Defining the window of opportunity and the target populations to prevent peanut allergy

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PII: S0091-6749(22)01656-6

DOI: https://doi.org/10.1016/j.jaci.2022.09.042

Reference: YMAI 15784

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

Received Date: 23 March 2022

Revised Date: 12 September 2022

Accepted Date: 21 September 2022

Please cite this article as: Roberts G, Bahnson HT, Du Toit G, O'Rourke C, Sever ML, Brittain E, Plaut M, Lack G, Defining the window of opportunity and the target populations to prevent peanut allergy, *Journal of Allergy and Clinical Immunology* (2023), doi: https://doi.org/10.1016/j.jaci.2022.09.042.

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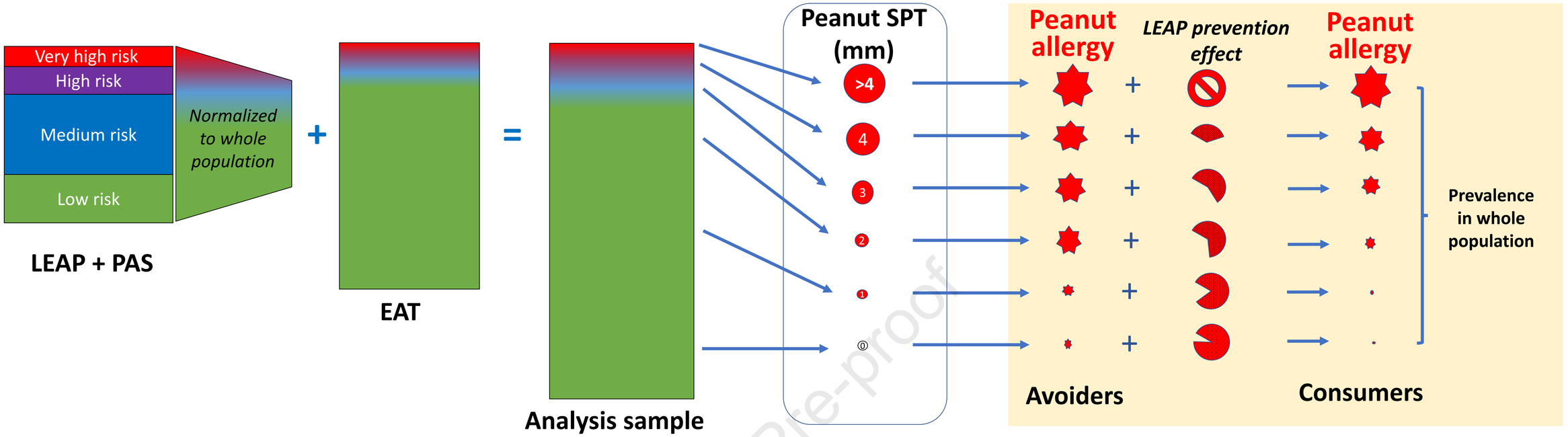

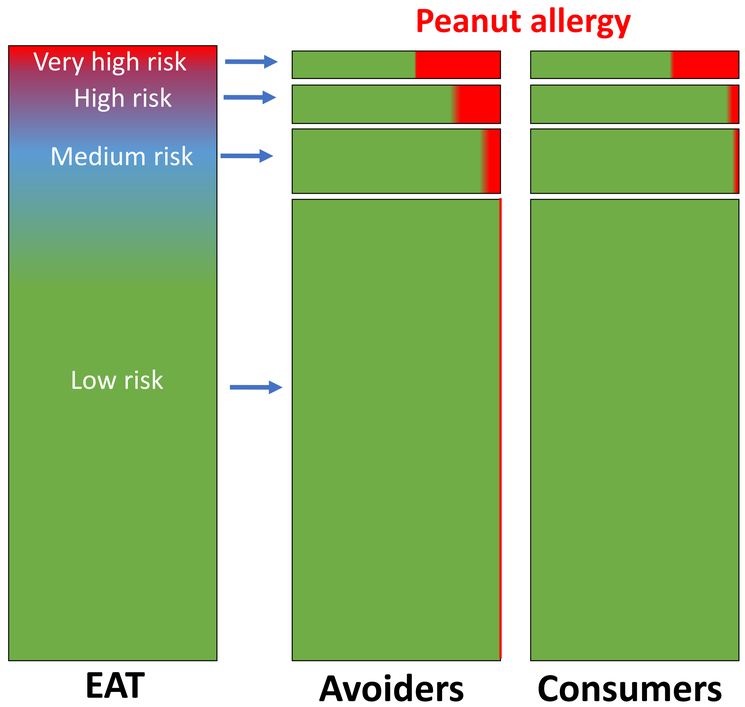

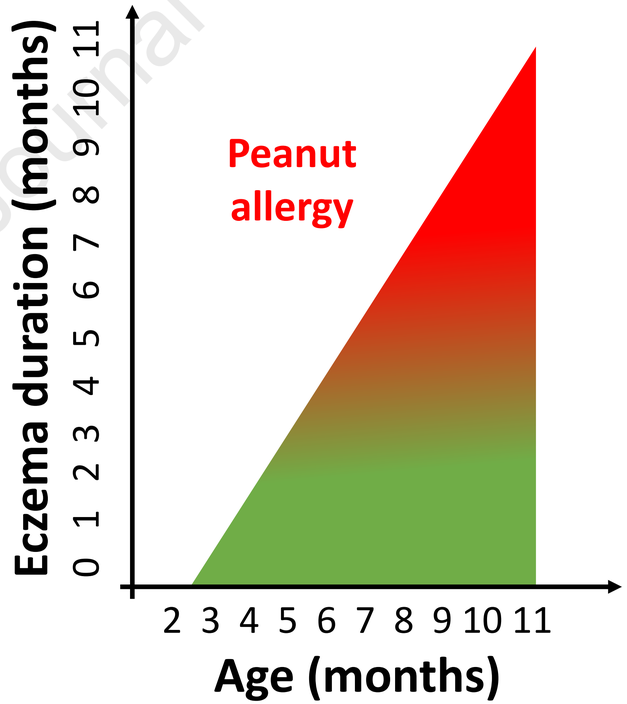

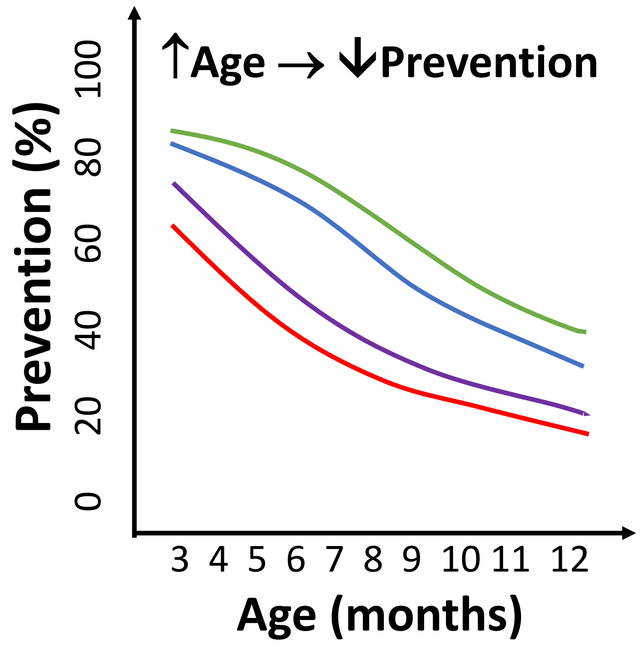

EAT: Enquiring About Tolerance trial; LEAP: Learning Early About Peanut allergy trial; SPT: skin prick test

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Word count: 3400

Short title: Preventing peanut allergy in the whole population

Clinical Implications

To maximise the prevention of peanut allergy in the population, all infants should start eating peanut products by 6 months of life; infants with eczema, especially severe eczema, should start from 4 months of age.

Capsule summary

The prevention of peanut allergy in the general population is best achieved by early introduction of peanut in all infants at 4-6 months of age.

Key words: peanut allergy, prevention, diet, early introduction, population

Abbreviations

EAACI European Academy of Allergy and Clinical Immunology
EAT Enquiring About Tolerance trial
LEAP Learning Early About Peanut allergy trial
NIAID National Institute of Allergy and Infectious Diseases
PAS Peanut Allergy Sensitization study
SPT skin prick test

Abstract

Background

Peanut allergy affects 1-2% of European children. Early introduction of peanut into the diet reduces allergy in high-risk infants.

Objective

We aimed to determine the optimal target populations and timing of introduction of peanut products to prevent peanut allergy in the general population.

Methods

Data from the EAT (n=1303; normal-risk; 3-year follow-up; ISRCTN14254740) and LEAP (n=640; high-risk; 5-year follow-up; NCT00329784) randomized controlled trials plus the PAS (n=194; low- and very high-risk; 5-year follow-up) observational study were used to model the intervention in a general population. Peanut allergy was defined by blinded peanut challenge or diagnostic skin prick test result.

Results

Targeting only the highest risk infants with severe eczema reduced the population disease burden by only 4.6%. Greatest reductions in peanut allergy were seen when the intervention was targeted only to the larger but lower risk groups. A 77% reduction in peanut allergy was estimated when peanuts were introduced to the diet of all infants, at 4 months with eczema and 6 months without eczema. The estimated reduction in peanut allergy diminished with every month of delayed introduction. If introduction was delayed to 12 months, peanut allergy was only reduced by 33%.

Conclusion

The preventive benefit of early introduction of peanut products into the diet decreases as age of introduction increases. In countries where peanut allergy is a public health concern, healthcare professionals should help parents to introduce peanut products into their infants' diet at 4-6 months of life.

BACKGROUND

Peanut allergy represents an important health burden affecting 1-2% of North American and European children[1,2] with considerable impact on quality of life.[3-6] The Learning Early About Peanut allergy (LEAP) trial demonstrated that early introduction of peanuts in a high-risk population of infants can reduce their risk of peanut allergy at age 5 years by 81%.[7,8] However, it should be noted that 76 of 834 infants in the LEAP screening study could not be enrolled because they had a skin prick test (SPT) >4mm and therefore had likely already developed peanut allergy.[9]

The 2017 National Institute of Allergy and Infectious Diseases (NIAID) sponsored prevention guideline advocated introducing peanuts into the infant diet at 4-6 months for those with severe eczema or egg allergy, around 6 months for those with mild-to-moderate eczema and at an age appropriate time in accordance with family preferences and cultural practices for other infants.[10] However, these recommendations were based on expert opinion, extrapolating from a high risk population.[11] More recently, the 2021 European Academy of Allergy and Clinical Immunology (EAACI) prevention guideline suggest introducing peanuts into the infant diet at 4-6 month in populations where there is a high prevalence of peanut allergy.[12] The EAACI guideline also highlighted that understanding the effectiveness of the early introduction of peanut products across the whole population is a high priority gap in our evidence base. Moreover, it should be noted that since the change in Australian guidelines in 2016, consumption of peanut during the first year of life increased from 28.4% before the guidelines (2007-2011) to 88.6% after the implementation of the guidelines (2016-2018).[13] Despite this change, a recent publication shows no decline in the observed prevalence of peanut allergy in Australia in 2020, which remained stable at 3.1%.[14]

This paper details an analysis that aimed to assess the impact of the early introduction of peanut into the infant diet on the prevention of peanut allergy across the whole population and may partially explain why the rate of peanut allergy in Australia has not decreased. Firstly, we assessed which readily identifiable factors were associated with developing peanut allergy in the first year of life. Different risk profiles may limit the effectiveness of the intervention by narrowing the window of opportunity in which peanut allergy can be prevented.[8] Secondly, we modeled the relative reduction in peanut allergy that is likely to occur at 5 years of life depending on when peanut is introduced into the diet in the whole population.[15] We assume that the prevalence of peanut allergy in the EAT trial at age 3 years is a predictive surrogate of peanut allergy at 5 years. This modeled approach provides an assessment

of the intervention's effectiveness across a whole population and across different risk strata according to the month of life that peanut is introduced into an infant's diet.

METHODS

Study design

This study utilized published data from the LEAP screening study,[9] published and unpublished data from the LEAP randomized controlled prevention trial,[7] unpublished data from the PAS (Peanut Allergy Sensitization) observation study and published data from the EAT (Enquiring About Tolerance) randomized controlled prevention trial **(Figure E1**).[16] Together the four studies covered the breadth of the risk factors for peanut allergy seen across a normal population. EAT provides information about low-risk individuals while the LEAP screening study, LEAP RCT and PAS provides information about high and very high-risk individuals. The analysis makes use of individual participant level data, and combining the datasets allows for many cases of peanut allergy to be modeled across the different cohorts and risk levels. The approach taken made several clearly identified assumptions, which are described and justified in **Table E1**.

Participants and interventions (see supplementary Methods sections 1B-1E)

LEAP screening study

The LEAP screening study was the recruitment phase of the LEAP trial.[7] Full details have been published.[9] Briefly, recruitment targeted infants between 4-11 months of age with severe eczema, egg allergy or both. Participants were separated into 4 groups: group I (low-risk PAS study) had mild or no eczema and no egg allergy (exclusion criteria for LEAP); group II (LEAP negative stratum) had severe eczema and/or egg allergy but no reaction on SPT to peanut; group III (LEAP positive stratum), had severe eczema and/or egg allergy and a 1-4 mm peanut wheal; group IV (high-risk PAS study) had severe eczema and/or egg allergy and peanut wheal responses of >4 mm (exclusion criteria for LEAP), which we will refer to as "likely allergy" (**Table E2**).

LEAP prevention trial

The LEAP trial randomized 640 infants, aged 4-11 months with severe eczema, egg allergy or both to early peanut introduction or avoidance during early life. These participants encompassed the LEAP Screening Study Groups II and III; each of these two cohorts were independently powered, randomized, and analysed.[7] The LEAP trial determined that peanut allergy was prevented in the early introduction group within both cohorts (**Table E2**).[7,17]

PAS study

The PAS study comprised two subgroups of participants who were not eligible for inclusion in the LEAP trial (**Table E2**).[9] LEAP Screening Group I was considered too low risk to be enrolled, and LEAP Screening Group IV was considered likely already allergic based on SPT wheal sizes >4mm. These participants did not receive the LEAP intervention; however, they were followed-up at 60 months of age and assessed for clinical allergy using the same LEAP trial protocol.[7]

EAT trial

The published EAT trial evaluated whether the early introduction of six allergenic foods into the diet of breast-fed infants would protect against the development of food allergy.[16] Briefly, the EAT trial recruited, from the whole UK population, 1303 exclusively breast-fed infants (aged 3 months) (**Table E2**). Participants were randomized to the early introduction of six allergenic foods (peanut, cooked egg, cow's milk, sesame, whitefish, and wheat; early introduction group) or to exclusive breast-feeding to 6 months of age (standard introduction group). The primary outcome was food allergy to one or more of the six foods at 1-3 years of age.

Assessing factors associated with the development of peanut allergy during the first year of life (see supplementary Methods section 1F)

In order to stratify the risk of peanut allergy during the first year of life and target populations for early prevention strategies, we selected key risk factors predictive of peanut allergy which could be readily screened for during a public health intervention. These key risk factors were ethnicity, eczema severity, duration of eczema, and age. Baseline peanut allergy was defined by oral food challenge (LEAP and EAT, early introduction groups) or peanut skin prick test wheal >4mm at the baseline or 1 year visit (other groups) (**Table E1**).[18,19,20,21]

Estimating the impact of early introduction of peanuts to the whole population and different risk groups

Potential impact of applying the LEAP intervention to EAT, a normal risk population

To assess the impact of the early introduction of peanuts into the infant diet in a normal risk population with good adherence to the intervention, the prevalence of peanut allergy at 36 months in the early introduction group was

156 estimated by applying the relative reduction of peanut allergy observed with the LEAP intervention in <15, 15-40
157 and >40 SCORAD (SCORing Atopic Dermatitis) bands in the LEAP trial.

158 Estimating the impact of early peanut introduction at different ages to the whole population

159 *Modeling the whole population using combined EAT, LEAP and PAS study data*

160 To model the whole population, LEAP and PAS participants were weighted such that the overall distribution of
161 eczema severity, egg allergy, and non-white ethnicity would match the normal EAT population using propensity
162 scores (see **supplementary Methods 1G** and **Figure E2**). These weights were applied in an ordinal logistic
163 regression model of SPT wheal size category at each month of age with peanut avoidance (**Figure E3)**.

164 *Estimation of the prevalence of allergy at 5 years with peanut avoidance or early introduction*

165 A logistic regression model was used to estimate the prevalence of allergy at 5 years of life depending on peanut
166 SPT size and age in the first year of life with peanut avoidance (**Figure E3**). The LEAP intention to treat
167 intervention effect was estimated using logistic regression (see **supplementary Methods section 1F**), where this
168 effect represents the reduction in allergy if introducing peanut conditional on each SPT size during the first year of
169 life versus avoiding peanut until age 5 (**Figure E4**).

170 *Estimating the optimal timing of introduction of peanut into the diet to prevent peanut allergy*

171 The LEAP intervention effect was applied, stratified by age and peanut SPT size, to determine the prevalence of
172 allergy at 5 years of age, under both strategies using different approaches (see **supplementary Methods section 1G**)
173 to estimate the relative reduction of peanut allergy by age of intervention.

174 Analyses were performed using R version 4.0.2 (Vienna, Austria), JMP Pro 15, and SAS 9.4 (Cary, NC).

175

176

RESULTS

The EAT, LEAP and PAS study participants are described in **Figure E5**. Together they covered the entire range of eczema severity (**Figure E6)**.

Impact of early introduction is not as effective among all participants screened in LEAP as many already had peanut allergy

Early introduction of peanuts in the LEAP study resulted in an 81% reduction in peanut allergy at 60 months of age in the intention-to-treat analysis (**Table 1**).[7] Many participants were excluded from LEAP as they had likely peanut allergy by 4-11 months of age when the intervention was applied.[18, 19] If all participants in the LEAP screening study had received the intervention, the overall reduction would have been 52% (**Table 1**).

Baseline factors associated with peanut allergy during infancy

Increasing age or duration and severity of eczema are related to likelihood of peanut allergy in first year of life.

In the LEAP screening study, the likelihood of peanut allergy at the baseline assessment increased with increasing age and severity of eczema (**Figure 1A**). There was a similar relationship between peanut allergy and increasing duration of eczema (**Figure 1B**) with duration being the more important risk factor (**Figure E7**).

Diameter of SPT wheal increases with age during infancy and most who develop peanut allergy by 5 years have allergy by 12 months

Data from the high-risk LEAP screening and normal-risk EAT studies showed that participants who were older at screening were more likely to present with higher SPT wheal to peanut (**Figure E8**) with none sensitized below 5 months of age. Looking longitudinally at avoidance participants, the SPT wheal diameter of those who ultimately developed peanut allergy increased rapidly during the first year of life (**Figure 2**) with most allergic at 12 months (peanut SPT >4mm, highly predictive of allergy[18-21]) (see **Table E1**).

Non-white ethnicity is associated with greater development of peanut allergy during first year of life

Combining the EAT and LEAP cohorts, non-white (including mixed) infants were estimated to have a higher likelihood of peanut allergy compared to white infants (relative risk=2.22, 95% confidence interval 1.45 to 3.33, p<0.001) (see **supplementary Methods section 2B**, **Figure E9**).

Estimating the impact of early introduction of peanut to the whole population and different risk groups

Potential impact of applying the LEAP intervention to EAT, a normal risk population

The adherence to early introduction of peanut in the infant diet was poor in the normal population EAT study. If adherence was similar to that seen in the LEAP study, peanut allergy prevalence would have reduced from 2.5% to 0.29% (**Table 2**). If the LEAP intervention were targeted exclusively at infants with severe eczema (SCORAD >40) at greatest risk, the total population burden of peanut allergy would be reduced by <5% (**Table 2**). Targeting the larger number of children with mild eczema (30% reduction) or no eczema (29% reduction) has much greater impact (**Table 2**).

Estimating the impact of early introduction of peanuts at different ages to the whole population

The estimation of treatment effect by timing in the whole population depends on a number of assumptions, so a few simpler estimates were also assessed to ensure the robustness of our whole population model.

We firstly estimated the effect of early introduction by age at first introduction for the observed results from EAT (ITT and PP effect) and the combined LEAP+PAS dataset (ITT effect) where no or minimal assumptions are required (**Figure 3A**). The impact is seen to decrease with increasing age of introduction. Secondly, the impact on the normal risk EAT population at 3 and 12 months was modelled using the LEAP effect size (**Table E1**) showing similar results (**Figure 3B**).

Then, we replicated the estimation of the impact of introducing peanut into the infant diet at different ages using our whole population model **(Figure 3B)**. Full details including assumptions are covered in **Table E1** and online results section 2D. The bootstrapped confidence intervals indicate a decreasing relative reduction of peanut allergy with increasing age of introduction to peanuts. The negative impact of delaying the introduction of peanuts into the diet was most apparent in infants with increasing severity of eczema; (**Figure 3C and Figure E12B**) and/or non-white ethnicity (**Figures E12C and D**).

We calculated the combined effect of intervening at different ages in infants with and without eczema on the peanut allergy burden in the total population. We chose three different illustrative scenarios: (i) introduction of peanuts to infants with and without eczema at 4 months resulted in an 82% relative reduction in peanut allergy; (ii) introduction in infants with eczema at 4 months and without eczema at 6 months, resulted in a 77% risk reduction, and (iii) introduction in infants with eczema at 4 months and at 12 months in infants with no history of eczema, resulted in a 58% relative risk reduction (**Table E3**) relative to peanut avoidance.

DISCUSSION

The LEAP trial findings have resulted in a fundamental shift in our approach to peanut allergy prevention.[22] They have now been replicated in both the UK EAT and Scandinavian PreventADALL randomized controlled trials[16,23]. We sought to evaluate the impact of timing the introduction of peanut products into different risk groups during infancy in a general population to reduce the burden of peanut allergy. In both the LEAP screening cohort and EAT trial we found that the majority of peanut allergy had already developed by the first year of life (**Figure 2**) especially among those with severe eczema, egg allergy and non-white ethnicity (**Figures 1-3, Figure E15**). Confining the intervention to the highest risk infants has a minimal impact on the overall population burden; the greatest benefit was achieved when the whole population is targeted, as the majority of peanut allergy occurs in the large lower risk groups (**Table 2**). The impact of the early introduction of peanut products was most effective when applied as early as possible. This reflects the experience in the Israel culture where peanut products are commonly introduced early into the infant diet and peanut allergy is very rare.[24]

Our analysis demonstrating the need to intervene at the whole population level agrees with previous publications extrapolating data from the LEAP trial. O'Connor *et al* estimated that if the intervention was applied only to Irish infants with severe eczema and egg allergy, the population burden of peanut allergy would only have been reduced by 29%.[25] Similarly, Koplin *et al* in an Australian cohort estimated that targeting the intervention to infants with severe eczema and/or egg allergy would have reduced the population disease burden by only 6%,[18] which is very similar to our estimate (**Table 2**). Applying simple, low cost and safe interventions to the whole population is a more effective preventive public health strategy than targeting selected groups.[26] Lastly there is the theoretical consequence that introducing peanuts exclusively to high risk infants may result in a greater environmental peanut exposure of lower risk infants who are not consuming peanuts. This could result in a higher rate of peanut allergy in this lower risk group who are not protected by early peanut consumption, as predicted by the dual allergen exposure hypothesis.[27]

Over several decades, the deliberate avoidance of peanut has understandably led to parental fear of early introduction. Applying early introduction of peanut to a whole population requires considerable education of healthcare professionals and families with detailed advice on weaning strategies and being able to address their concerns. The safety of early introduction of peanut products has been observed in LEAP and EAT[16,28]. We need to be aware of

unintended consequences[29] such as the possibility of parents giving infants whole nuts leading to a risk of nut inhalation. It is critical that education stresses the need to introduce peanut products, such as a butter or puffs, and not as a whole nut.

We have shown that in both a high risk and normal population, the majority of peanut allergy has already developed in the first year of life (**Figure 2**). This aligns with the Australian HealthNuts cohort where 3.1% of infants had challenge-proven peanut allergy at 1 year of age.[2,30] The 3.1% is similar to the overall peanut allergy rate expected in the Australian population. A recent US publication also confirms that a high rate of challenge proven peanut allergy is seen in the first year of life (18% in infants with moderate to severe eczema which is similar to that seen in LEAP).[31] Additionally infants under 6 months of age had a much lower likelihood of having peanut allergy compared to those over 6 months, even with severe eczema. In their series of 321 infants aged 4-11 months whose parents responded to publicity about the study, twice as many as in the LEAP screening study would have defined as already having peanut allergy by the LEAP study criteria.[9] This highlights the necessity for early intervention. While our results may not be exactly applicable to all populations, it is reassuring from the PreventADALL study that early introduction of peanut products was able to significantly prevent peanut allergy in a randomized controlled trial in Sweden and Norway.[23] The easily identifiable factors in early infancy that are associated with early development of peanut allergy are severity and duration of eczema plus non-white ethnicity which could be used to identify high risk infants (**Figures 1, and Figures E8, E12C and E12D**). The important question as to whether age of introduction of peanuts into the diet affects the efficacy has been previously raised.[32] Our analysis of only the LEAP RCT cohorts found that the intervention was equally effective in younger and older infants.[33] However, when the entire LEAP screening study cohort is assessed, increasing age of introduction reduces the efficacy (**Figure 3A**). This is because some of the infants developed peanut allergy early in infancy before the intervention could have commenced and so were excluded from LEAP RCT (**Figures 2 and 3**). Also, the intervention itself was less effective in children with increasing wheal diameters to peanut (**Figure E4**) and we observed that wheal size increased with age (**Figures 2, 3 and E10**).

Our modelled approach, consistent with the raw data, points to the need for early intervention by six months of age for the whole population, with even earlier intervention from four months of age in those with eczema (**Figure 3C**). This reflects the relatively narrow window of opportunity to prevent peanut allergy which appears to be most time critical in infants with eczema (especially severe eczema) and in UK non-white infants (**Figure E9)**. A simpler

approach would be to recommend early introduction of peanut products to all children by 6 months of age, but this would fail to prevent the development of allergy in a substantial proportion of infants with eczema (**Figure E12B**).

This analysis provides meaningful insight into the benefits of early introduction of peanut as it uses RCT data including participants with all levels of risk of developing peanut allergy as well as follow up data from participants who failed the LEAP entry criteria. Additionally, this analysis has challenge-proven primary outcomes for most participants and all of the studies had high completion rates (89%). However, this analysis has some limitations. In generating the population model, several assumptions are made which are highlighted and justified (**Table E1**). One important assumption is the LEAP treatment effect for each risk group was used in our modelled approach. However, it should be noted that this treatment effect may be a conservative estimate given the very high per protocol effect sizes in both the LEAP and EAT trials (98% and 100% relative reduction respectively).[7,16] The LEAP and EAT trials differed in how the intervention was applied and the length of follow up so the preventative effect may have been underestimated in EAT due to the potential for some resolution of allergy from 3-5 years of age. In some analyses we have used a SPT >4mm as indicative of allergy given that there are published data suggesting 75% of these infants have peanut allergy.[18-21] These data used the same SPT solutions (ALK Abello) and methodology as the LEAP and EAT cohorts, and our diagnostic assumptions are presented in detail in supplemental **Table E1** and **Figures E1** and **E3**. Another potential criticism is that the EAT participants were all exclusively breastfed until at least 3 months of age, a narrower population than the full UK general risk group. A systematic review has concluded that breastfeeding is not associated with food allergy;[34] additional analysis in the LEAP study did not show a significant effect of breastfeeding on the efficacy of the intervention (**Table E1**).

As acknowledged, our whole population model (Figure 3B) relies on assumptions, and furthermore there are inherent vulnerabilities associated with linking the multiple data sources Therefore, it is reassuring that the much more simply estimated treatment effect by age in the combined LEAP/PAS high-risk analysis (**Figure 3A**) has a similar slope to the modelled general population curve (**Figure 3B**), as did the modelled treatment effect in the EAT study (**Figure 3B**). That said, the LEAP/PAS sensitivity analyses include the possibility of a substantial decrease in benefit between four and five months followed by a relatively smaller decline between 5 and 8 months (see point estimates in **Figure 3A and Figure E13**).

315 We have generated a model for the burden of peanut allergy across a whole UK population. Our estimates show that
316 it is most advantageous to intervene in the whole population. If we were to introduce peanut products in high-risk
317 infants with any eczema at 4 months of age and in all other infants at 6 months of age, we estimate that we could
318 reduce the burden of peanut allergy in the population by 77%. This provides the evidence for the recommendations
319 in the recent North American and European guidelines that suggest the early introduction of peanut products for all
320 infants based on an extrapolation from the previously published evidence from the LEAP and EAT studies.[12,35] We
321 would advocate that public health policies should recommend that peanut products are introduced at 4-6 months of
322 age in countries where peanut is an important allergen. Healthcare professionals supporting families with
323 introducing complementary feeding should encourage introduction at 4 months when eczema is present. Support
324 will be needed to help families to know when their infant is ready for solids and to the most appropriate peanut
325 product. Encouragingly, data now indicates that 88.6% of Australia infants are consuming peanut in the first year of
326 life following changes to their national infant feeding guidelines (2016).[13] While this prevention strategy appears to
327 have practically influenced behavior in a real-world setting, the rate of peanut allergy has disappointedly remained
328 stable at 3.1%.[14,36] Interestingly, the authors of this study report that earlier introduction, especially less than 6
329 months of age compared to after 12 months of age, is significantly associated with a substantially reduced risk of
330 peanut allergy among those of Australian ancestry. Our findings both support and explain these observations while
331 emphasizing the need for earlier introduction to prevent peanut allergy in the general population.

Funding

The LEAP study was supported by grants (NO1-AI-15416, UM1AI109565, HHSN272200800029C, and UM2AI117870) from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health and by Food Allergy Research and Education, the Medical Research Council and Asthma U.K. Centre, and the U.K. Department of Health through a National Institute for Health Research comprehensive Biomedical Research Centre award to Guy's and St. Thomas' NHS Foundation Trust, in partnership with King's College London and King's College Hospital NHS Foundation Trust. The U.K. Food Standards Agency provided additional support for the costs of phlebotomy. The EAT study was Supported by grants from the Food Standards Agency and the Medical Research Council, by the NIHR Biomedical Research Centre and Comprehensive Biomedical Research Centre plus a NIHR Clinician Scientist Award (NIHRCS/01/2008/009) to Professor Flohr. The clinical trials unit is supported in part by the National Peanut Board, Atlanta, USA.

Declarations of interest

The authors (GR, HTB, GDT, COR, MLS, GL) report that their institutions received funding from the above funders for undertaking the LEAP and EAT studies. G Roberts additionally reports being employed by the University of Southampton plus honorary contracts at University Hospital Southampton NHS Foundation Trust and the Isle of Wight Trust; the positions of Editor in Chief of Clinical and Experimental Allergy and President Elect of British Society of Allergy and Clinical Immunology; and authorship of the European Academy of Allergy and Clinical Immunology food allergy and anaphylaxis guidelines. HTB additionally reports consultancy fees from King's College London, DBV Technologies, and MyOR diagnostics. G Lack additionally reports grants from The Davis Foundation during the conduct of the study plus personal fees from DBV Technologies, Mighty Mission Me, Novartis, Sanofi-Genyzme, Regeneron, ALK-Abello and Lurie Children's Hospital outside the submitted work.

Contributions

GR, HTB, GDT, COR, MLS, EB, MP and GL all participated in the conception and design of the study. HTB and COR performed the statistical analysis of the results. All authors had full access to and verified all the data. All authors contributed to the interpretation of the results. GR, HTB, GDT and GL led the writing of the initial drafts of the manuscript on which all authors commented. All authors agreed with the decision to submit.

Acknowledgements

We thank Dr Daniel Rotrosen, Dr Alkis Togias, and Dr Gerald Nepom for their critical insights and helpful comments. 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 LEAP, EAT and PAS studies and Poling Lau and Alyssa Ylescupidez for support in the preparation and editing of this manuscript. Above all, we are indebted to all of the children and their families who generously took part in this study.

Data sharing statement

All data for the analyses presented are available as described in the **supplementary Methods**.

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Figure 1. Relationship between age at baseline, reported duration and severity of eczema on the likelihood of peanut allergy at baseline in the first year of life

Bars represent prevalence of peanut allergy at baseline (raw data), defined by baseline oral food challenge or SPT > 4mm at screening, for participants in the LEAP screening cohort (7 LEAP RCT and 76 PAS group IV participants). Participants aged 4 to 11 months were assessed in the study at baseline and defined as low risk (all Group I subjects, assumed to be tolerant), high risk and high risk-sensitized (Groups II and III from early introduction group, assessed by baseline peanut challenge) and likely allergy (Group IV, assumed to be peanut allergic as peanut wheal >4mm (**Table E1**)). Those randomized to peanut avoidance (Groups II and III) were omitted from figure as they were not assessed for peanut allergy by oral food challenge at baseline. Part A presents proportion with infant peanut allergy by tertile of age at screening (months) and part B by tertile of duration of eczema at screening (months); duration was the more important risk factor (**Figure E7**). The number with baseline peanut allergy is annotated above each bar and the sample size is below each bar.

Figure 2. Trajectory of peanut wheal sizes of avoidance group participants allergic to peanut at the final assessment (n=53, 36 months for EAT; 60 months for LEAP and PAS participants)

Each line represents an allergic participant's SPT values over the course of the study starting with their age in months at baseline. SPT was not collected in the EAT avoidance group at 3 months; therefore, a distribution was imputed based on the EAT early introduction group SPT distribution at baseline. Since 99% of SPT distribution at 3 months in the EAT early introduction group was between 0mm and 1mm, points were jittered within this interval so that lines could be connected between the 3, 12, and 36-month assessments. Participants with a >4mm wheal at screening are identified by red lines (PAS Group IV) and only had SPT data available at the screening visit and the 60 month visit. Orange lines represent EAT and LEAP allergic, avoidance group participants whose wheal sizes were greater than 4mm by their 12 month visit. Black lines represent allergic participants from the avoidance group whose wheal sizes were <4mm by their 12 month visit. Assuming that participants with a SPT >4mm are allergic to peanut,18-21 approximately 60% of participants with peanut allergy at the end of the study were allergic at or before their 12 month visit based on wheal sizes >4mm. PA: peanut allergy.

Figure 3. Relative reduction in burden of peanut allergy in a normalized population by age of introduction for (A) raw data from each study; (B) EAT modeled effect plus whole population model and (C) whole population model by eczema severity

All relative reductions in this figure estimate the treatment effect between early peanut introduction and avoidance. In panel (A) The EAT intention to treat (ITT) and per protocol (PP, restricted to only those

exposed to intervention) point estimates are displayed as red squares and are calculated as relative reductions between the standard introduction and early introduction arms. The blue points and blue smoothed regression line using a spline term for age shows relative reduction estimates from the raw high risk LEAP screening population data, (that is, LEAP+ PAS, with imputed treatment effect among the PAS cohort, where the imputed benefit in PAS group IV was 0%). In panel (B) the red dashed line shows the EAT modeled estimates using the LEAP ITT treatment effect (Figure E4) applied at 3 months and 12 months. The whole population (EAT+LEAP+PAS) modelled ITT effect with bootstrapped 95% confidence intervals is shown in black and gray (see **Figure E14** for sensitivity analyses). In panel (C) the whole population modelled ITT effect is shown by eczema severity. Additional sensitivity analyses and modeling details relevant to these analyses are shown in the supplemental appendix (**Figures E12 and E13, Tables S4, E5, and E6**).

LEAP screening study groups	Sample size	Peanut allergy in avoidance group at 60 months of age	Peanut allergy in early introduction group at 60 months of age	Reduction in each group	Reduction in LEAP trial participants
I (low risk)	118	0.8%*	NA	NA**	
II (high risk)	542	13.7%	1.9%	86.1%	81.0%
III (high risk-sensitised)	98	35.3%	10.6%	70.0%	
IV (likely peanut allergic)	76	81.4%	NA	NA***	
All groups	834	20.4%			

Table 1. Impact of early peanut introduction on allergy in the LEAP screening cohort

The LEAP screening cohort includes two groups (groups II and III), and two other groups, a high risk and a low risk groups that were not included in the randomised controlled trial. Group IV (n=76) were considered already allergic (peanut SPT >4mm). Group I (n=118) had mild eczema and no egg allergy, and were considered too low risk to be entered into the trial. Groups II and III were randomized to early introduction or avoidance of peanuts. All groups were assessed for peanut allergy by the same method at 60 months. *Any participants in Group I not assessed at 60 months was assumed to be not peanut allergic. **Intervention not applied. ***Intervention not applicable as assumed to already be allergic. If Groups I and IV had received the intervention (and if we assume complete benefit in Group I and no benefit in Group IV), the reduction in peanut allergy across the LEAP screening cohort (Groups I-IV) would be 52% ([(0.019*542)+(0.106*98)+(1*76)]/[118+542+98+76]/ [(0.137*542)+(0.353*98)+1.000*76]/[118+542+98+76)]), rather than the 81% seen in the LEAP trial.

Eczema risk groups by SCORAD	Proportion of EAT avoidance group (n)	Peanut allergy at 36 months		Peanut allergy burden (proportion of total allergy in avoidance group by stratum)
		Avoidance group (observed data from EAT)	Early introduction group	
>40	0.5% (3)	33.3%	10.32%	6.64%
15-40	4.9% (29)	13.8%	0.69%	25.58%
1-14	18.5% (110)	4.6%	0.55%	33.61%
0	76.2% (454)	1.1%	0.13%	33.17%
All	100% (596)	2.5%	0.29%	

Table 2. Prevalence and population burden of peanut allergy at 36 months by SCORAD bands and the potential impact of applying the LEAP intervention to EAT, a normal risk population

Observed proportions of peanut allergy in the EAT avoidance group are shown for each eczema risk strata.[16] The prevalence of peanut allergy at 36 months in the early introduction group was estimated by applying the relative reduction of peanut allergy observed with the LEAP intervention for that SCORAD band (**Figure E11**). The burden of peanut allergy explained by each stratum takes into account the size of the risk stratum and the allergy rate within each stratum. If the intervention was applied only to the >40 (severe eczema), 15-40 (moderate eczema), 1-14 (mild eczema) or 0 SCORAD bands, the population burden of peanut allergy would be reduced by 4.55%, 25.43%, 29.65% or 29.20% respectively.

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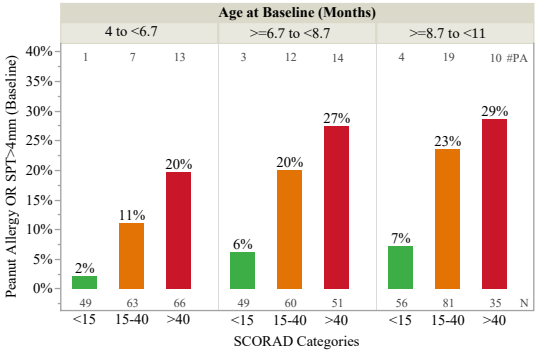

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