, the differences in tree nut allergy cannot be attributed to early tree nut consumption as there were no differences in the age at which tree nuts were introduced between the two

countries. Thus the low levels of tree nut allergy may be the result of cross-tolerance induced through earlier, higher and more frequent consumption of peanut and/or sesame in Israel compared with the UK.

Given the possible clinical relevance of cross reactivities between proteins in different foods, and that there is low grade evidence that allergen immunotherapy may prevent new-onset aeroallergen sensitization (16, 17), it is reasonable to investigate whether, similarly, early dietary allergen exposure has an influence on the onset or resolution of co-existent food allergies and/or other atopic diseases.

METHODS

Study design

This is an *a priori* analysis of the LEAP and LEAP-On Study secondary allergic outcomes.(10, 18) The LEAP Study was a randomized, open-label, controlled trial comparing two strategies to prevent peanut allergy: consumption or avoidance of peanut by high-risk infants until 60 months of age. The LEAP-On Study was a two-sample comparison employing all evaluable study participants from the LEAP Study assessed at 72 months of age after 12 months of peanut avoidance. Both trials were approved by the institutional review board and were overseen by a NIAID Allergy and Asthma Data and Safety Monitoring Board. Informed written consent was obtained for all LEAP and LEAP-On participants from their parent/guardian; full study details have been previously published.

Enrolment and study procedures

The LEAP Study enrolled infants aged ≥4 to <11 months with severe eczema and/or egg allergy from December 2006 to May 2009.(10) Participants were stratified at baseline into two separate study populations (strata) based on skin prick test (SPT) results for peanut and then randomly assigned to avoid (LEAP avoiders) or consume peanut (LEAP consumers). Analysis in this manuscript combines data from both the SPT positive and SPT negative strata. Participants randomly assigned to consumption were fed at least 6g of peanut protein/week until age 60 months. Clinical assessments were undertaken at baseline (age 4-11 months) and at age 12, 30 and 60 months which included the determination of protocol-defined eczema, asthma, seasonal and perennial rhinoconjunctivitis (further detailed in the Online Repository). The LEAP-On clinical assessment was undertaken at 72 months of age, after 12 months of peanut avoidance in both groups.(18)

SPT and Specific IgE measurement

Immune assessments including skin prick testing (SPT) and specific IgE measurements were conducted; test methodologies and skin prick testing materials have been published.(10) SPT to food allergens: peanut, hen's egg white (using standardized extract as well as prick-to-prick testing using raw hen’s egg white), cow's milk, sesame and soya were assessed at baseline, 12, 30, and 60 months (ALK-Abello, Hørshom, Denmark). SPT to all allergens except soya was repeated at 72 months. At 60 and 72 months, Brazil nut, hazelnut, cashew, walnut and almond were also included. Allergen-specific IgE to peanut, hen's egg white, cow's milk, sesame, Brazil nut, hazelnut, cashew, walnut and almond was measured at screening, 12, 30, 60 and 72 months using ImmunoCAP (Thermo Fisher, Uppsala, Sweden) Specific IgE to aeroallergens: house dust

mite, cat, dog, timothy grass pollen, birch pollen and alternaria mold were measured at 30, 60 and 72 months (Thermo Fisher, Uppsala, Sweden).

Mean SPT and specific IgE values were calculated for the above allergens at all available time points; these means are presented for the Intention-to-Treat (ITT) and Per-Protocol (PP) study populations. We defined sensitization *a priori* for food allergens as SPT wheal diameter ≥ 3 mm or specific IgE ≥ 0.35 KU/L and aeroallergens as specific IgE ≥ 0.35 KU/L. Based on a previous publication, and on the optimal predictive value for peanut allergic participants in the avoidance arm of LEAP (Online Repository, Page 3.) we make use of high-level cut offs of SPT wheal diameter ≥ 5mm and/or specific IgE ≥ 10 KU/L to define 'likely food allergy' in post hoc analyses.(19)

Reported allergic reactions and association with specific IgE sensitization

At 60 months of age, a study questionnaire recorded details of suspected allergic reactions that had occurred over the duration of the trial. Two by two comparisons were made comparing tree nut and sesame reported allergic reactions and specific IgE ≥ 0.35 KU/L to each allergen.

Consumption of tree nuts and sesame

Participant-reported consumption of Brazil nut, hazelnut, cashew, walnut, almond or sesame, on at least one occasion, was assessed from 3-day food diaries completed at 6 study time points.

Statistical analysis

Statistical analyses were performed on all LEAP and LEAP-On Study participants for whom an outcome measurement was obtained on an ITT basis comparing the two randomized treatment groups cross-sectionally. Analyses were also performed on those who met PP criteria for LEAP (details of which have been previously published). Chi-squared, Fisher's Exact tests, or multivariate logistic regression were used to compare the proportion of participants with each disease outcome of interest at the 0.05 level of significance. These were planned analyses on secondary outcomes, and no adjustments have been made for multiple comparisons. All analyses were performed using SAS software version 9.4 or JMP version 12.

RESULTS

Participants

The characteristics of participants screened and enrolled in the LEAP and LEAP-On Studies have been published.(10, 18)

No difference in development of allergic disease between the LEAP Study intervention groups

No differences were noted between LEAP avoiders and consumers in the rate of asthma, eczema, seasonal rhinoconjunctivitis and perennial rhinoconjunctivitis at 30, 60 and 72 months of age in the ITT population (Figure 1 and Table E1, Figure 2 and Table E3). These findings were replicated in the PP population (Table E2 and Table E4).

i) Eczema

The majority of participants in the ITT population had eczema (defined by SCORAD > 0) at baseline (97% in the avoidance group and 98% in the consumption group); this decreased across study time points to 72 months of age, where 39% of participants in the avoidance group and 37% in the consumption group had eczema (Figure 2). Overall, eczema severity (measured by SCORAD mean (SD)) decreased across study time points from 34.4 (18.9) at baseline to 6.8 (11.2) at 72 months of age (after 12 months of peanut avoidance) (Table E3). There were no significant differences in the presence or severity of SCORAD between LEAP avoiders and consumers at any time point (Figure 2, Table E3). These findings were replicated in the PP population (Table E4).

ii) Asthma

In the ITT population, the overall rate of asthma increased from 11.2% at 30 months to 16.5% at 60 months and 16.3% at 72 months of age (Table E1). There were no significant differences in rates of asthma diagnosis or the protocol-defined diagnostic criteria between the LEAP avoiders and consumers at 30, 60 or 72 months **(**Figure 1, Table E1). These findings were replicated in the PP population (Table E2).

iii) Rhinoconjunctivitis:

In the ITT population, the overall rate of seasonal allergic rhinoconjunctivitis (SAR) increased from 14.4% at 30 months to 35.2% at 60 months and 46.3% at 72 months of age (Table E1). The rate of perennial allergic rhinoconjunctivitis (PAR) increased from 26.4% at 30 months to 42.4% at 60 months and 51.8% at 72 months of age. Rates of SAR and PAR were similar between

LEAP groups at 30, 60 and 72 months of age. (Figure 1, Table E1). These findings were replicated in the PP population (Table E2).

No protective effect on surrogate markers of tree nut and sesame allergy (SPT, specific IgE and reported allergic reactions) in the LEAP Study consumption group

We compared rates of sensitization to tree nut and sesame with peanut. As previously published for peanut, in the consumption group, the mean peanut SPT wheal diameter was significantly lower at all time points after randomization in both the ITT and PP populations (Figure 3). In contrast, the mean peanut specific IgE was only lower in the consumption group at one time point at 72 months of age and only lower in the PP population (Figure 3). Mean Ara h2 IgE was significantly lower in the consumption group at 60 and 72 months in both the ITT and PP populations (Figure 3).

For tree nuts and sesame, using *a priori* sensitization levels (SPT wheal diameter ≥ 3 mm or specific IgE ≥ 0.35 kU/L), the only significant difference noted was for walnut in the ITT population; the consumption group had an increased rate of walnut sensitization at 72 months compared with the avoidance group (28.2% vs. 19.9%, p=0.025; Table E5). This difference in walnut sensitization was not seen in the PP population (Table E6).

In *post hoc* analyses, using higher cut-off levels (SPT wheal diameter ≥ 5mm or specific IgE ≥ 10 kU/L) as a marker of 'likely food allergy', there were significant increases in rates to hazelnut, cashew and walnut in the consumption group in the ITT population (Table E7). These

differences were largely attenuated in the PP population (Table E8). Considering sensitization by SPT only, mean SPT wheal diameters to tree nuts and sesame were broadly similar between the consumption and avoidance groups in the ITT population. The exceptions were to walnut and cashew at 60 months and to hazelnut at 60 and 72 months, where the mean wheal diameters were larger in the consumption group (Figure 4). In the PP population the only difference between groups was to hazelnut at 72 months (Figure 4). Considering sensitization by IgE only, in the ITT population, mean specific IgE to tree nuts and sesame were generally similar between the consumption and avoidance groups; however, specific IgE was higher in the consumption group for some nuts at more than one time point (Figure 5). Most of these differences were not apparent in the PP population. Only for walnut in the ITT population was specific IgE higher in the consumption group at all time points after baseline. These differences in walnut specific IgE were also apparent in the PP population at 30 and 60 months.

When we compared reported reactions to tree nuts and sesame between the LEAP intervention groups, the only significant difference noted was for Brazil nut in the ITT population where 5 participants in the consumption group reported Brazil nut reactions as compared to 0 in the avoidance group ($p=0.031$). A similar difference was noted for Brazil nut in the PP population (Table E9). Statistically significant differences were also noted when we compared the number of individuals reporting any or more than one reaction to tree nuts and sesame in both the ITT and PP populations (Table E9). In the ITT population 40 (12.7%) participants in the consumption group reported a reaction to any nut as compared to 23 (7.3%) participants in the avoidance group ($p=0.023$). Most individuals who reported reactions to a tree nut also had specific IgE $\geq$ 0.35 kU/L to that nut. However, this was not the case in all subjects. For example, 10 of 26

individuals who reported a reaction to cashew did not have specific IgE of≥ 0.35 kU/L (Table E10).

To assess whether there were differences in consumption of tree nuts or sesame between groups, we compared the number of participants who ever reported eating tree nuts or sesame in the 3-day food diaries (Table E11). The large majority of participants did not report consumption of tree nuts or sesame. Statistically significant differences were noted for hazelnuts and mixed nuts. For hazelnuts, 42 (13.2%) consumers reported eating hazelnut as compared with 21 (6.5%) of participants in the avoidance arm (p=0.005). For mixed nuts, 5 participants in the consumption group reported mixed nut consumption as compared to 0 in the avoidance group (p=0.030).

No difference in rates of and resolution of sensitization to other common foods between the LEAP intervention groups

There were no differences in rates of sensitization to cow's milk and egg white at any time point in the ITT (Table E12) or PP (Table E13) populations. No differences were noted in 'likely allergy' rates using high-level cut offs of ≥ 5mm or ≥ 10 kU/L for SPT and specific IgE respectively (Tables E14 and E15).

The high rate of raw egg white sensitization of 69.7%, in the overall ITT population at baseline decreased with age to 39.1% by 72 months (Table E12). A similar decrease was evident for the rate of SPT wheal ≥ 3 mm to egg white extract (Table E12). Rates of soya sensitization and 'likely allergy' in the ITT and PP populations were low, and equivalent between LEAP groups, at all measured time points (Tables E12, E13, E14, and E15).

Increase in aeroallergen sensitization with age in both LEAP Study intervention groups

Sensitization rates increased from 30 to 60 and 72 months for all aeroallergens (house dust mite, cat, dog, timothy grass pollen, birch pollen and Alternaria mold) in both consumption and avoidance groups in the ITT (Figure 6 and Table E16) and PP (Table E17) populations. The most striking increase was for timothy grass pollen sensitization. In the ITT population, the rate in the combined avoiders and consumers group increased from 19.9% at 30 months to 48.7% at 60 months and 57.5% at 72 months (Table E16). There were no significant differences in aeroallergen sensitization between the consumption and avoidance groups at any time point (Figure 6 and Table E16). These findings were replicated in the PP population (Table E17).

Similar cumulative allergic disease burden in both LEAP Study intervention groups

At 60 months of age, LEAP participants carried a high cumulative allergic disease burden, considering together eczema, asthma, rhinoconjunctivitis, or any likely food allergy defined as any food allergen SPT ≥ 5mm (Figure 7). The cumulative disease burden was not different between LEAP avoiders and consumers in the ITT population at 60 or 72 months of age (Table E18). When considering the cumulative disease burden in the combined avoiders and consumers group in the ITT population at 60 months, 76% of participants had at least one allergic disease (seasonal and perennial rhinoconjunctivitis, asthma, eczema and likely food allergy) at 60 months of age and 44% had multiple allergic diseases (Figure 7, Table E18).

Strong association between peanut allergy and allergic disease

We constructed six multivariate logistic regression models including peanut allergy outcome, baseline egg allergy, and baseline SCORAD to assess their impact on the development of asthma, seasonal rhinoconjunctivitis, and perennial rhinoconjunctivitis separately at 60 and 72 months of age. Peanut allergy at 60 and 72 months was strongly associated with asthma, seasonal rhinoconjunctivitis, and perennial rhinoconjunctivitis in the ITT population at the same time point (Figure 8 and Table E19, $p < 0.001$ for the association of peanut allergy with all three allergic diseases at both time points). Similarly, baseline egg allergy was associated with seasonal rhinoconjunctivitis ($p=0.019$) and perennial rhinoconjunctivitis ($p=0.042$) but not with asthma ($p=0.848$) at 60 months. Similar findings were apparent at 72 months (Figure 8 and Table E19). The association of asthma with peanut allergy, as opposed to its lack of association with egg allergy, is not explained by baseline SCORAD since the latter does not influence the development of asthma (Table E19).

DISCUSSION

This study found that oral tolerance induction to peanut in the LEAP Study is specific for both allergen and allergic disease, i.e. early consumption of peanut had no preventative effect on development of asthma, allergic rhinoconjunctivitis or surrogate markers of co-existent food allergies (SPT, specific IgE and reported tree nut and sesame reactions), and did not hasten the resolution of the eczema or egg allergy that were key inclusion criteria for LEAP participation. The noted similarities in allergic disease burden between LEAP intervention groups is in contrast with the marked reduction in peanut allergy observed in the consumption group (Figure E1).

The allergen-specificity of the LEAP intervention is confirmed by the finding that manifestations of allergic disease in the LEAP population followed the typical trajectory in young children with no differences noted between groups (excepting peanut allergy in LEAP consumers). Sensitization to hen's egg white and cow's milk (Tables E12 – E15) and rates and severity of eczema decreased across all time points (Table E3 and Table E4). In contrast, we observed a significant rise in aeroallergen sensitization and both seasonal and perennial rhinoconjunctivitis across all measured time points (Figure 1 and Figure 6). The burden of asthma was high and equal between LEAP groups rising from 11.2% at 30 months of age to 16.3% at 72 months of age (Table E1).

When considering the association between peanut allergy, baseline egg allergy and other allergic diseases, strong associations were noted with eczema, seasonal and perennial rhinoconjunctivitis at 60 and 72 months of age (Figure 8, Table E19). Peanut allergy was also strongly associated with asthma; this relationship was independent of baseline eczema and/or egg allergy (Figure 8). The LEAP study demonstrated that peanut consumption was strongly associated with the prevention of peanut allergy but did not prevent asthma. (Figure E1) The environmental and genetic risk factors for asthma and peanut allergy are therefore likely distinct.

There was no evidence that peanut consumption protected against tree nut and sesame sensitization. Surprisingly there was a small signal that peanut consumption was associated with an increase in sensitization to tree nuts and sesame. We found higher SPT and specific IgE levels to tree nuts and sesame in the LEAP consumption group compared with the avoidance group at most time points, and at times these differences met statistical significance. In addition, a significantly higher proportion of individuals (p=0.023) in the consumption group reported an

allergic reaction to one or more tree nuts. These findings contrast with the LEAP study findings at 60 months of age where challenge-proven peanut allergy, peanut SPT diameter and Ara h 2 levels (Figure 3) were all markedly reduced within the LEAP consumption group compared with the avoidance group.

It is possible that early peanut consumption did result in the slightly increased rate of sensitization to tree nuts and could potentially result from exposure to small quantities of epitopes cross-reactive with those of tree nuts. There is literature to suggest that low-level allergen exposure (to aeroallergens) results in allergic responses whereas high-level allergen exposure drives tolerance.(20, 21) In addition, individuals in the consumption group may have had levels exposure to tree nuts potentially sufficient to drive sensitisation but insufficient to induce tolerance.

However, there are a number of other explanations for these unexpected findings. First, the increase in tree nut sensitization observed in the consumption group was not statistically consistent over time in that the effect sizes were smaller and more variable compared to peanut. Second, to minimize false negatives, no adjustments were made for multiple comparisons which increases the likelihood of false positive findings. Third, if eating peanut causes an increase in tree nut sensitization and reported allergic reactions, we would expect to see a greater effect in the PP analyses where infants ate more peanut compared to the ITT analyses; however, this was not evident for either the *a priori* sensitization thresholds (compare Tables E5 and E6) nor the high-level sensitization thresholds which are more indicative of clinical allergy. This suggests that these small statistically significant differences in sensitisation do not represent important

clinical differences (compare Tables E7 and E8). Fourth, the differences in reported allergic reactions may arise through an ascertainment bias as a consequence of increased exposure to tree nuts and sesame in participants randomised to peanut consumption (Table E9). In support of this, consumption data recorded in 3-day food diaries does suggest more frequent consumption in the LEAP consumption group (Table E11). In addition this method may underestimate differences in consumption patterns, as compared to a food frequency questionnaire (as was used to record both frequency and quantity of peanut consumption in LEAP participants). Finally, although there was overall a significant increase in reported reactions to tree nuts and sesame in the consumers compared to avoiders, between 20 to 50% of individuals with a reported reaction had specific IgE $\leq$ 0.35 kU/L to the reported nut which suggests that some reported reactions do not represent true allergic reactions (Table E10).

In contrast with allergy and dietary data in Israel (where higher and more frequent peanut consumption patterns are associated with low rates of reported tree nut and sesame allergy, we demonstrate that peanut consumption in the LEAP Study does not protect against tree nut and sesame allergy and, furthermore our data raise the possibility that peanut consumption may cause sensitization to tree nuts (14, 15). However, in the absence of oral food challenges to tree nuts and sesame, the clinical significance of these small and inconsistent differences in surrogate markers of food allergy remains unclear. The LEAP Trio Study will make a more detailed assessment of these differences at age 10 years.

A strength of this study is that we describe secondary allergy outcomes for eczema, asthma, seasonal and perennial rhinoconjunctivitis using rigorous *a priori* criteria in a population of

infants with a high allergic disease burden and for which peanut consumption successfully reduced the rate of peanut allergy. The major limitation of this study is the absence of OFCs to tree nuts and sesame. An additional limitation is that severe eczema and/or egg allergy served as enrolment criteria thereby minimising the opportunity to assess peanut consumption as an intervention to prevent the onset of these allergic conditions.

Despite the dramatic decrease in peanut allergy in participants randomized to peanut consumption, the overall allergic disease burden in LEAP Study participants is high, but equivalent, between LEAP groups at 60 months and 72 months of age (after 12 months of peanut avoidance). This demonstrates that oral tolerance induction to peanut in the LEAP Study is specific for both allergen and allergic disease. The underlying immune mechanisms associated with tolerance to peanut do not alter the natural history of allergic disease.

Different prevention strategies, or strategies that include multiple dietary interventions, need to be tested to assess whether the reduction in peanut allergy observed in the LEAP consumption group can be extended to other common food allergens and allergic diseases.

Acknowledgements

Research reported in this publication was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under award numbers NO1-AI-15416, UM1AI109565, HHSN272200800029C and UM2AI117870. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Additional support came from Food Allergy Research & Education (FARE),

McLean, VA; the Medical Research Council & Asthma UK Centre; the UK Department of Health through the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy's & St. Thomas' NHS Foundation Trust, in partnership with King's College London and King's College Hospital NHS Foundation Trust. The clinical trials unit is supported by the National Peanut Board, Atlanta, Ga. The UK Food Standards Agency provided additional support for the costs of phlebotomy. Prof Gideon Lack acknowledges the Davis Foundation for academic support.

We thank the many nurses, dietitians, doctors and administrative staff of the Guy's and St Thomas' NHS Foundation Trust Children's Allergy Service for clinical and logistical assistance over the period of the study; Poling Lau for administrative support in the preparation of this manuscript. Above all, we are indebted to all of the children and their families who generously took part in this study.

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Figure Legends

Figure 1. Asthma and Rhinoconjunctivitis Burden Over Time

The rate of protocol-defined asthma, seasonal rhinoconjunctivitis and perennial rhinoconjunctivitis in the consumption (green bars) and avoidance (gray bars) groups in the ITT population at 30, 60 and 72 months are shown. There are no significant differences between the two groups at any time point as assessed by Chi-Squared Tests.

Figure 2. Eczema Severity Bands Over Time (SCORAD)

The percent of individuals with SCORAD assessments for eczema of 0, >0-15, ≥15-40 and >40 are shown at baseline and at 12, 30, 60 and 72 months in the avoidance (left bar of each pair) and

534 consumption groups (right bar of each pair) in the ITT population. There are no significant
535 differences between the two groups at any time point as assessed by Chi-Squared Tests.
536
537 **Figure 3.** Peanut SPT, Peanut S-IgE, and Ara h2 S-IgE
538 Peanut SPT (top panel), Peanut IgE (middle panel), and Ara h2 IgE (bottom panel) in the
539 consumption and avoidance groups in the ITT (left column) and LEAP Per Protocol (right
540 column) populations at 4-11, 12, 30, 60, and 72 months are shown. Boxes represent 25th and
541 75th centiles and error bars represent 2.5th and 97.5th centiles. Lines connect the means over
542 time for each randomized group. Solid grey lines represent the LEAP avoiders. Dashed green
543 lines represent LEAP consumers. Grey circles represent LEAP avoiders. Green circles represent
544 LEAP consumers. The '*' represent a p-value ≤0.05 resulting from a comparison between the
545 LEAP avoidance and LEAP consumption groups using a two sample t-test. The '**' represent a
546 p-value ≤0.01 resulting from a comparison between the LEAP avoidance and LEAP
547 consumption groups using a two sample t-test.
548
549 **Figure 4.** Tree Nut and Sesame SPT (mm)
550 Sesame, Brazil nut, Walnut, Cashew, Almond, and Hazelnut SPT (mm) results in the
551 consumption and avoidance groups in the ITT (top row) and LEAP Per Protocol (bottom row)
552 populations at 4-11, 12, 30, 60, and 72 months is shown for Sesame and at 60 and 72 months for
553 the other Tree Nut outcomes. Boxes represent 25th and 75th centiles and error bars represent
554 2.5th and 97.5th centiles. Lines connect the means over time for each randomized group. Solid
555 grey lines represent the LEAP avoiders. Dashed green lines represent LEAP consumers. Grey
556 circles represent LEAP avoiders. Green circles represent LEAP consumers. The '*' represent a

p-value ≤0.05 resulting from a comparison between the LEAP avoidance and LEAP consumption groups using a two sample t-test. The '**' represent a p-value ≤0.01 resulting from a comparison between the LEAP avoidance and LEAP consumption groups using a two sample t-test.

Figure 5. Tree Nut and Sesame Specific IgE (kU/L)

Sesame, Brazil nut, Walnut, Cashew, Almond, and Hazelnut specific IgE (kU/L) in the consumption and avoidance groups in the ITT (top row) and LEAP Per Protocol (bottom row) populations at 4-11, 12, 30, 60, and 72 months are shown. Boxes represent 25th and 75th centiles and error bars represent 2.5th and 97.5th centiles. Lines connect the means over time for each randomized group. Solid grey lines represent the LEAP avoiders. Dashed green lines represent LEAP consumers. Grey circles represent LEAP avoiders. Green circles represent LEAP consumers. The '*' represent a p-value ≤0.05 resulting from a comparison between the LEAP avoidance and LEAP consumption groups using a two sample t-test. The '**' represent a p-value ≤0.01 resulting from a comparison between the LEAP avoidance and LEAP consumption groups using a two sample t-test.

Figure 6. Aeroallergen Sensitization

The prevalence of IgE ≥0.35 for several aeroallergens in the consumption (green bars) and avoidance (gray bars) groups at 30, 60 and 72 months are shown. There are no significant differences between the two groups at any time point as assessed by Chi-Squared Tests.

Figure 7. Cumulative Burden Venn Diagram at 60 Months of Age

The number of participants in the ITT population with protocol defined eczema, rhinoconjunctivitis, asthma or any likely food allergy are shown for the avoidance group (top left), consumption group (top right) and total study group (bottom). This illustrates the very high rate of single and multiple allergic diseases in the study population. Figures are numbers (percentage) of participants.

Figure 8. Peanut and Egg Allergy Associations with Development of Allergic Diseases
The rate of protocol-defined asthma (left), seasonal rhinoconjunctivitis (middle) and perennial rhinoconjunctivitis (right) at 60 (top) and 72 (bottom) months are shown in those with neither egg nor peanut allergy, egg allergy only, peanut allergy only or both egg and peanut allergy. The number of subjects contributing to each group is presented in the denominator while the number of subjects with each allergic disease within each group is presented in the numerator of the values annotated within each bar. Presence of egg allergy was defined per inclusion criteria at baseline, whereas peanut allergy was defined at 60 and 72 months. P-values resulting from a multivariate logistic regression model (outcome of interest being each allergic disease) adjusted for peanut allergy, baseline egg allergy and baseline SCORAD are annotated within each panel.

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Figure 1 - Asthma and Rhinoconjunctivitis Burden Over Time

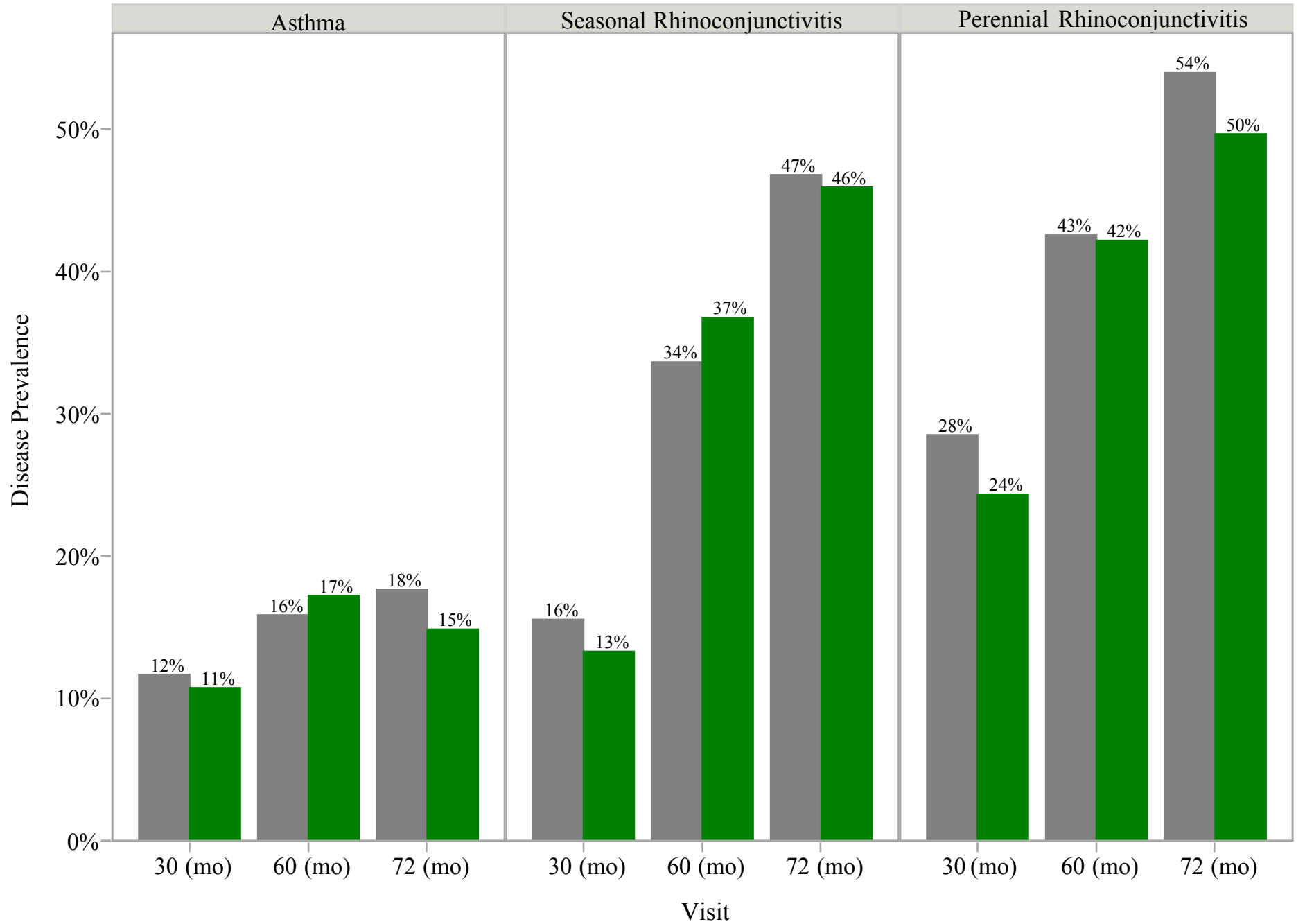


Figure 2 - Eczema Severity Bands Over Time (SCORAD)

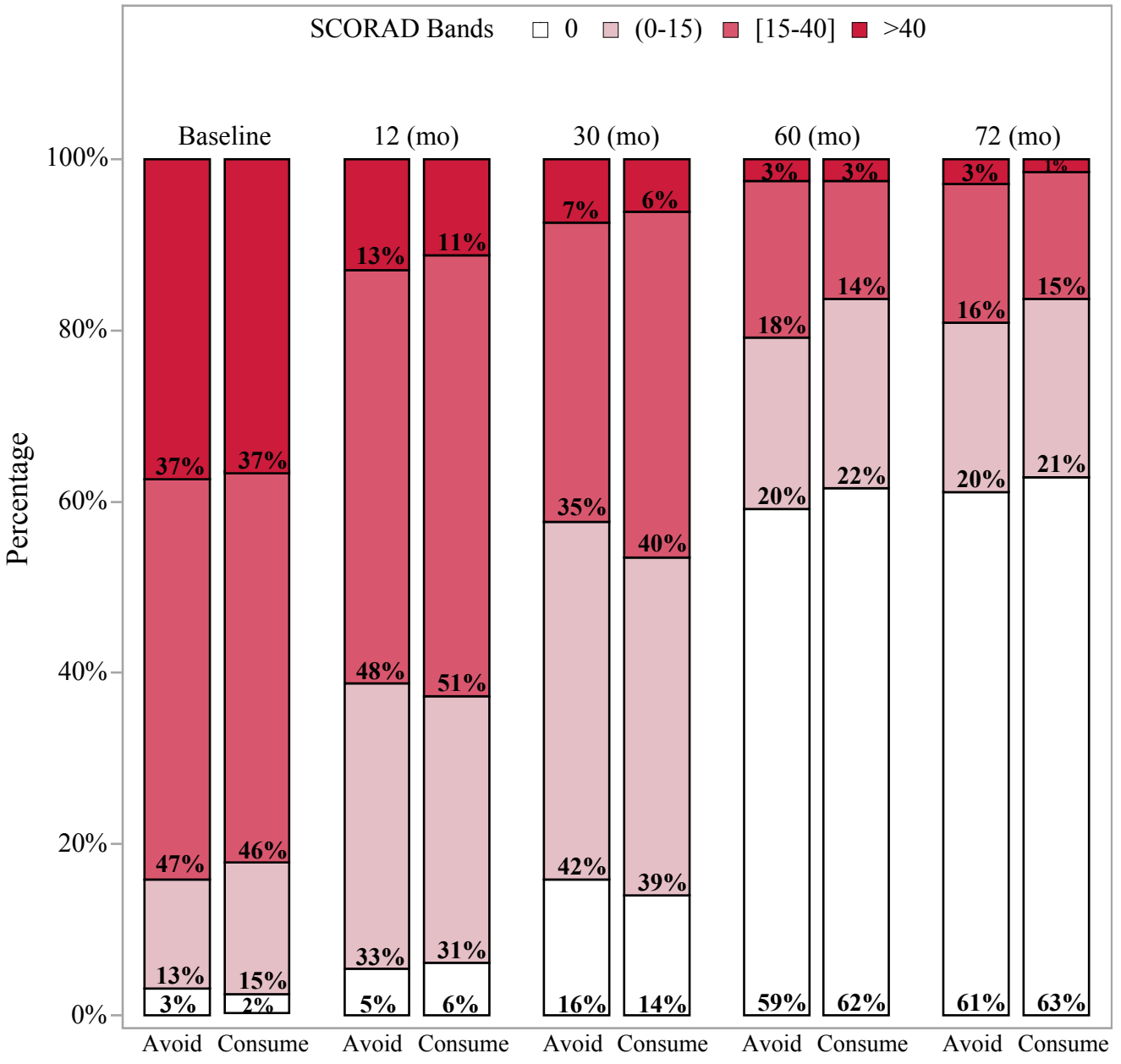


Figure 3 - Peanut SPT, Peanut IgE, and Ara h2 IgE

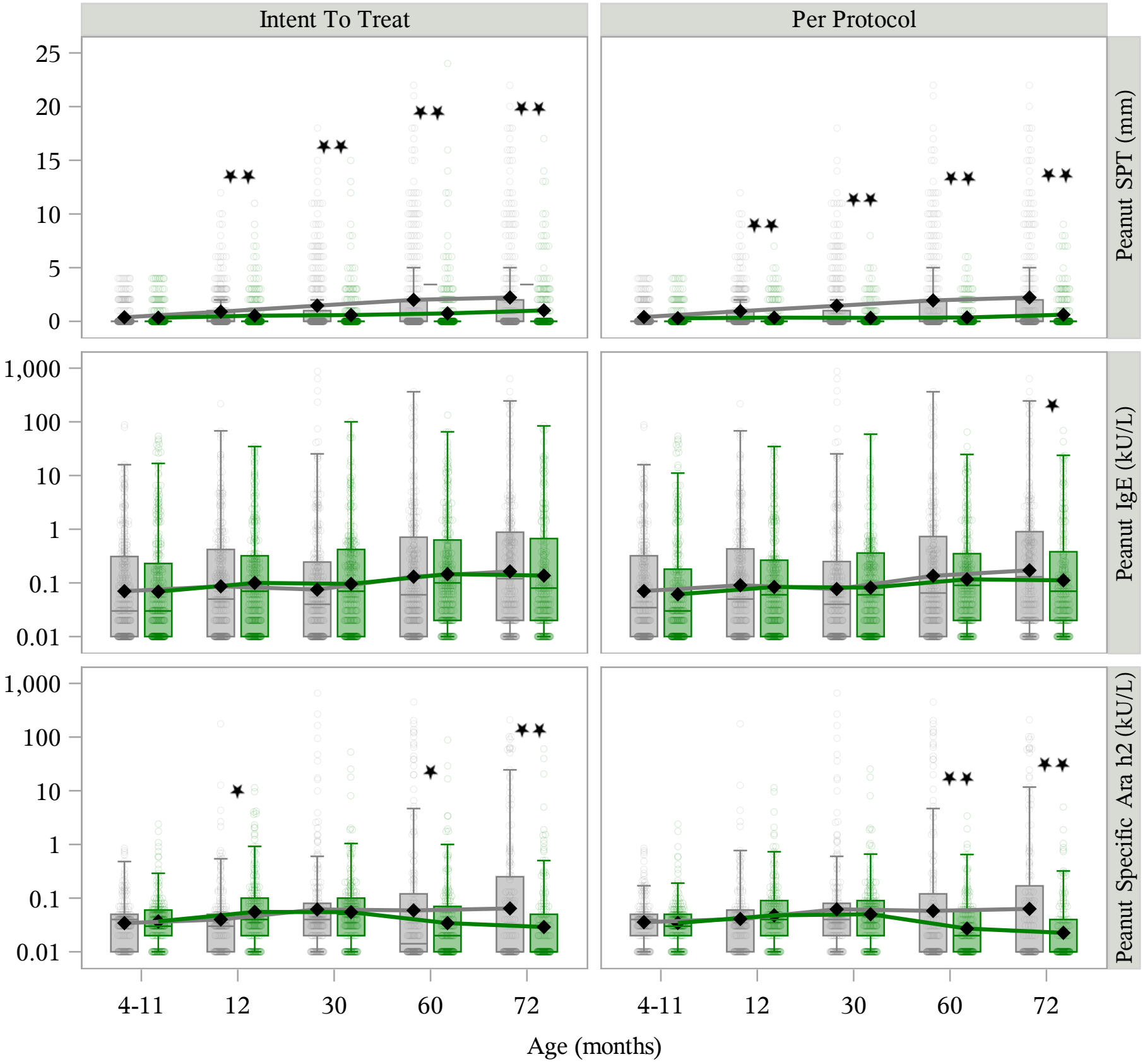


Figure 4 - Tree Nut and Sesame SPT (mm)

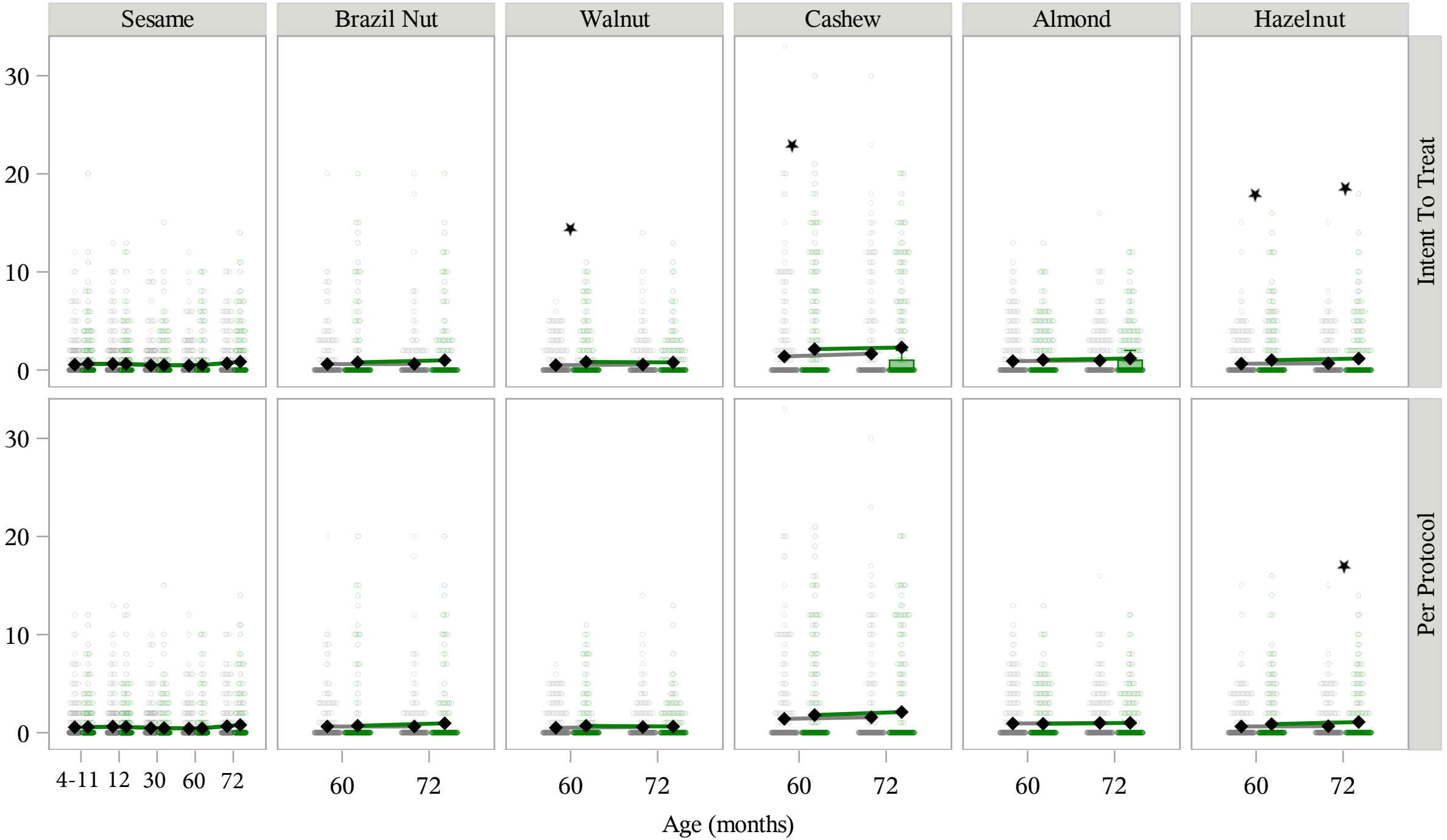


Figure 5 - Tree Nut and Sesame Specific IgE (kU/L)

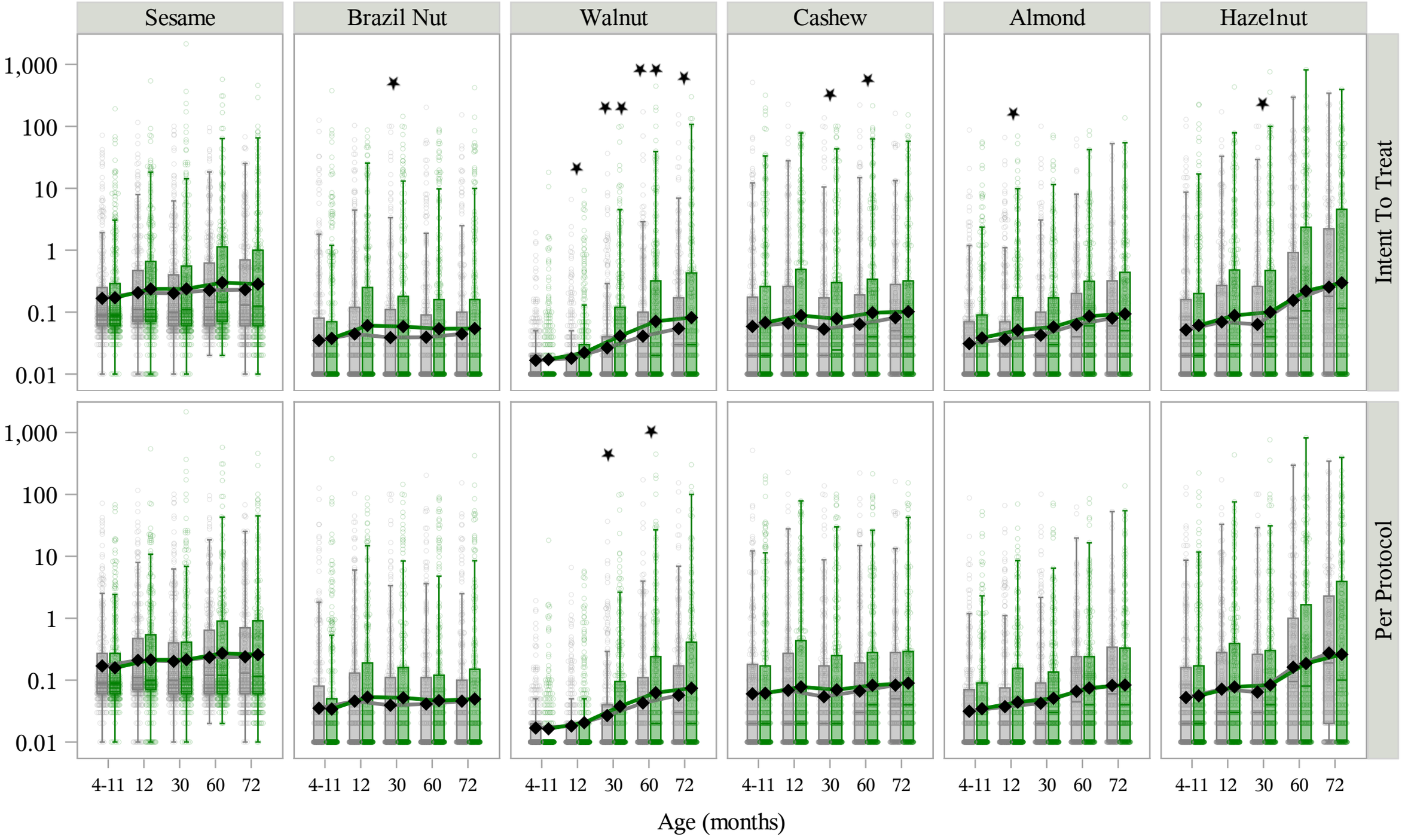


Figure 6 - Aeroallergen Sensitization

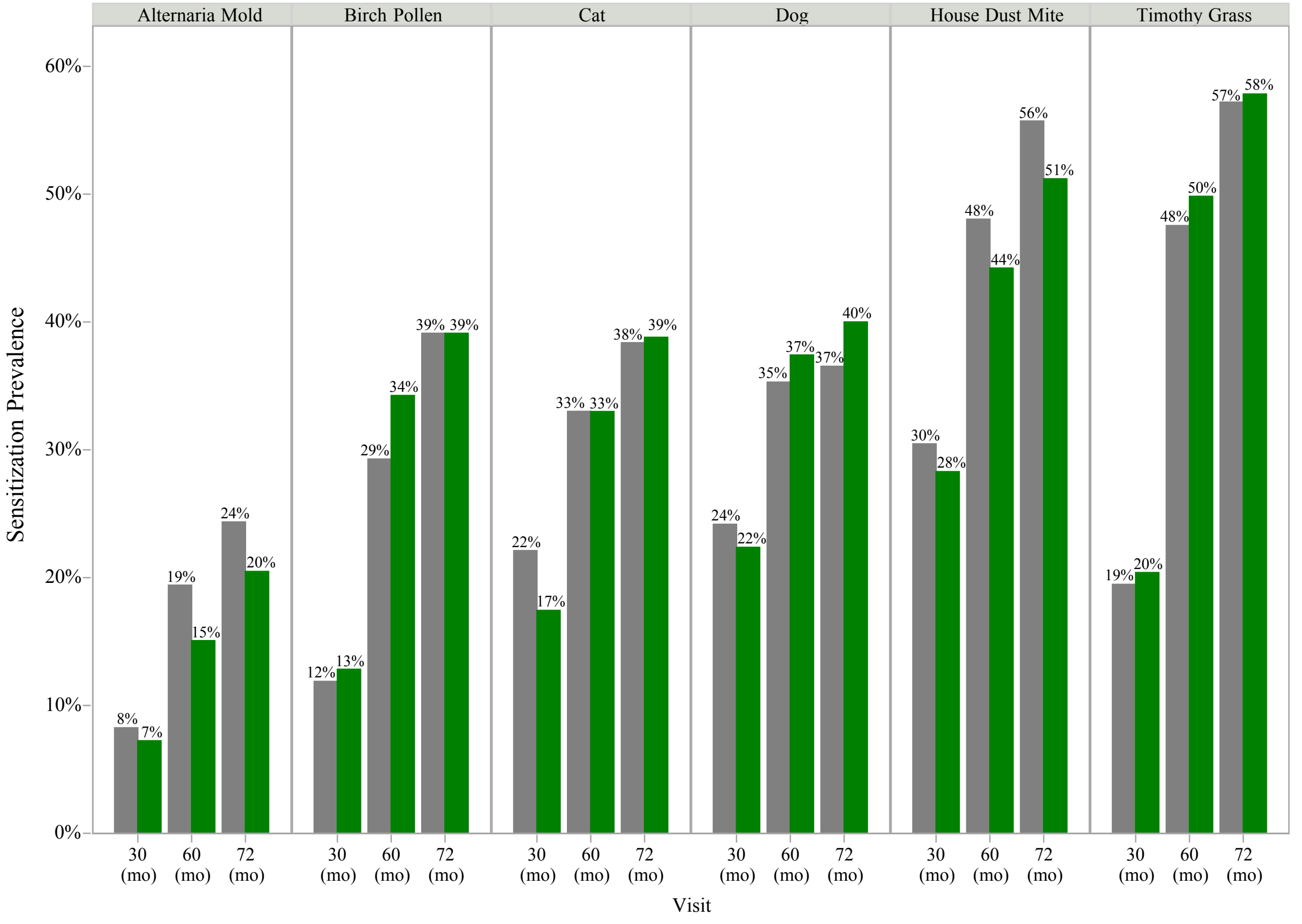
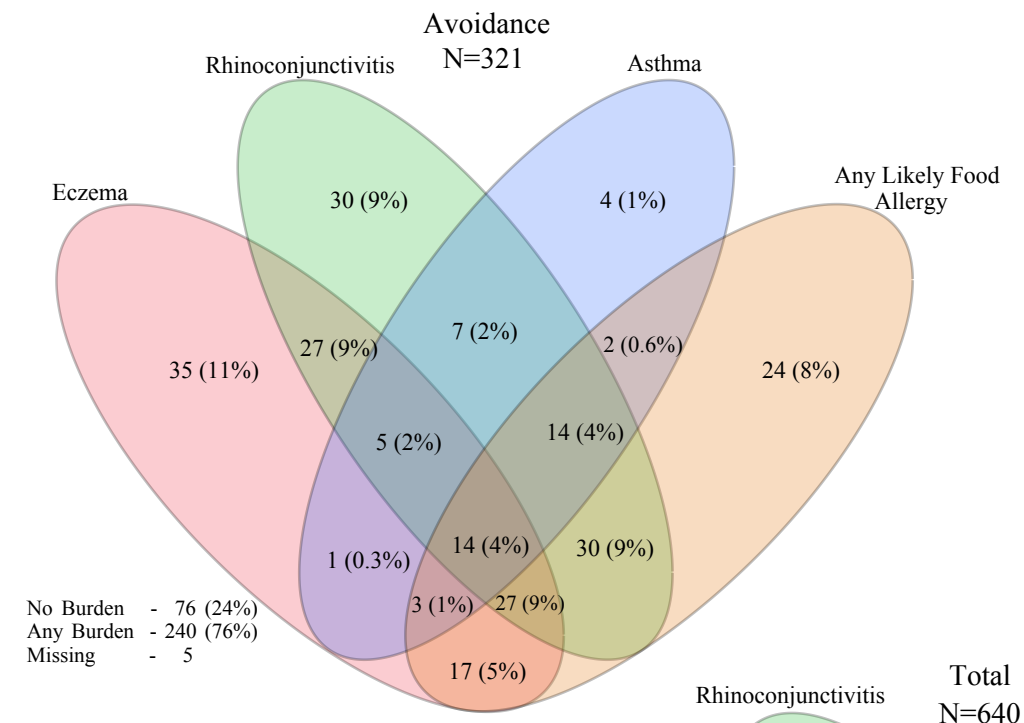
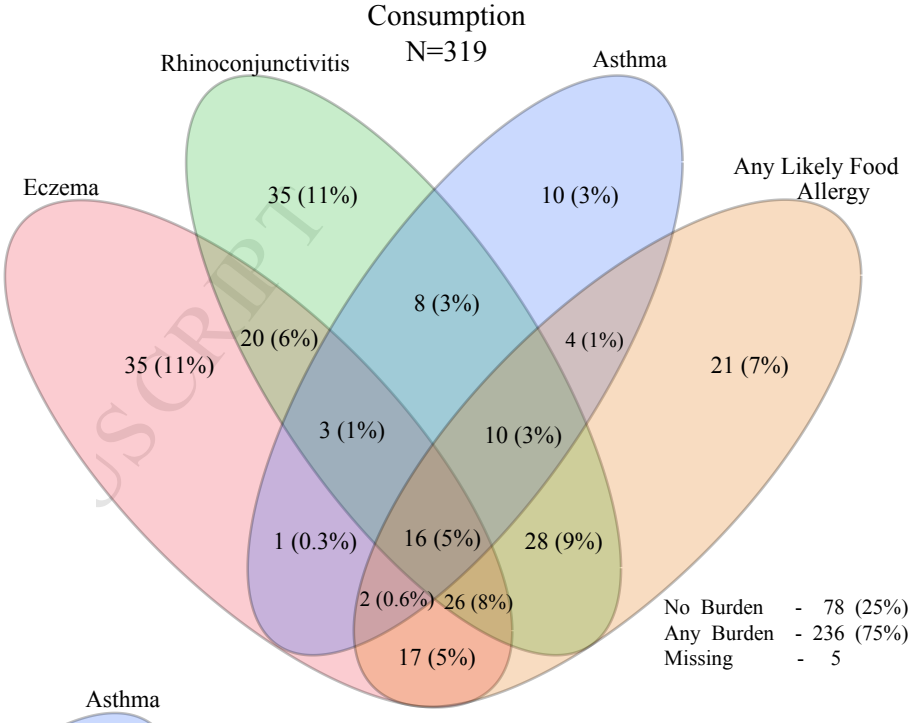


Figure 7 - Cumulative Burden Venn Diagram at 60 Months of Age





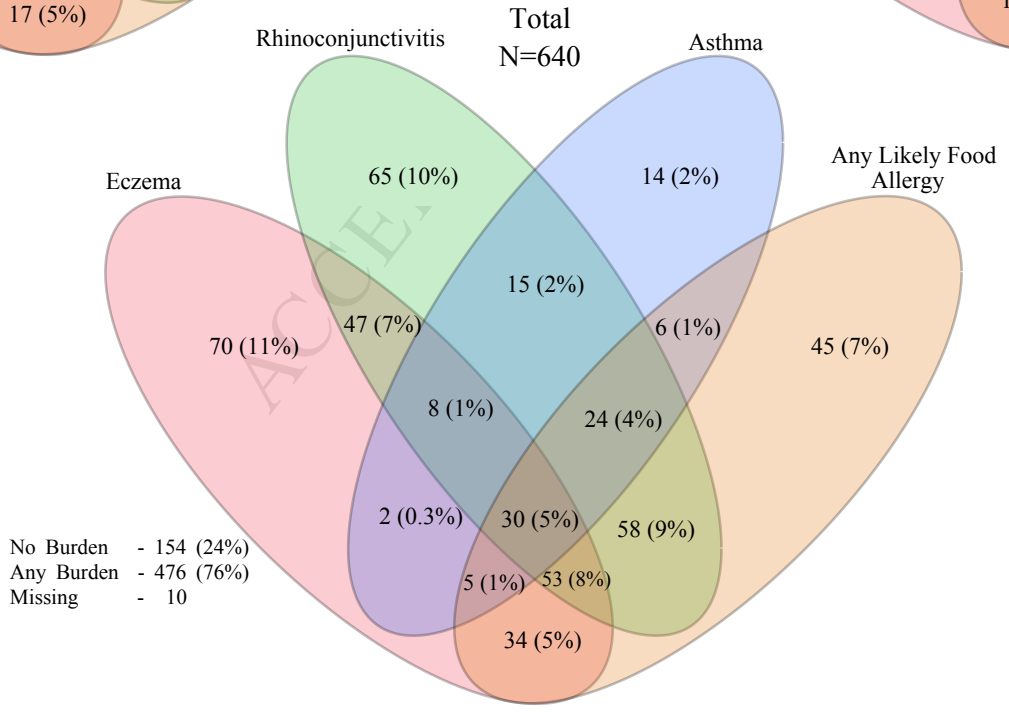


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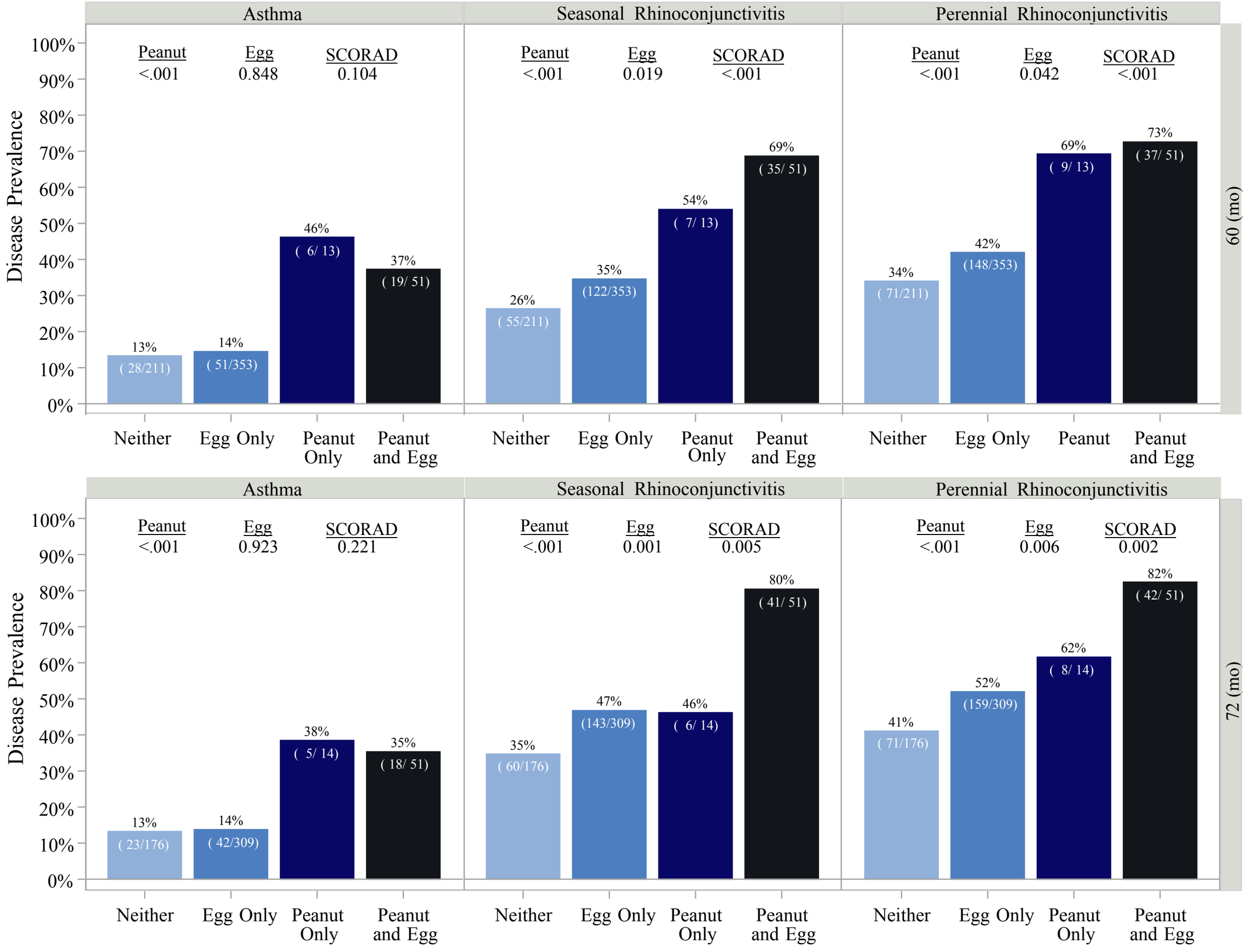
Figure 8 - Peanut and Egg Allergy Associations with Development of Allergic Diseases



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SUPPLEMENTARY APPENDIX

The allergen-specificity of early peanut consumption and the impact on the development of allergic disease in the LEAP Study Cohort

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1. SUPPLEMENT TO THE METHODS

Immune Markers

i) **Skin Prick Test:** Skin-prick tests for food allergens were performed in duplicate.The average of the diameter of the two widest wheals was recorded. The tests were performed on the ventral surface of the forearm using a stainless steel shouldered lancet. Mean wheal diameters were rounded off to the nearest millimeter. A cut point of 5mm was used to define 'Likely Food Allergy'. The following table shows how the 5mm cut off for Peanut allergen discriminates between those who are allergic to Peanut as determined using an Oral Food Challenge:

LEAP Primary Outcome by Peanut Wheal at 60 (mo)

	<5mm (N=559)	≥5mm (N=68)	Total (N=627)
LEAP Primary Outcome			
Negative	552 (98.7%)	11 (16.2%)	563 (89.8%)
Positive	7 (1.3%)	57 (83.8%)	64 (10.2%)

ii) Serum IgE: Serum levels of food specific IgE antibodies were measured as these are known biomarkers of allergic responses. Immunoglobulin measurements were made with the use of the ImmunoCAP 100 and 250 assays (Thermo Fisher, Uppsala, Sweden).

Blinding

Study personnel carrying out clinical assessments were not blinded to the participant's treatment allocation, however, outcomes of asthma, perennial and seasonal rhinoconjunctivitis were determined on the basis of meeting strict protocol definitions of asthma, perennial and seasonal rhinoconjunctivitis set *a priori* (definitions now included in the supplementary appendix).[1] Eczema severity was assessed using objective components of the modified *SCORing Atopic Dermatitis (SCORAD)* score.[2] Food and aeroallergen sensitization were assessed using objective measures of skin prick test (procedures and interpretation defined *a priori* in the Study Protocol) and specific IgE (laboratory personnel were blinded to treatment allocation).[1]

Clinical Assessments

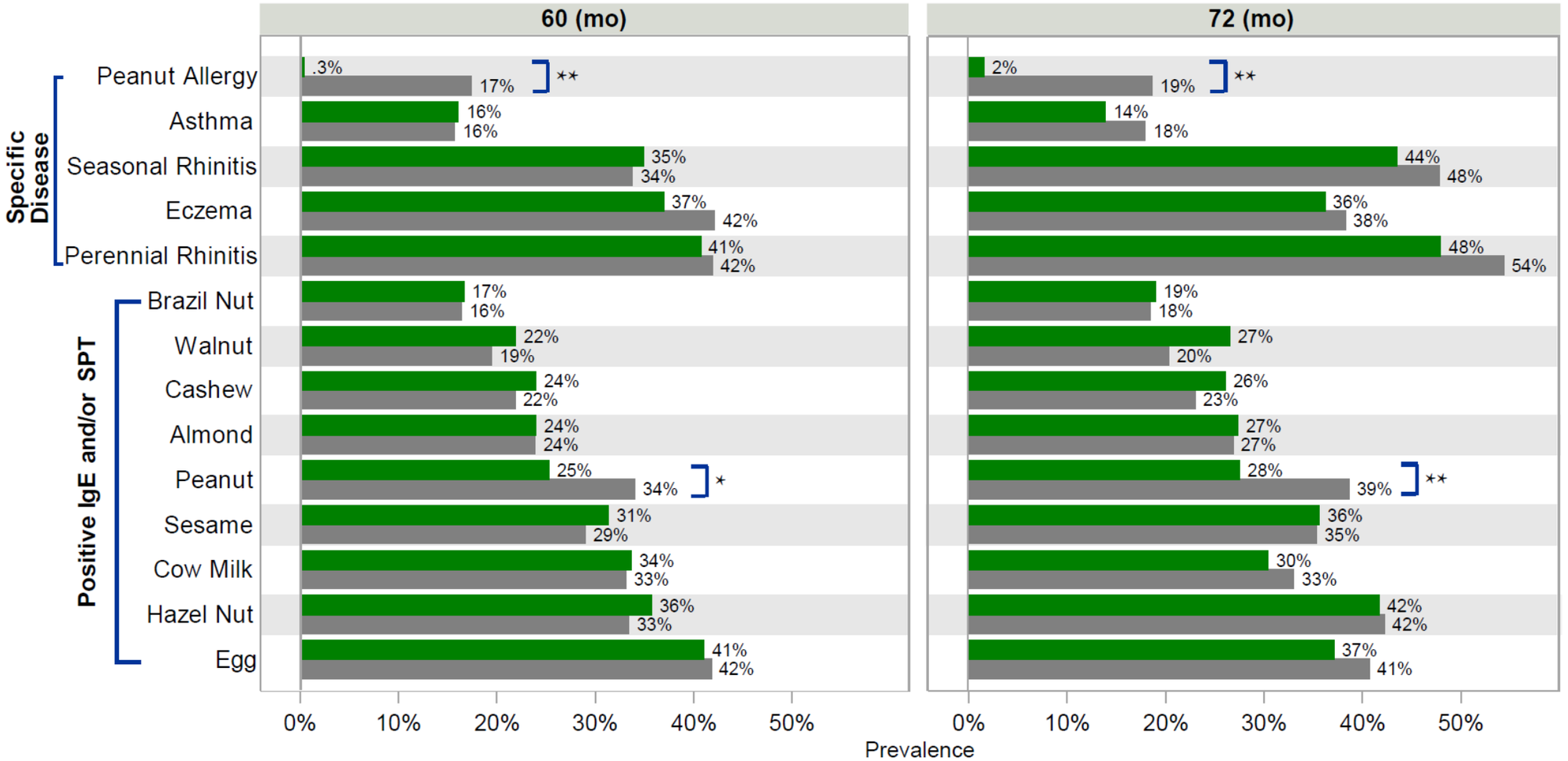
i) **Asthma:** A history of cough, wheeze, or shortness of breath that (1) was responsive to therapy with bronchodilators on two or more occasions in the previous 24 months, (2) required one visit to a physician in the previous 24 months, and (3) occurred during the night, during early morning, or upon exercising in the intervals between exacerbations at any time in the previous 12 months.

ii) **Perennial rhinoconjunctivitis:** Sensitization to a perennial allergen and clinical history of rhinoconjunctivitis symptoms experienced when exposed to the relevant allergen.

iii) **Seasonal rhinoconjunctivitis:** Sensitization to a seasonal allergen and clinical history of rhinoconjunctivitis symptoms experienced during the relevant season.

2. SUPPLEMENTARY FIGURES

Figure E1. Overall Disease Burden Prevalence in the LEAP Per Protocol Population



Data is presented for participants who met the LEAP per protocol definition. Grey bars represent LEAP avoiders. Green bars represent LEAP consumers. The '*' represent a p-value ≤0.05 resulting from a comparison between the LEAP avoidance and LEAP consumption groups using a chi-squared test. The '**' represents a p-value ≤0.01 resulting from a comparison between the LEAP avoidance and LEAP consumption groups using a chi-squared test.

3. SUPPLEMENTARY TABLES

Table E1. Specific Allergic Disease Burden – Asthma and Rhinoconjunctivitis in the LEAP and LEAP-On ITT Populations

	30 (mo)				60 (mo)				72 (mo)			
	Avoiders (N=321)	**Consumers (N=319)**	**Total (N=640)**	**p value**	**Avoiders (N=321)**	**Consumers (N=319)**	**Total (N=640)**	**p value**	**Avoiders (N=282)**	**Consumers (N=274)**	**Total (N=556)**	**p value**
Asthma?				0.712				0.642				0.383
Missing	12	11	23		5	5	10		4	5	9	
No	273 (88.3%)	275 (89.3%)	548 (88.8%)		266 (84.2%)	260 (82.8%)	526 (83.5%)		229 (82.4%)	229 (85.1%)	458 (83.7%)	
Yes	36 (11.7%)	33 (10.7%)	69 (11.2%)		50 (15.8%)	54 (17.2%)	104 (16.5%)		49 (17.6%)	40 (14.9%)	89 (16.3%)	
Responsive to bronchodilators?				0.710				0.509				0.437
Missing	12	11	23		5	5	10		6	7	13	
No	241 (78.0%)	244 (79.2%)	485 (78.6%)		225 (71.2%)	216 (68.8%)	441 (70.0%)		171 (62.0%)	174 (65.2%)	345 (63.5%)	
Yes	68 (22.0%)	64 (20.8%)	132 (21.4%)		91 (28.8%)	98 (31.2%)	189 (30.0%)		105 (38.0%)	93 (34.8%)	198 (36.5%)	
Required physician visit?				0.617				0.563				0.178
Missing	12	11	23		5	5	10		6	7	13	
No	213 (68.9%)	218 (70.8%)	431 (69.9%)		228 (72.2%)	220 (70.1%)	448 (71.1%)		187 (67.8%)	195 (73.0%)	382 (70.3%)	
Yes	96 (31.1%)	90 (29.2%)	186 (30.1%)		88 (27.8%)	94 (29.9%)	182 (28.9%)		89 (32.2%)	72 (27.0%)	161 (29.7%)	
Occurred between exacerbations?				0.812				0.593				0.451
Missing	12	11	23		5	5	10		6	7	13	
No	261 (84.5%)	258 (83.8%)	519 (84.1%)		254 (80.4%)	247 (78.7%)	501 (79.5%)		215 (77.9%)	215 (80.5%)	430 (79.2%)	
Yes	48 (15.5%)	50 (16.2%)	98 (15.9%)		62 (19.6%)	67 (21.3%)	129 (20.5%)		61 (22.1%)	52 (19.5%)	113 (20.8%)	
Seasonal Rhinoconjunctivitis?				0.432				0.417				0.839
Missing	12	11	23		6	6	12		4	6	10	
No	261 (84.5%)	267 (86.7%)	528 (85.6%)		209 (66.3%)	198 (63.3%)	407 (64.8%)		148 (53.2%)	145 (54.1%)	293 (53.7%)	
Yes	48 (15.5%)	41 (13.3%)	89 (14.4%)		106 (33.7%)	115 (36.7%)	221 (35.2%)		130 (46.8%)	123 (45.9%)	253 (46.3%)	
Perennial Rhinoconjunctivitis?				0.245				0.926				0.311
Missing	12	11	23		6	6	12		4	6	10	
No	221 (71.5%)	233 (75.6%)	454 (73.6%)		181 (57.5%)	181 (57.8%)	362 (57.6%)		128 (46.0%)	135 (50.4%)	263 (48.2%)	
Yes	88 (28.5%)	75 (24.4%)	163 (26.4%)		134 (42.5%)	132 (42.2%)	266 (42.4%)		150 (54.0%)	133 (49.6%)	283 (51.8%)	

Note: P-values are based on Chi-Squared Tests.

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Table E2. Specific Allergic Disease Burden – Asthma and Rhinoconjunctivitis in the LEAP Per Protocol Population

	30 (mo)				60 (mo)				72 (mo)			
	Avoiders (N=295)	**Consumers (N=294)**	**Total (N=589)**	**p value**	**Avoiders (N=295)**	**Consumers (N=294)**	**Total (N=589)**	**p value**	**Avoiders (N=264)**	**Consumers (N=256)**	**Total (N=520)**	**p value**
Asthma?				0.814				0.896				0.210
Missing	7	8	15		0	0	0		3	5	8	
No	255 (88.5%)	255 (89.2%)	510 (88.9%)		249 (84.4%)	247 (84.0%)	496 (84.2%)		214 (82.0%)	216 (86.1%)	430 (84.0%)	
Yes	33 (11.5%)	31 (10.8%)	64 (11.1%)		46 (15.6%)	47 (16.0%)	93 (15.8%)		47 (18.0%)	35 (13.9%)	82 (16.0%)	
Responsive to bronchodilators?				0.639				0.628				0.329
Missing	7	8	15		0	0	0		5	7	12	
No	225 (78.1%)	228 (79.7%)	453 (78.9%)		215 (72.9%)	209 (71.1%)	424 (72.0%)		163 (62.9%)	167 (67.1%)	330 (65.0%)	
Yes	63 (21.9%)	58 (20.3%)	121 (21.1%)		80 (27.1%)	85 (28.9%)	165 (28.0%)		96 (37.1%)	82 (32.9%)	178 (35.0%)	
Required physician visit?				0.559				0.906				0.075
Missing	7	8	15		0	0	0		5	7	12	
No	199 (69.1%)	204 (71.3%)	403 (70.2%)		214 (72.5%)	212 (72.1%)	426 (72.3%)		176 (68.0%)	187 (75.1%)	363 (71.5%)	
Yes	89 (30.9%)	82 (28.7%)	171 (29.8%)		81 (27.5%)	82 (27.9%)	163 (27.7%)		83 (32.0%)	62 (24.9%)	145 (28.5%)	
Occurred between exacerbations?				0.623				0.741				0.274
Missing	7	8	15		0	0	0		5	7	12	
No	244 (84.7%)	238 (83.2%)	482 (84.0%)		238 (80.7%)	234 (79.6%)	472 (80.1%)		201 (77.6%)	203 (81.5%)	404 (79.5%)	
Yes	44 (15.3%)	48 (16.8%)	92 (16.0%)		57 (19.3%)	60 (20.4%)	117 (19.9%)		58 (22.4%)	46 (18.5%)	104 (20.5%)	
Seasonal Rhnioconjunctivitis?				0.199				0.771				0.330
Missing	7	8	15		1	1	2		3	6	9	
No	242 (84.0%)	251 (87.8%)	493 (85.9%)		195 (66.3%)	191 (65.2%)	386 (65.8%)		136 (52.1%)	141 (56.4%)	277 (54.2%)	
Yes	46 (16.0%)	35 (12.2%)	81 (14.1%)		99 (33.7%)	102 (34.8%)	201 (34.2%)		125 (47.9%)	109 (43.6%)	234 (45.8%)	
Perennial Rhnioconjunctivitis?				0.196				0.764				0.148
Missing	7	8	15		1	1	2		3	6	9	
No	208 (72.2%)	220 (76.9%)	428 (74.6%)		171 (58.2%)	174 (59.4%)	345 (58.8%)		119 (45.6%)	130 (52.0%)	249 (48.7%)	
Yes	80 (27.8%)	66 (23.1%)	146 (25.4%)		123 (41.8%)	119 (40.6%)	242 (41.2%)		142 (54.4%)	120 (48.0%)	262 (51.3%)	

Note: P-values are based on Chi-Squared Tests.

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Table E3. Specific Allergic Disease Burden – Eczema in the LEAP and LEAP-On ITT Populations

	4-11 (mo)				12 (mo)				30 (mo)				60 (mo)				72 (mo)			
	Avoiders (N=321)	**Consumers (N=319)**	**Total (N=640)**	**p value**	**Avoiders (N=321)**	**Consumers (N=319)**	**Total (N=640)**	**p value**	**Avoiders (N=321)**	**Consumers (N=319)**	**Total (N=640)**	**p value**	**Avoiders (N=321)**	**Consumers (N=319)**	**Total (N=640)**	**p value**	**Avoiders (N=282)**	**Consumers (N=274)**	**Total (N=556)**	**p value**
SCORAD				0.694				0.734				0.172				0.369				0.493
Missing	0	0	0		6	8	14		12	12	24		5	7	12		4	5	9	
Mean (SD)	34.8 (19.3)	34.0 (18.4)	34.4 (18.9)		21.5 (14.9)	21.8 (14.6)	21.7 (14.7)		15.6 (13.6)	17.0 (14.2)	16.3 (13.9)		7.6 (11.6)	6.6 (10.7)	7.1 (11.2)		7.4 (12.0)	6.2 (10.3)	6.8 (11.2)	
Median	32.5	32.5	32.5		18.5	20.0	19.3		12.1	13.5	13.0		0.0	0.0	0.0		0.0	0.0	0.0	
Q1, Q3	20.5, 50.0	19.5, 47.0	20.0, 47.5		10.0, 29.5	10.9, 30.5	10.7, 30.0		7.4, 20.5	8.0, 23.5	7.4, 22.5		0.0, 12.0	0.0, 11.3	0.0, 11.5		0.0, 11.3	0.0, 10.9	0.0, 11.0	
SCORAD Band				0.730				0.782				0.547				0.464				0.704
Missing	0	0	0		6	8	14		12	12	24		5	7	12		4	5	9	
0	10 (3.1%)	7 (2.2%)	17 (2.7%)		17 (5.4%)	19 (6.1%)	36 (5.8%)		49 (15.9%)	43 (14.0%)	92 (14.9%)		187 (59.2%)	192 (61.5%)	379 (60.4%)		170 (61.2%)	169 (62.8%)	339 (62.0%)	
(0-15)	41 (12.8%)	49 (15.4%)	90 (14.1%)		105 (33.3%)	97 (31.2%)	202 (32.3%)		129 (41.7%)	121 (39.4%)	250 (40.6%)		63 (19.9%)	69 (22.1%)	132 (21.0%)		55 (19.8%)	56 (20.8%)	111 (20.3%)	
[15-40]	150 (46.7%)	146 (45.8%)	296 (46.3%)		152 (48.3%)	160 (51.4%)	312 (49.8%)		108 (35.0%)	124 (40.4%)	232 (37.7%)		58 (18.4%)	43 (13.8%)	101 (16.1%)		45 (16.2%)	40 (14.9%)	85 (15.5%)	
>40	120 (37.4%)	117 (36.7%)	237 (37.0%)		41 (13.0%)	35 (11.3%)	76 (12.1%)		23 (7.4%)	19 (6.2%)	42 (6.8%)		8 (2.5%)	8 (2.6%)	16 (2.5%)		8 (2.9%)	4 (1.5%)	12 (2.2%)	

Note: P-values for SCORAD are based on Wilcoxon Rank Sum Tests.
Note: P-values for SCORAD Band are based on Chi-Squared Tests.

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Table E4. Specific Allergic Disease Burden – Eczema in the LEAP Per Protocol Population

	4-11 (mo)				12 (mo)				30 (mo)				60 (mo)				72 (mo)			
	Avoiders (N=295)	**Consumers (N=294)**	**Total (N=589)**	**p value**	**Avoiders (N=295)**	**Consumers (N=294)**	**Total (N=589)**	**p value**	**Avoiders (N=295)**	**Consumers (N=294)**	**Total (N=589)**	**p value**	**Avoiders (N=295)**	**Consumers (N=294)**	**Total (N=589)**	**p value**	**Avoiders (N=264)**	**Consumers (N=256)**	**Total (N=520)**	**p value**
SCORAD				0.627				0.667				0.396				0.093				0.355
Missing	0	0	0		1	2	3		7	9	16		0	1	1		3	5	8	
Mean (SD)	34.5 (19.4)	33.4 (18.3)	33.9 (18.8)		21.7 (14.8)	21.1 (14.4)	21.4 (14.6)		15.7 (13.4)	16.4 (13.5)	16.1 (13.4)		7.7 (11.7)	5.9 (9.5)	6.8 (10.7)		7.4 (12.1)	5.8 (9.5)	6.6 (10.9)	
Median	32.5	32.5	32.5		19.0	18.5	18.7		12.5	13.0	12.5		0.0	0.0	0.0		0.0	0.0	0.0	
Q1, Q3	20.0, 47.5	19.0, 47.0	19.5, 47.0		10.7, 29.5	10.3, 30.0	10.7, 30.0		7.4, 20.8	8.0, 23.0	7.5, 22.0		0.0, 12.5	0.0, 11.1	0.0, 11.5		0.0, 11.5	0.0, 10.9	0.0, 10.9	
SCORAD Band				0.894				0.666				0.716				0.127				0.344
Missing	0	0	0		1	2	3		7	9	16		0	1	1		3	5	8	
0	9 (3.1%)	7 (2.4%)	16 (2.7%)		16 (5.4%)	19 (6.5%)	35 (6.0%)		43 (14.9%)	41 (14.4%)	84 (14.7%)		171 (58.0%)	185 (63.1%)	356 (60.5%)		161 (61.7%)	160 (63.7%)	321 (62.7%)	
(0-15)	40 (13.6%)	45 (15.3%)	85 (14.4%)		97 (33.0%)	95 (32.5%)	192 (32.8%)		121 (42.0%)	115 (40.4%)	236 (41.2%)		61 (20.7%)	66 (22.5%)	127 (21.6%)		49 (18.8%)	54 (21.5%)	103 (20.1%)	
[15-40]	138 (46.8%)	138 (46.9%)	276 (46.9%)		142 (48.3%)	148 (50.7%)	290 (49.5%)		104 (36.1%)	114 (40.0%)	218 (38.0%)		55 (18.6%)	39 (13.3%)	94 (16.0%)		43 (16.5%)	34 (13.5%)	77 (15.0%)	
>40	108 (36.6%)	104 (35.4%)	212 (36.0%)		39 (13.3%)	30 (10.3%)	69 (11.8%)		20 (6.9%)	15 (5.3%)	35 (6.1%)		8 (2.7%)	3 (1.0%)	11 (1.9%)		8 (3.1%)	3 (1.2%)	11 (2.1%)	

Note: P-values for SCORAD are based on Wilcoxon Rank Sum Tests.
Note: P-values for SCORAD Band are based on Chi-Squared Tests.

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Table E5. A Priori Cutoff Sensitization to Peanut, Tree Nuts, and Sesame in the LEAP and LEAP-On ITT Populations

	4-11 (mo)				12 (mo)				30 (mo)				60 (mo)				72 (mo)			
	Avoiders (N=321)	Consumers (N=319)	Total (N=640)	p value	Avoiders (N=321)	Consumers (N=319)	Total (N=640)	p value	Avoiders (N=321)	Consumers (N=319)	Total (N=640)	p value	Avoiders (N=321)	Consumers (N=319)	Total (N=640)	p value	Avoiders (N=282)	Consumers (N=274)	Total (N=556)	p value
Peanut				0.612				0.208				0.573				0.217				0.096
Missing	0	0	0		6	8	14		12	11	23		5	5	10		4	6	10	
Not Sensitized	240 (74.8%)	244 (76.5%)	484 (75.6%)		224 (71.1%)	235 (75.6%)	459 (73.3%)		226 (73.1%)	219 (71.1%)	445 (72.1%)		210 (66.5%)	223 (71.0%)	433 (68.7%)		172 (61.9%)	184 (68.7%)	356 (65.2%)	
Sensitized	81 (25.2%)	75 (23.5%)	156 (24.4%)		91 (28.9%)	76 (24.4%)	167 (26.7%)		83 (26.9%)	89 (28.9%)	172 (27.9%)		106 (33.5%)	91 (29.0%)	197 (31.3%)		106 (38.1%)	84 (31.3%)	190 (34.8%)	
Sesame				0.746				0.221				0.518				0.180				0.521
Missing	0	0	0		6	8	14		12	11	23		6	9	15		6	15	21	
Not Sensitized	248 (77.3%)	243 (76.2%)	491 (76.7%)		222 (70.5%)	205 (65.9%)	427 (68.2%)		223 (72.2%)	215 (69.8%)	438 (71.0%)		224 (71.1%)	205 (66.1%)	429 (68.6%)		180 (65.2%)	162 (62.5%)	342 (63.9%)	
Sensitized	73 (22.7%)	76 (23.8%)	149 (23.3%)		93 (29.5%)	106 (34.1%)	199 (31.8%)		86 (27.8%)	93 (30.2%)	179 (29.0%)		91 (28.9%)	105 (33.9%)	196 (31.4%)		96 (34.8%)	97 (37.5%)	193 (36.1%)	
Brazil Nut																0.245				0.504
Missing													6	10	16		6	14	20	
Not Sensitized													265 (84.1%)	249 (80.6%)	514 (82.4%)		225 (81.5%)	206 (79.2%)	431 (80.4%)	
Sensitized													50 (15.9%)	60 (19.4%)	110 (17.6%)		51 (18.5%)	54 (20.8%)	105 (19.6%)	
Hazelnut																0.144				0.671
Missing													6	11	17		6	14	20	
Not Sensitized													210 (66.7%)	188 (61.0%)	398 (63.9%)		160 (58.0%)	146 (56.2%)	306 (57.1%)	
Sensitized													105 (33.3%)	120 (39.0%)	225 (36.1%)		116 (42.0%)	114 (43.8%)	230 (42.9%)	
Cashew																0.140				0.155
Missing													6	11	17		6	15	21	
Not Sensitized													248 (78.7%)	227 (73.7%)	475 (76.2%)		212 (76.8%)	185 (71.4%)	397 (74.2%)	
Sensitized													67 (21.3%)	81 (26.3%)	148 (23.8%)		64 (23.2%)	74 (28.6%)	138 (25.8%)	
Walnut																0.086				0.025
Missing													6	11	17		6	15	21	
Not Sensitized													257 (81.6%)	234 (76.0%)	491 (78.8%)		221 (80.1%)	186 (71.8%)	407 (76.1%)	
Sensitized													58 (18.4%)	74 (24.0%)	132 (21.2%)		55 (19.9%)	73 (28.2%)	128 (23.9%)	
Almond																0.275				0.346
Missing													6	11	17		6	15	21	
Not Sensitized													244 (77.5%)	227 (73.7%)	471 (75.6%)		203 (73.6%)	181 (69.9%)	384 (71.8%)	
Sensitized													71 (22.5%)	81 (26.3%)	152 (24.4%)		73 (26.4%)	78 (30.1%)	151 (28.2%)	

Note: A subject is defined as 'Sensitized' if the SPT wheal ≥3mm or Specific IgE ≥ 0.35 kU/L.
Note: P-values are based on Chi-Squared Tests.
Note: Specific IgE and SPT for Brazil Nut, Hazelnut, Cashew, Walnut, and Almond were only collected at 60 and 72 months.

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Table E6. A Priori Cutoff Sensitization to Peanut, Tree Nuts, and Sesame in the LEAP Per Protocol Population

	4-11 (mo)				12 (mo)				30 (mo)				60 (mo)				72 (mo)			
	Avoiders (N=295)	Consumers (N=294)	Total (N=589)	p value	Avoiders (N=295)	Consumers (N=294)	Total (N=589)	p value	Avoiders (N=295)	Consumers (N=294)	Total (N=589)	p value	Avoiders (N=295)	Consumers (N=294)	Total (N=589)	p value	Avoiders (N=264)	Consumers (N=256)	Total (N=520)	p value
Peanut				0.150				0.020				0.605				0.020				0.008
Missing	0	0	0		1	2	3		7	8	15		0	0	0		3	6	9	
Not Sensitized	219 (74.2%)	233 (79.3%)	452 (76.7%)		207 (70.4%)	230 (78.8%)	437 (74.6%)		209 (72.6%)	213 (74.5%)	422 (73.5%)		195 (66.1%)	220 (74.8%)	415 (70.5%)		160 (61.3%)	181 (72.4%)	341 (66.7%)	
Sensitized	76 (25.8%)	61 (20.7%)	137 (23.3%)		87 (29.6%)	62 (21.2%)	149 (25.4%)		79 (27.4%)	73 (25.5%)	152 (26.5%)		100 (33.9%)	74 (25.2%)	174 (29.5%)		101 (38.7%)	69 (27.6%)	170 (33.3%)	
Sesame				0.712				0.615				0.885				0.534				0.944
Missing	0	0	0		1	2	3		7	8	15		1	3	4		4	15	19	
Not Sensitized	225 (76.3%)	228 (77.6%)	453 (76.9%)		206 (70.1%)	199 (68.2%)	405 (69.1%)		208 (72.2%)	205 (71.7%)	413 (72.0%)		209 (71.1%)	200 (68.7%)	409 (69.9%)		168 (64.6%)	155 (64.3%)	323 (64.5%)	
Sensitized	70 (23.7%)	66 (22.4%)	136 (23.1%)		88 (29.9%)	93 (31.8%)	181 (30.9%)		80 (27.8%)	81 (28.3%)	161 (28.0%)		85 (28.9%)	91 (31.3%)	176 (30.1%)		92 (35.4%)	86 (35.7%)	178 (35.5%)	
Brazil Nut																0.941				0.875
Missing													1	4	5		4	14	18	
Not Sensitized													246 (83.7%)	242 (83.4%)	488 (83.6%)		212 (81.5%)	196 (81.0%)	408 (81.3%)	
Sensitized													48 (16.3%)	48 (16.6%)	96 (16.4%)		48 (18.5%)	46 (19.0%)	94 (18.7%)	
Hazelnut																0.558				0.897
Missing													1	5	6		4	14	18	
Not Sensitized													196 (66.7%)	186 (64.4%)	382 (65.5%)		150 (57.7%)	141 (58.3%)	291 (58.0%)	
Sensitized													98 (33.3%)	103 (35.6%)	201 (34.5%)		110 (42.3%)	101 (41.7%)	211 (42.0%)	
Cashew																0.544				0.426
Missing													1	5	6		4	15	19	
Not Sensitized													230 (78.2%)	220 (76.1%)	450 (77.2%)		200 (76.9%)	178 (73.9%)	378 (75.4%)	
Sensitized													64 (21.8%)	69 (23.9%)	133 (22.8%)		60 (23.1%)	63 (26.1%)	123 (24.6%)	
Walnut																0.471				0.103
Missing													1	5	6		4	15	19	
Not Sensitized													237 (80.6%)	226 (78.2%)	463 (79.4%)		207 (79.6%)	177 (73.4%)	384 (76.6%)	
Sensitized													57 (19.4%)	63 (21.8%)	120 (20.6%)		53 (20.4%)	64 (26.6%)	117 (23.4%)	
Almond																0.985				0.907
Missing													1	5	6		4	15	19	
Not Sensitized													224 (76.2%)	220 (76.1%)	444 (76.2%)		190 (73.1%)	175 (72.6%)	365 (72.9%)	
Sensitized													70 (23.8%)	69 (23.9%)	139 (23.8%)		70 (26.9%)	66 (27.4%)	136 (27.1%)	

Note: A subject is defined as 'Sensitized' if the SPT wheal ≥3mm or Specific IgE ≥ 0.35 kU/L.
Note: P-values are based on Chi-Squared Tests.
Note: Specific IgE and SPT for Brazil Nut, Hazelnut, Cashew, Walnut, and Almond were only collected at 60 and 72 months.

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Table E7. High Level Cutoff Sensitization to Peanut, Tree Nuts, and Sesame in the LEAP and LEAP-On ITT Populations

	4-11 (mo)				12 (mo)				30 (mo)				60 (mo)				72 (mo)			
	Avoiders (N=321)	**Consumers (N=319)**	**Total (N=640)**	**p value**	**Avoiders (N=321)**	**Consumers (N=319)**	**Total (N=640)**	**p value**	**Avoiders (N=321)**	**Consumers (N=319)**	**Total (N=640)**	**p value**	**Avoiders (N=321)**	**Consumers (N=319)**	**Total (N=640)**	**p value**	**Avoiders (N=282)**	**Consumers (N=274)**	**Total (N=556)**	**p value**
Peanut				0.117				0.912				<0.001				0.001				0.017
Missing	0	0	0		6	8	14		12	11	23		5	5	10		4	6	10	
Not Sensitized	314 (97.8%)	305 (95.6%)	619 (96.7%)		292 (92.7%)	289 (92.9%)	581 (92.8%)		265 (85.8%)	291 (94.5%)	556 (90.1%)		262 (82.9%)	287 (91.4%)	549 (87.1%)		228 (82.0%)	239 (89.2%)	467 (85.5%)	
Sensitized	7 (2.2%)	14 (4.4%)	21 (3.3%)		23 (7.3%)	22 (7.1%)	45 (7.2%)		44 (14.2%)	17 (5.5%)	61 (9.9%)		54 (17.1%)	27 (8.6%)	81 (12.9%)		50 (18.0%)	29 (10.8%)	79 (14.5%)	
Sesame				0.621				0.930				0.532				0.286				0.089
Missing	0	0	0		6	8	14		12	11	23		6	9	15		6	15	21	
Not Sensitized	301 (93.8%)	296 (92.8%)	597 (93.3%)		286 (90.8%)	283 (91.0%)	569 (90.9%)		288 (93.2%)	283 (91.9%)	571 (92.5%)		292 (92.7%)	280 (90.3%)	572 (91.5%)		255 (92.4%)	228 (88.0%)	483 (90.3%)	
Sensitized	20 (6.2%)	23 (7.2%)	43 (6.7%)		29 (9.2%)	28 (9.0%)	57 (9.1%)		21 (6.8%)	25 (8.1%)	46 (7.5%)		23 (7.3%)	30 (9.7%)	53 (8.5%)		21 (7.6%)	31 (12.0%)	52 (9.7%)	
Brazil Nut																0.088				0.054
Missing													6	10	16		6	14	20	
Not Sensitized													296 (94.0%)	279 (90.3%)	575 (92.1%)		259 (93.8%)	232 (89.2%)	491 (91.6%)	
Sensitized													19 (6.0%)	30 (9.7%)	49 (7.9%)		17 (6.2%)	28 (10.8%)	45 (8.4%)	
Hazelnut																0.025				0.021
Missing													6	11	17		6	14	20	
Not Sensitized													277 (87.9%)	251 (81.5%)	528 (84.8%)		234 (84.8%)	200 (76.9%)	434 (81.0%)	
Sensitized													38 (12.1%)	57 (18.5%)	95 (15.2%)		42 (15.2%)	60 (23.1%)	102 (19.0%)	
Cashew																0.034				0.050
Missing													6	11	17		6	15	21	
Not Sensitized													282 (89.5%)	258 (83.8%)	540 (86.7%)		239 (86.6%)	208 (80.3%)	447 (83.6%)	
Sensitized													33 (10.5%)	50 (16.2%)	83 (13.3%)		37 (13.4%)	51 (19.7%)	88 (16.4%)	
Walnut																0.014				0.121
Missing													6	11	17		6	15	21	
Not Sensitized													301 (95.6%)	279 (90.6%)	580 (93.1%)		261 (94.6%)	236 (91.1%)	497 (92.9%)	
Sensitized													14 (4.4%)	29 (9.4%)	43 (6.9%)		15 (5.4%)	23 (8.9%)	38 (7.1%)	
Almond																0.526				0.199
Missing													6	11	17		6	15	21	
Not Sensitized													287 (91.1%)	276 (89.6%)	563 (90.4%)		255 (92.4%)	231 (89.2%)	486 (90.8%)	
Sensitized													28 (8.9%)	32 (10.4%)	60 (9.6%)		21 (7.6%)	28 (10.8%)	49 (9.2%)	

Note: A subject is defined as 'Sensitized' if the SPT wheal ≥5mm and/or a Specific IgE ≥ 10 kU/L.
Note: P-values are computed using Chi-Squared Tests.
Note: Specific IgE and SPT for Brazil Nut, Hazelnut, Cashew, Walnut, and Almond were only collected at 60 and 72 months.

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Table E8. High Level Cutoff Sensitization to Peanut, Tree Nuts, and Sesame in the LEAP Per Protocol Popuation

	4-11 (mo)				12 (mo)				30 (mo)				60 (mo)				72 (mo)			
	Avoiders (N=295)	**Consumers (N=294)**	**Total (N=589)**	**p value**	**Avoiders (N=295)**	**Consumers (N=294)**	**Total (N=589)**	**p value**	**Avoiders (N=295)**	**Consumers (N=294)**	**Total (N=589)**	**p value**	**Avoiders (N=295)**	**Consumers (N=294)**	**Total (N=589)**	**p value**	**Avoiders (N=264)**	**Consumers (N=256)**	**Total (N=520)**	**p value**
Peanut				0.216				0.081				<0.001				<0.001				<0.001
Missing	0	0	0		1	2	3		7	8	15		0	0	0		3	6	9	
Not Sensitized	289 (98.0%)	283 (96.3%)	572 (97.1%)		272 (92.5%)	280 (95.9%)	552 (94.2%)		248 (86.1%)	276 (96.5%)	524 (91.3%)		246 (83.4%)	279 (94.9%)	525 (89.1%)		214 (82.0%)	231 (92.4%)	445 (87.1%)	
Sensitized	6 (2.0%)	11 (3.7%)	17 (2.9%)		22 (7.5%)	12 (4.1%)	34 (5.8%)		40 (13.9%)	10 (3.5%)	50 (8.7%)		49 (16.6%)	15 (5.1%)	64 (10.9%)		47 (18.0%)	19 (7.6%)	66 (12.9%)	
Sesame				0.991				0.679				0.731				0.731				0.131
Missing	0	0	0		1	2	3		7	8	15		1	3	4		4	15	19	
Not Sensitized	276 (93.6%)	275 (93.5%)	551 (93.5%)		267 (90.8%)	268 (91.8%)	535 (91.3%)		268 (93.1%)	264 (92.3%)	532 (92.7%)		272 (92.5%)	267 (91.8%)	539 (92.1%)		241 (92.7%)	214 (88.8%)	455 (90.8%)	
Sensitized	19 (6.4%)	19 (6.5%)	38 (6.5%)		27 (9.2%)	24 (8.2%)	51 (8.7%)		20 (6.9%)	22 (7.7%)	42 (7.3%)		22 (7.5%)	24 (8.2%)	46 (7.9%)		19 (7.3%)	27 (11.2%)	46 (9.2%)	
Brazil Nut																0.323				0.093
Missing													1	4	5		4	14	18	
Not Sensitized													275 (93.5%)	265 (91.4%)	540 (92.5%)		243 (93.5%)	216 (89.3%)	459 (91.4%)	
Sensitized													19 (6.5%)	25 (8.6%)	44 (7.5%)		17 (6.5%)	26 (10.7%)	43 (8.6%)	
Hazelnut																0.107				0.048
Missing													1	5	6		4	14	18	
Not Sensitized													258 (87.8%)	240 (83.0%)	498 (85.4%)		219 (84.2%)	187 (77.3%)	406 (80.9%)	
Sensitized													36 (12.2%)	49 (17.0%)	85 (14.6%)		41 (15.8%)	55 (22.7%)	96 (19.1%)	
Cashew																0.146				0.086
Missing													1	5	6		4	15	19	
Not Sensitized													263 (89.5%)	247 (85.5%)	510 (87.5%)		226 (86.9%)	196 (81.3%)	422 (84.2%)	
Sensitized													31 (10.5%)	42 (14.5%)	73 (12.5%)		34 (13.1%)	45 (18.7%)	79 (15.8%)	
Walnut																0.113				0.557
Missing													1	5	6		4	15	19	
Not Sensitized													280 (95.2%)	266 (92.0%)	546 (93.7%)		245 (94.2%)	224 (92.9%)	469 (93.6%)	
Sensitized													14 (4.8%)	23 (8.0%)	37 (6.3%)		15 (5.8%)	17 (7.1%)	32 (6.4%)	
Almond																0.940				0.562
Missing													1	5	6		4	15	19	
Not Sensitized													266 (90.5%)	262 (90.7%)	528 (90.6%)		239 (91.9%)	218 (90.5%)	457 (91.2%)	
Sensitized													28 (9.5%)	27 (9.3%)	55 (9.4%)		21 (8.1%)	23 (9.5%)	44 (8.8%)	

Note: A subject is defined as 'Sensitized' if the SPT wheal ≥5mm and/or a Specific IgE ≥ 10 kU/L.
Note: P-values are computed using Chi-Squared Tests.
Note: Specific IgE and SPT for Brazil Nut, Hazelnut, Cashew, Walnut, and Almond were only collected at 60 and 72 months.

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Table E9. Reported Tree Nut Reactions at 60 Months in the LEAP ITT and Per-Protocol Populations

	Intent to Treat				Per Protocol			
	Avoiders (N=321)	**Consumers (N=319)**	**Total (N=640)**	**p value**	**Avoiders (N=295)**	**Consumers (N=294)**	**Total (N=589)**	**p value**
Brazil Nut Reaction				0.031				0.030
Missing	4	3	7		0	0	0	
No	317 (100.0%)	311 (98.4%)	628 (99.2%)		295 (100.0%)	289 (98.3%)	584 (99.2%)	
Yes	0 (0.0%)	5 (1.6%)	5 (0.8%)		0 (0.0%)	5 (1.7%)	5 (0.8%)	
Hazelnut Reaction				0.073				0.174
Missing	4	3	7		0	0	0	
No	313 (98.7%)	305 (96.5%)	618 (97.6%)		291 (98.6%)	285 (96.9%)	576 (97.8%)	
Yes	4 (1.3%)	11 (3.5%)	15 (2.4%)		4 (1.4%)	9 (3.1%)	13 (2.2%)	
Cashew Reaction				0.114				0.219
Missing	4	3	7		0	0	0	
No	308 (97.2%)	299 (94.6%)	607 (95.9%)		286 (96.9%)	279 (94.9%)	565 (95.9%)	
Yes	9 (2.8%)	17 (5.4%)	26 (4.1%)		9 (3.1%)	15 (5.1%)	24 (4.1%)	
Walnut Reaction				0.686				0.686
Missing	4	3	7		0	0	0	
No	315 (99.4%)	313 (99.1%)	628 (99.2%)		293 (99.3%)	291 (99.0%)	584 (99.2%)	
Yes	2 (0.6%)	3 (0.9%)	5 (0.8%)		2 (0.7%)	3 (1.0%)	5 (0.8%)	
Almond Reaction				0.624				0.624
Missing	4	3	7		0	0	0	
No	316 (99.7%)	314 (99.4%)	630 (99.5%)		294 (99.7%)	292 (99.3%)	586 (99.5%)	
Yes	1 (0.3%)	2 (0.6%)	3 (0.5%)		1 (0.3%)	2 (0.7%)	3 (0.5%)	
Sesame Reaction				0.684				0.395
Missing	4	3	7		0	0	0	
No	306 (96.5%)	303 (95.9%)	609 (96.2%)		286 (96.9%)	281 (95.6%)	567 (96.3%)	
Yes	11 (3.5%)	13 (4.1%)	24 (3.8%)		9 (3.1%)	13 (4.4%)	22 (3.7%)	
Any Nut Reaction				0.023				0.026
Missing	4	3	7		0	0	0	
No	294 (92.7%)	276 (87.3%)	570 (90.0%)		274 (92.9%)	257 (87.4%)	531 (90.2%)	
Yes	23 (7.3%)	40 (12.7%)	63 (10.0%)		21 (7.1%)	37 (12.6%)	58 (9.8%)	
Number of Tree Nut Reactions				0.016				0.022
Missing	4	3	7		0	0	0	
0	294 (92.7%)	276 (87.3%)	570 (90.0%)		274 (92.9%)	257 (87.4%)	531 (90.2%)	
1	19 (6.0%)	30 (9.5%)	49 (7.7%)		17 (5.8%)	28 (9.5%)	45 (7.6%)	
2	4 (1.3%)	9 (2.8%)	13 (2.1%)		4 (1.4%)	8 (2.7%)	12 (2.0%)	
3	0 (0.0%)	1 (0.3%)	1 (0.2%)		0 (0.0%)	1 (0.3%)	1 (0.2%)	
4	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	0 (0.0%)	
5	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	0 (0.0%)	
6	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	0 (0.0%)	

Note: P-Values for Binary outcomes are based on Fisher's Exact Tests. P-Values for Number of Reactions are based on Armitage Trend Tests.

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Table E10. Association Between IgE Levels and Reported Reactions to Tree Nut and Sesame by Treatment Group in the LEAP ITT Population

	Peanut Avoiders			Peanut Consumers			Avoiders and Consumers		
	No Reported Reaction	Reported Reaction	Total	No Reported Reaction	Reported Reaction	Total	No Reported Reaction	Reported Reaction	Total
Brazil Nut IgE		Brazil Nut Reported Reaction			Brazil Nut Reported Reaction			Brazil Nut Reported Reaction	
<0.35 kU/L	261 (85.3%)	0 (0.0%)	261 (85.3%)	240 (82.2%)	1 (25.0%)	241 (81.4%)	501 (83.8%)	1 (25.0%)	502 (83.4%)
≥0.35 kU/L	45 (14.7%)	0 (0.0%)	45 (14.7%)	52 (17.8%)	3 (75.0%)	55 (18.6%)	97 (16.2%)	3 (75.0%)	100 (16.6%)
Hazelnut IgE		Hazelnut Reported Reaction			Hazelnut Reported Reaction			Hazelnut Reported Reaction	
<0.35 kU/L	206 (68.0%)	0 (0.0%)	206 (67.1%)	178 (62.5%)	2 (18.2%)	180 (60.8%)	384 (65.3%)	2 (13.3%)	386 (64.0%)
≥0.35 kU/L	97 (32.0%)	4 (100.0%)	101 (32.9%)	107 (37.5%)	9 (81.8%)	116 (39.2%)	204 (34.7%)	13 (86.7%)	217 (36.0%)
Cashew IgE		Cashew Reported Reaction			Cashew Reported Reaction			Cashew Reported Reaction	
<0.35 kU/L	241 (81.1%)	4 (44.4%)	245 (80.1%)	216 (77.7%)	6 (35.3%)	222 (75.3%)	457 (79.5%)	10 (38.5%)	467 (77.7%)
≥0.35 kU/L	56 (18.9%)	5 (55.6%)	61 (19.9%)	62 (22.3%)	11 (64.7%)	73 (24.7%)	118 (20.5%)	16 (61.5%)	134 (22.3%)
Walnut IgE		Walnut Reported Reaction			Walnut Reported Reaction			Walnut Reported Reaction	
<0.35 kU/L	253 (83.2%)	1 (50.0%)	254 (83.0%)	224 (76.7%)	1 (33.3%)	225 (76.3%)	477 (80.0%)	2 (40.0%)	479 (79.7%)
≥0.35 kU/L	51 (16.8%)	1 (50.0%)	52 (17.0%)	68 (23.3%)	2 (66.7%)	70 (23.7%)	119 (20.0%)	3 (60.0%)	122 (20.3%)
Almond IgE		Almond Reported Reaction			Almond Reported Reaction			Almond Reported Reaction	
<0.35 kU/L	244 (79.7%)	1 (100.0%)	245 (79.8%)	224 (76.2%)	1 (50.0%)	225 (76.0%)	468 (78.0%)	2 (66.7%)	470 (77.9%)
≥0.35 kU/L	62 (20.3%)	0 (0.0%)	62 (20.2%)	70 (23.8%)	1 (50.0%)	71 (24.0%)	132 (22.0%)	1 (33.3%)	133 (22.1%)
Sesame IgE		Sesame Reported Reaction			Sesame Reported Reaction			Sesame Reported Reaction	
<0.35 kU/L	213 (72.0%)	5 (45.5%)	218 (71.0%)	186 (65.7%)	6 (46.2%)	192 (64.9%)	399 (68.9%)	11 (45.8%)	410 (68.0%)
≥0.35 kU/L	83 (28.0%)	6 (54.5%)	89 (29.0%)	97 (34.3%)	7 (53.8%)	104 (35.1%)	180 (31.1%)	13 (54.2%)	193 (32.0%)

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Table E11. Frequency of Tree Nut and Sesame Consumption by Treatment Group in the LEAP ITT Population

	Avoiders (N=321)	Consumers (N=319)	Total (N=640)	p value
Hazelnuts				0.005
No	300 (93.5%)	277 (86.8%)	577 (90.2%)	
Yes	21 (6.5%)	42 (13.2%)	63 (9.8%)	
Cashews				0.223
No	313 (97.5%)	316 (99.1%)	629 (98.3%)	
Yes	8 (2.5%)	3 (0.9%)	11 (1.7%)	
Walnuts				0.686
No	319 (99.4%)	316 (99.1%)	635 (99.2%)	
Yes	2 (0.6%)	3 (0.9%)	5 (0.8%)	
Almonds				>0.999
No	313 (97.5%)	311 (97.5%)	624 (97.5%)	
Yes	8 (2.5%)	8 (2.5%)	16 (2.5%)	
Sesame				0.374
No	259 (80.7%)	266 (83.4%)	525 (82.0%)	
Yes	62 (19.3%)	53 (16.6%)	115 (18.0%)	
Mixed Nuts				0.030
No	321 (100.0%)	314 (98.4%)	635 (99.2%)	
Yes	0 (0.0%)	5 (1.6%)	5 (0.8%)	

Note: Information about consumption of the Tree Nuts and Sesame comes from the 3 day food diaries collected during the LEAP trial. A subject is a 'Yes' if they reported consuming a certain nut or sesame in at least one of their returned food diaries. Hazelnuts inclue raw hazelnuts and chocolate nut spreads. P-Values for Cashews, Walnuts, Almonds, and Mixed Nuts are based on Fisher's Exact Tests. P-Values for Hazelnuts and Sesame are based on Chi-Squared Tests.

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Table E12. A Priori Sensitization to Other Common Foods in the LEAP and LEAP-On ITT Populations

	4-11 (mo)				12 (mo)				30 (mo)				60 (mo)				72 (mo)			
	Avoiders (N=321)	Consumers (N=319)	Total (N=640)	p value	Avoiders (N=321)	Consumers (N=319)	Total (N=640)	p value	Avoiders (N=321)	Consumers (N=319)	Total (N=640)	p value	Avoiders (N=321)	Consumers (N=319)	Total (N=640)	p value	Avoiders (N=282)	Consumers (N=274)	Total (N=556)	p value
Cow's Milk Sensitized				0.846				0.886				0.520				0.591				0.578
Missing	0	0	0		6	8	14		12	11	23		6	8	14		6	13	19	
No	211 (65.7%)	212 (66.5%)	423 (66.1%)		211 (67.0%)	210 (67.5%)	421 (67.3%)		196 (63.4%)	203 (65.9%)	399 (64.7%)		213 (67.6%)	204 (65.6%)	417 (66.6%)		182 (65.9%)	178 (68.2%)	360 (67.0%)	
Yes	110 (34.3%)	107 (33.5%)	217 (33.9%)		104 (33.0%)	101 (32.5%)	205 (32.7%)		113 (36.6%)	105 (34.1%)	218 (35.3%)		102 (32.4%)	107 (34.4%)	209 (33.4%)		94 (34.1%)	83 (31.8%)	177 (33.0%)	
Raw Egg Sensitized				0.823				0.714				0.843				0.956				0.730
Missing	0	0	0		6	8	14		12	11	23		5	7	12		6	11	17	
No	96 (29.9%)	98 (30.7%)	194 (30.3%)		84 (26.7%)	87 (28.0%)	171 (27.3%)		130 (42.1%)	132 (42.9%)	262 (42.5%)		183 (57.9%)	180 (57.7%)	363 (57.8%)		166 (60.1%)	162 (61.6%)	328 (60.9%)	
Yes	225 (70.1%)	221 (69.3%)	446 (69.7%)		231 (73.3%)	224 (72.0%)	455 (72.7%)		179 (57.9%)	176 (57.1%)	355 (57.5%)		133 (42.1%)	132 (42.3%)	265 (42.2%)		110 (39.9%)	101 (38.4%)	211 (39.1%)	
Pasteurized Egg Wheal				0.882				0.954				0.568				0.865				0.854
Missing	0	0	0		7	8	15		12	13	25		11	15	26		18	21	39	
<3 mm	137 (42.7%)	138 (43.3%)	275 (43.0%)		135 (43.0%)	133 (42.8%)	268 (42.9%)		189 (61.2%)	194 (63.4%)	383 (62.3%)		243 (78.4%)	240 (78.9%)	483 (78.7%)		208 (78.8%)	201 (79.4%)	409 (79.1%)	
≥3 mm	184 (57.3%)	181 (56.7%)	365 (57.0%)		179 (57.0%)	178 (57.2%)	357 (57.1%)		120 (38.8%)	112 (36.6%)	232 (37.7%)		67 (21.6%)	64 (21.1%)	131 (21.3%)		56 (21.2%)	52 (20.6%)	108 (20.9%)	
Soya Wheal				0.597				0.262				0.617				0.236				
Missing	0	0	0		6	10	16		13	12	25		18	32	50					
<3 mm	313 (97.5%)	313 (98.1%)	626 (97.8%)		303 (96.2%)	302 (97.7%)	605 (97.0%)		299 (97.1%)	300 (97.7%)	599 (97.4%)		298 (98.3%)	278 (96.9%)	576 (97.6%)					
≥3 mm	8 (2.5%)	6 (1.9%)	14 (2.2%)		12 (3.8%)	7 (2.3%)	19 (3.0%)		9 (2.9%)	7 (2.3%)	16 (2.6%)		5 (1.7%)	9 (3.1%)	14 (2.4%)					

Note: A subject is defined as 'Sensitized' if the SPT wheal ≥3mm or Specific IgE ≥ 0.35 kU/L.
Note: P-values are computed using Chi-Squared Tests.
Note: Soya specific IgE and SPT were not collected at 72 months.

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Table E13. A Priori Sensitization to Other Common Foods in the LEAP Per Protocol Population

	4-11 (mo)				12 (mo)				30 (mo)				60 (mo)				72 (mo)			
	Avoiders (N=295)	**Consumers (N=294)**	**Total (N=589)**	**p value**	**Avoiders (N=295)**	**Consumers (N=294)**	**Total (N=589)**	**p value**	**Avoiders (N=295)**	**Consumers (N=294)**	**Total (N=589)**	**p value**	**Avoiders (N=295)**	**Consumers (N=294)**	**Total (N=589)**	**p value**	**Avoiders (N=264)**	**Consumers (N=256)**	**Total (N=520)**	**p value**
Cow's Milk Sensitized				0.564				0.411				0.322				0.884				0.528
Missing	0	0	0		1	2	3		7	8	15		1	2	3		4	13	17	
No	190 (64.4%)	196 (66.7%)	386 (65.5%)		193 (65.6%)	201 (68.8%)	394 (67.2%)		182 (63.2%)	192 (67.1%)	374 (65.2%)		197 (67.0%)	194 (66.4%)	391 (66.7%)		174 (66.9%)	169 (69.5%)	343 (68.2%)	
Yes	105 (35.6%)	98 (33.3%)	203 (34.5%)		101 (34.4%)	91 (31.2%)	192 (32.8%)		106 (36.8%)	94 (32.9%)	200 (34.8%)		97 (33.0%)	98 (33.6%)	195 (33.3%)		86 (33.1%)	74 (30.5%)	160 (31.8%)	
Raw Egg Sensitized				0.511				0.330				0.507				0.856				0.404
Missing	0	0	0		1	2	3		7	8	15		0	1	1		4	11	15	
No	84 (28.5%)	91 (31.0%)	175 (29.7%)		76 (25.9%)	86 (29.5%)	162 (27.6%)		119 (41.3%)	126 (44.1%)	245 (42.7%)		172 (58.3%)	173 (59.0%)	345 (58.7%)		154 (59.2%)	154 (62.9%)	308 (61.0%)	
Yes	211 (71.5%)	203 (69.0%)	414 (70.3%)		218 (74.1%)	206 (70.5%)	424 (72.4%)		169 (58.7%)	160 (55.9%)	329 (57.3%)		123 (41.7%)	120 (41.0%)	243 (41.3%)		106 (40.8%)	91 (37.1%)	197 (39.0%)	
Pasteurized Egg Wheal				0.482				0.535				0.280				0.558				0.565
Missing	0	0	0		2	2	4		7	10	17		6	7	13		13	20	33	
<3 mm	120 (40.7%)	128 (43.5%)	248 (42.1%)		124 (42.3%)	131 (44.9%)	255 (43.6%)		174 (60.4%)	184 (64.8%)	358 (62.6%)		229 (79.2%)	233 (81.2%)	462 (80.2%)		199 (79.3%)	192 (81.4%)	391 (80.3%)	
≥3 mm	175 (59.3%)	166 (56.5%)	341 (57.9%)		169 (57.7%)	161 (55.1%)	330 (56.4%)		114 (39.6%)	100 (35.2%)	214 (37.4%)		60 (20.8%)	54 (18.8%)	114 (19.8%)		52 (20.7%)	44 (18.6%)	96 (19.7%)	
Soya Wheal				0.593				0.090				0.285				0.936				
Missing	0	0	0		1	4	5		8	9	17		10	23	33					
<3 mm	287 (97.3%)	288 (98.0%)	575 (97.6%)		282 (95.9%)	285 (98.3%)	567 (97.1%)		278 (96.9%)	280 (98.2%)	558 (97.6%)		280 (98.2%)	266 (98.2%)	546 (98.2%)					
≥3 mm	8 (2.7%)	6 (2.0%)	14 (2.4%)		12 (4.1%)	5 (1.7%)	17 (2.9%)		9 (3.1%)	5 (1.8%)	14 (2.4%)		5 (1.8%)	5 (1.8%)	10 (1.8%)					

Note: A subject is defined as 'Sensitized' if the SPT wheal ≥3mm or Specific IgE ≥ 0.35 kU/L.
Note: P-values are computed using Chi-Squared Tests.
Note: Soya specific IgE and SPT were not collected at 72 months.

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Table E14. High Level Cutoff Sensitization to Other Common Foods in the LEAP and LEAP-On ITT Populations

	4-11 (mo)				12 (mo)				30 (mo)				60 (mo)				72 (mo)			
	Avoiders (N=321)	Consumers (N=319)	Total (N=640)	p value	Avoiders (N=321)	Consumers (N=319)	Total (N=640)	p value	Avoiders (N=321)	Consumers (N=319)	Total (N=640)	p value	Avoiders (N=321)	Consumers (N=319)	Total (N=640)	p value	Avoiders (N=282)	Consumers (N=274)	Total (N=556)	p value
Cow's Milk Sensitized				0.406				0.554				0.480				0.963				0.885
Missing	0	0	0		6	8	14		12	11	23		6	8	14		6	13	19	
No	280 (87.2%)	285 (89.3%)	565 (88.3%)		279 (88.6%)	280 (90.0%)	559 (89.3%)		280 (90.6%)	284 (92.2%)	564 (91.4%)		291 (92.4%)	287 (92.3%)	578 (92.3%)		255 (92.4%)	242 (92.7%)	497 (92.6%)	
Yes	41 (12.8%)	34 (10.7%)	75 (11.7%)		36 (11.4%)	31 (10.0%)	67 (10.7%)		29 (9.4%)	24 (7.8%)	53 (8.6%)		24 (7.6%)	24 (7.7%)	48 (7.7%)		21 (7.6%)	19 (7.3%)	40 (7.4%)	
Raw Egg Sensitized				0.697				0.750				0.601				0.587				0.871
Missing	0	0	0		6	8	14		12	11	23		5	7	12		6	11	17	
No	111 (34.6%)	115 (36.1%)	226 (35.3%)		103 (32.7%)	98 (31.5%)	201 (32.1%)		152 (49.2%)	158 (51.3%)	310 (50.2%)		229 (72.5%)	220 (70.5%)	449 (71.5%)		204 (73.9%)	196 (74.5%)	400 (74.2%)	
Yes	210 (65.4%)	204 (63.9%)	414 (64.7%)		212 (67.3%)	213 (68.5%)	425 (67.9%)		157 (50.8%)	150 (48.7%)	307 (49.8%)		87 (27.5%)	92 (29.5%)	179 (28.5%)		72 (26.1%)	67 (25.5%)	139 (25.8%)	
Pasteurized Egg Wheal				0.500				0.989				0.824				0.740				0.586
Missing	0	0	0		7	8	15		12	13	25		11	15	26		18	21	39	
<5 mm	197 (61.4%)	204 (63.9%)	401 (62.7%)		192 (61.1%)	190 (61.1%)	382 (61.1%)		237 (76.7%)	237 (77.5%)	474 (77.1%)		270 (87.1%)	262 (86.2%)	532 (86.6%)		223 (84.5%)	218 (86.2%)	441 (85.3%)	
≥5 mm	124 (38.6%)	115 (36.1%)	239 (37.3%)		122 (38.9%)	121 (38.9%)	243 (38.9%)		72 (23.3%)	69 (22.5%)	141 (22.9%)		40 (12.9%)	42 (13.8%)	82 (13.4%)		41 (15.5%)	35 (13.8%)	76 (14.7%)	
Soya Wheal				0.498				0.723				>0.999				>0.999				
Missing	0	0	0		6	10	16		13	12	25		18	32	50					
<5 mm	321 (100.0%)	318 (99.7%)	639 (99.8%)		312 (99.0%)	305 (98.7%)	617 (98.9%)		306 (99.4%)	305 (99.3%)	611 (99.3%)		301 (99.3%)	285 (99.3%)	586 (99.3%)					
≥5 mm	0 (0.0%)	1 (0.3%)	1 (0.2%)		3 (1.0%)	4 (1.3%)	7 (1.1%)		2 (0.6%)	2 (0.7%)	4 (0.7%)		2 (0.7%)	2 (0.7%)	4 (0.7%)					

Note: A subject is defined as 'Sensitized' if the SPT wheal ≥5mm and/or a Specific IgE ≥ 10 kU/L.
Note: P-values for Cow's Milk Sensitization, Raw Egg Sensitization, and Pasteurized Egg Wheal are computed using Chi-Squared tests. P-values for Soya Wheal are computed using Fisher's Exact Tests.
Note: Soya specific IgE and SPT were not collected at 72 months.

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Table E15. High Level Cutoff Sensitization to Other Common Foods in the LEAP Per Protocol Population

	4-11 (mo)				12 (mo)				30 (mo)				60 (mo)				72 (mo)			
	Avoiders (N=295)	**Consumers (N=294)**	**Total (N=589)**	**p value**	**Avoiders (N=295)**	**Consumers (N=294)**	**Total (N=589)**	**p value**	**Avoiders (N=295)**	**Consumers (N=294)**	**Total (N=589)**	**p value**	**Avoiders (N=295)**	**Consumers (N=294)**	**Total (N=589)**	**p value**	**Avoiders (N=264)**	**Consumers (N=256)**	**Total (N=520)**	**p value**
Cow's Milk Sensitized				0.261				0.303				0.317				0.772				0.630
Missing	0	0	0		1	2	3		7	8	15		1	2	3		4	13	17	
No	255 (86.4%)	263 (89.5%)	518 (87.9%)		258 (87.8%)	264 (90.4%)	522 (89.1%)		259 (89.9%)	264 (92.3%)	523 (91.1%)		271 (92.2%)	271 (92.8%)	542 (92.5%)		240 (92.3%)	227 (93.4%)	467 (92.8%)	
Yes	40 (13.6%)	31 (10.5%)	71 (12.1%)		36 (12.2%)	28 (9.6%)	64 (10.9%)		29 (10.1%)	22 (7.7%)	51 (8.9%)		23 (7.8%)	21 (7.2%)	44 (7.5%)		20 (7.7%)	16 (6.6%)	36 (7.2%)	
Raw Egg Sensitized				0.419				0.815				0.358				0.960				0.526
Missing	0	0	0		1	2	3		7	8	15		0	1	1		4	11	15	
No	98 (33.2%)	107 (36.4%)	205 (34.8%)		94 (32.0%)	96 (32.9%)	190 (32.4%)		140 (48.6%)	150 (52.4%)	290 (50.5%)		215 (72.9%)	213 (72.7%)	428 (72.8%)		191 (73.5%)	186 (75.9%)	377 (74.7%)	
Yes	197 (66.8%)	187 (63.6%)	384 (65.2%)		200 (68.0%)	196 (67.1%)	396 (67.6%)		148 (51.4%)	136 (47.6%)	284 (49.5%)		80 (27.1%)	80 (27.3%)	160 (27.2%)		69 (26.5%)	59 (24.1%)	128 (25.3%)	
Pasteurized Egg Wheal				0.324				0.517				0.611				0.823				0.281
Missing	0	0	0		2	2	4		7	10	17		6	7	13		13	20	33	
<5 mm	177 (60.0%)	188 (63.9%)	365 (62.0%)		177 (60.4%)	184 (63.0%)	361 (61.7%)		220 (76.4%)	222 (78.2%)	442 (77.3%)		253 (87.5%)	253 (88.2%)	506 (87.8%)		214 (85.3%)	209 (88.6%)	423 (86.9%)	
≥5 mm	118 (40.0%)	106 (36.1%)	224 (38.0%)		116 (39.6%)	108 (37.0%)	224 (38.3%)		68 (23.6%)	62 (21.8%)	130 (22.7%)		36 (12.5%)	34 (11.8%)	70 (12.2%)		37 (14.7%)	27 (11.4%)	64 (13.1%)	
Soya Wheal				0.499				>0.999				>0.999				>0.999				
Missing	0	0	0		1	4	5		8	9	17		10	23	33					
<5 mm	295 (100.0%)	293 (99.7%)	588 (99.8%)		291 (99.0%)	287 (99.0%)	578 (99.0%)		285 (99.3%)	283 (99.3%)	568 (99.3%)		283 (99.3%)	270 (99.6%)	553 (99.5%)					
≥5 mm	0 (0.0%)	1 (0.3%)	1 (0.2%)		3 (1.0%)	3 (1.0%)	6 (1.0%)		2 (0.7%)	2 (0.7%)	4 (0.7%)		2 (0.7%)	1 (0.4%)	3 (0.5%)					

Note: A subject is defined as 'Sensitized' if the SPT wheal ≥5mm and/or a Specific IgE ≥ 10 kU/L.
Note: P-values for Cow's Milk Sensitization, Raw Egg Sensitization, and Pasteurized Egg Wheal are computed using Chi-Squared tests. P-values for Soya Wheal are computed using Fisher's Exact Tests.
Note: Soya specific IgE and SPT were not collected at 72 months.

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Table E16. Aero Allergen Specific IgE Sensitization in the LEAP and LEAP-On ITT Populations

	30 (mo)				60 (mo)				72 (mo)			
	Avoiders (N=321)	**Consumers (N=319)**	**Total (N=640)**	**p value**	**Avoiders (N=321)**	**Consumers (N=319)**	**Total (N=640)**	**p value**	**Avoiders (N=282)**	**Consumers (N=274)**	**Total (N=556)**	**p value**
House Dust Mite sIgE				0.557				0.348				0.301
Missing	19	15	34		15	25	40		11	24	35	
< 0.35 kU/L	210 (69.5%)	218 (71.7%)	428 (70.6%)		159 (52.0%)	164 (55.8%)	323 (53.8%)		120 (44.3%)	122 (48.8%)	242 (46.4%)	
≥ 0.35 kU/L	92 (30.5%)	86 (28.3%)	178 (29.4%)		147 (48.0%)	130 (44.2%)	277 (46.2%)		151 (55.7%)	128 (51.2%)	279 (53.6%)	
Cat sIgE				0.148				0.997				0.921
Missing	18	15	33		15	25	40		11	24	35	
< 0.35 kU/L	236 (77.9%)	251 (82.6%)	487 (80.2%)		205 (67.0%)	197 (67.0%)	402 (67.0%)		167 (61.6%)	153 (61.2%)	320 (61.4%)	
≥ 0.35 kU/L	67 (22.1%)	53 (17.4%)	120 (19.8%)		101 (33.0%)	97 (33.0%)	198 (33.0%)		104 (38.4%)	97 (38.8%)	201 (38.6%)	
Dog sIgE				0.599				0.589				0.416
Missing	19	15	34		15	25	40		11	24	35	
< 0.35 kU/L	229 (75.8%)	236 (77.6%)	465 (76.7%)		198 (64.7%)	184 (62.6%)	382 (63.7%)		172 (63.5%)	150 (60.0%)	322 (61.8%)	
≥ 0.35 kU/L	73 (24.2%)	68 (22.4%)	141 (23.3%)		108 (35.3%)	110 (37.4%)	218 (36.3%)		99 (36.5%)	100 (40.0%)	199 (38.2%)	
Timothy Grass sIgE				0.776				0.576				0.884
Missing	18	15	33		16	26	42		11	25	36	
< 0.35 kU/L	244 (80.5%)	242 (79.6%)	486 (80.1%)		160 (52.5%)	147 (50.2%)	307 (51.3%)		116 (42.8%)	105 (42.2%)	221 (42.5%)	
≥ 0.35 kU/L	59 (19.5%)	62 (20.4%)	121 (19.9%)		145 (47.5%)	146 (49.8%)	291 (48.7%)		155 (57.2%)	144 (57.8%)	299 (57.5%)	
Birch Pollen sIgE				0.723				0.192				>0.999
Missing	18	15	33		17	27	44		11	26	37	
< 0.35 kU/L	267 (88.1%)	265 (87.2%)	532 (87.6%)		215 (70.7%)	192 (65.8%)	407 (68.3%)		165 (60.9%)	151 (60.9%)	316 (60.9%)	
≥ 0.35 kU/L	36 (11.9%)	39 (12.8%)	75 (12.4%)		89 (29.3%)	100 (34.2%)	189 (31.7%)		106 (39.1%)	97 (39.1%)	203 (39.1%)	
Alternaria Mold sIgE				0.640				0.161				0.291
Missing	18	15	33		17	27	44		11	25	36	
< 0.35 kU/L	278 (91.7%)	282 (92.8%)	560 (92.3%)		245 (80.6%)	248 (84.9%)	493 (82.7%)		205 (75.6%)	198 (79.5%)	403 (77.5%)	
≥ 0.35 kU/L	25 (8.3%)	22 (7.2%)	47 (7.7%)		59 (19.4%)	44 (15.1%)	103 (17.3%)		66 (24.4%)	51 (20.5%)	117 (22.5%)	

Note: P-values are computed using Chi-Squared Tests.

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Table E17. Aero Allergen Specific IgE Sensitization in the LEAP Per Protocol Population

	30 (mo)				60 (mo)				72 (mo)			
	Avoiders (N=295)	**Consumers (N=294)**	**Total (N=589)**	**p value**	**Avoiders (N=295)**	**Consumers (N=294)**	**Total (N=589)**	**p value**	**Avoiders (N=264)**	**Consumers (N=256)**	**Total (N=520)**	**p value**
House Dust Mite sIgE				0.425				0.068				0.122
Missing	14	11	25		10	19	29		9	22	31	
< 0.35 kU/L	196 (69.8%)	206 (72.8%)	402 (71.3%)		146 (51.2%)	162 (58.9%)	308 (55.0%)		114 (44.7%)	121 (51.7%)	235 (48.1%)	
≥ 0.35 kU/L	85 (30.2%)	77 (27.2%)	162 (28.7%)		139 (48.8%)	113 (41.1%)	252 (45.0%)		141 (55.3%)	113 (48.3%)	254 (51.9%)	
Cat sIgE				0.108				0.602				0.715
Missing	13	11	24		10	19	29		9	22	31	
< 0.35 kU/L	219 (77.7%)	235 (83.0%)	454 (80.4%)		190 (66.7%)	189 (68.7%)	379 (67.7%)		155 (60.8%)	146 (62.4%)	301 (61.6%)	
≥ 0.35 kU/L	63 (22.3%)	48 (17.0%)	111 (19.6%)		95 (33.3%)	86 (31.3%)	181 (32.3%)		100 (39.2%)	88 (37.6%)	188 (38.4%)	
Dog sIgE				0.208				0.758				0.922
Missing	14	11	25		10	19	29		9	22	31	
< 0.35 kU/L	212 (75.4%)	226 (79.9%)	438 (77.7%)		183 (64.2%)	180 (65.5%)	363 (64.8%)		158 (62.0%)	146 (62.4%)	304 (62.2%)	
≥ 0.35 kU/L	69 (24.6%)	57 (20.1%)	126 (22.3%)		102 (35.8%)	95 (34.5%)	197 (35.2%)		97 (38.0%)	88 (37.6%)	185 (37.8%)	
Timothy Grass sIgE				0.580				0.846				0.494
Missing	13	11	24		11	20	31		9	23	32	
< 0.35 kU/L	225 (79.8%)	231 (81.6%)	456 (80.7%)		149 (52.5%)	146 (53.3%)	295 (52.9%)		106 (41.6%)	104 (44.6%)	210 (43.0%)	
≥ 0.35 kU/L	57 (20.2%)	52 (18.4%)	109 (19.3%)		135 (47.5%)	128 (46.7%)	263 (47.1%)		149 (58.4%)	129 (55.4%)	278 (57.0%)	
Birch sIgE				0.685				0.708				0.507
Missing	13	11	24		12	21	33		9	24	33	
< 0.35 kU/L	247 (87.6%)	251 (88.7%)	498 (88.1%)		198 (70.0%)	187 (68.5%)	385 (69.2%)		153 (60.0%)	146 (62.9%)	299 (61.4%)	
≥ 0.35 kU/L	35 (12.4%)	32 (11.3%)	67 (11.9%)		85 (30.0%)	86 (31.5%)	171 (30.8%)		102 (40.0%)	86 (37.1%)	188 (38.6%)	
Mold sIgE				0.734				0.130				0.152
Missing	13	11	24		12	21	33		9	23	32	
< 0.35 kU/L	261 (92.6%)	264 (93.3%)	525 (92.9%)		229 (80.9%)	234 (85.7%)	463 (83.3%)		192 (75.3%)	188 (80.7%)	380 (77.9%)	
≥ 0.35 kU/L	21 (7.4%)	19 (6.7%)	40 (7.1%)		54 (19.1%)	39 (14.3%)	93 (16.7%)		63 (24.7%)	45 (19.3%)	108 (22.1%)	

Note: P-values are computed using Chi-Squared Tests.

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Table E18. Cumulative Burden of Allergic Disease at 60 and 72 Months of Age in the LEAP and LEAP-On ITT Populations

	60 (mo)				72 (mo)			
	Avoiders (N=321)	Consumers (N=319)	Total (N=640)	p value	Avoiders (N=282)	Consumers (N=274)	Total (N=556)	p value
Eczema				0.545				0.687
Missing	5	7	12		4	5	9	
No	187 (59.2%)	192 (61.5%)	379 (60.4%)		170 (61.2%)	169 (62.8%)	339 (62.0%)	
Yes	129 (40.8%)	120 (38.5%)	249 (39.6%)		108 (38.8%)	100 (37.2%)	208 (38.0%)	
Rhinoconjunctivitis				0.574				0.376
Missing	6	6	12		4	6	10	
No	161 (51.1%)	167 (53.4%)	328 (52.2%)		112 (40.3%)	118 (44.0%)	230 (42.1%)	
Yes	154 (48.9%)	146 (46.6%)	300 (47.8%)		166 (59.7%)	150 (56.0%)	316 (57.9%)	
Asthma				0.642				0.383
Missing	5	5	10		4	5	9	
No	266 (84.2%)	260 (82.8%)	526 (83.5%)		229 (82.4%)	229 (85.1%)	458 (83.7%)	
Yes	50 (15.8%)	54 (17.2%)	104 (16.5%)		49 (17.6%)	40 (14.9%)	89 (16.3%)	
Any Suspected Food Allergy?				0.639				0.222
Missing	5	6	11		4	8	12	
No	185 (58.5%)	189 (60.4%)	374 (59.5%)		156 (56.1%)	163 (61.3%)	319 (58.6%)	
Yes	131 (41.5%)	124 (39.6%)	255 (40.5%)		122 (43.9%)	103 (38.7%)	225 (41.4%)	
Number of Allergic Diseases				0.551				0.147
Missing	5	5	10		4	5	9	
0	76 (24.1%)	78 (24.8%)	154 (24.4%)		58 (20.9%)	61 (22.7%)	119 (21.8%)	
1	93 (29.4%)	101 (32.2%)	194 (30.8%)		72 (25.9%)	84 (31.2%)	156 (28.5%)	
2	84 (26.6%)	78 (24.8%)	162 (25.7%)		83 (29.9%)	73 (27.1%)	156 (28.5%)	
3	49 (15.5%)	41 (13.1%)	90 (14.3%)		53 (19.1%)	41 (15.2%)	94 (17.2%)	
4	14 (4.4%)	16 (5.1%)	30 (4.8%)		12 (4.3%)	10 (3.7%)	22 (4.0%)	

Note: 'Any Likely Food Allergy' combines Peanut, Raw Hen's Egg, Cow's Milk, Sesame, Brazil Nut, Hazel Nut, Cashew, Walnut, and Almond Skin Prick Tests. A subject is considered to have 'Any Likely Food Allergy' if any of the SPT results is ≥ 5 mm. Rhinoconjunctivitis combines Seasonal and Perennial Rhinoconjunctivitis. Eczema is defined as SCORAD > 0. 'Number of Allergic Diseases' combines Eczema, Rhinoconjunctivitis, Asthma, and Any Likely Food Allergy (which counts as 1 Allergic Disease no matter how many SPTs ≥ 5mm). P-Values for Eczema, Rhinoconjunctivitis, Asthma, and Any Likely Food Allergy are based on Chi-Squared Tests. P-Values for Number of Allergic Diseases are based on Armitage Trend Tests.

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Table E19. Multivariate Logistic Regresison Model for Peanut and Egg Allergy Associations with Development of Allergic Diseases in the LEAP and LEAP-On ITT Populations

Allergic Disease at 60 Months Covariate	60 (mo) Odds Ratio	95% Confidence Interval	p-value	Allergic Disease at 72 Months Covariate	72 (mo) Odds Ratio	95% Confidence Interval	p-value
Asthma				Asthma			
Peanut Allergy at 60 Months	3.681	{2.089, 6.485}	<0.001	Peanut Allergy at 72 Months	3.429	{1.913, 6.144}	<0.001
Baseline Egg Allergy	1.046	{0.661, 1.656}	0.848	Baseline Egg Allergy	1.025	{0.621, 1.692}	0.923
Baseline SCORAD	1.009	{0.998, 1.021}	0.104	Baseline SCORAD	1.008	{0.995, 1.020}	0.221
Seasonal Rhinoconjunctivitis				Seasonal Rhinoconjunctivitis			
Peanut Allergy Allergy at 60 Months	3.593	{2.061, 6.265}	<0.001	Peanut Allergy at 72 Months	3.284	{1.814, 5.943}	<0.001
Baseline Egg Allergy	1.548	{1.074, 2.231}	0.019	Baseline Egg Allergy	1.858	{1.277, 2.701}	0.001
Baseline SCORAD	1.016	{1.007, 1.025}	0.0007	Baseline SCORAD	1.013	{1.004, 1.023}	0.005
Perennial Rhinoconjunctivitis				Perennial Rhinoconjunctivitis			
Peanut Allergy Allergy at 60 Months	3.457	{1.932, 6.187}	<0.001	Peanut Allergy at 72 Months	3.390	{1.808, 6.355}	<0.001
Baseline Egg Allergy	1.434	{1.013, 2.031}	0.042	Baseline Egg Allergy	1.683	{1.165, 2.432}	0.006
Baseline SCORAD	1.019	{1.010, 1.028}	<0.001	Baseline SCORAD	1.015	{1.006, 1.025}	0.002

Note: P-values are computed from a Multivariate Logistic Regression model including covariates for peanut allergy, baseline egg allergy and baseline SCORAD.

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4. REFERENCES

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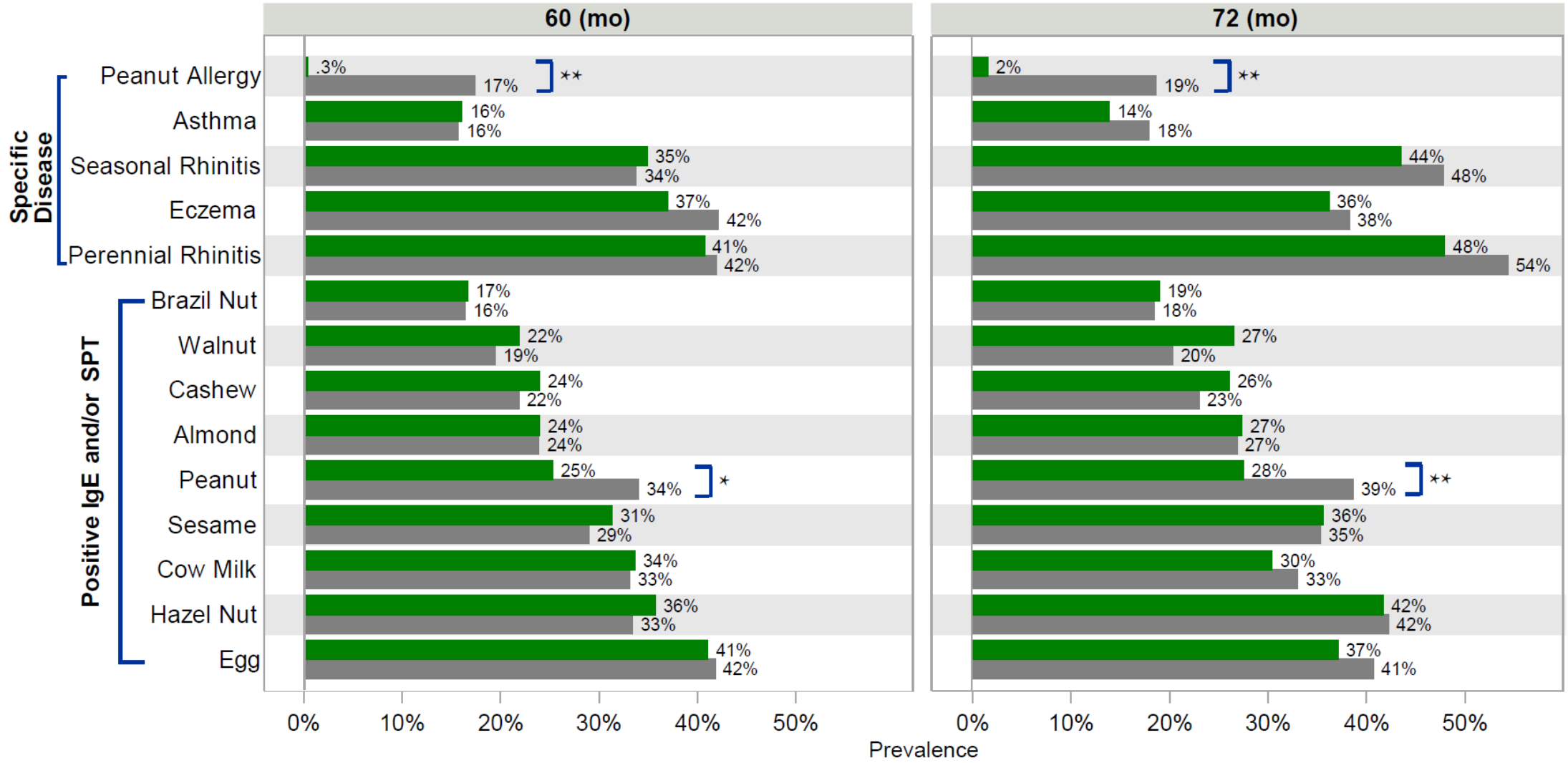
Figure E1. Overall Disease Burden Prevalence in the LEAP Per Protocol Population



Data is presented for participants who met the LEAP per protocol definition. Grey bars represent LEAP avoiders. Green bars represent LEAP consumers. The '*' represent a p-value ≤0.05 resulting from a comparison between the LEAP avoidance and LEAP consumption groups using a chi-squared test. The '**' represents a p-value ≤0.01 resulting from a comparison between the LEAP avoidance and LEAP consumption groups using a chi-squared test.