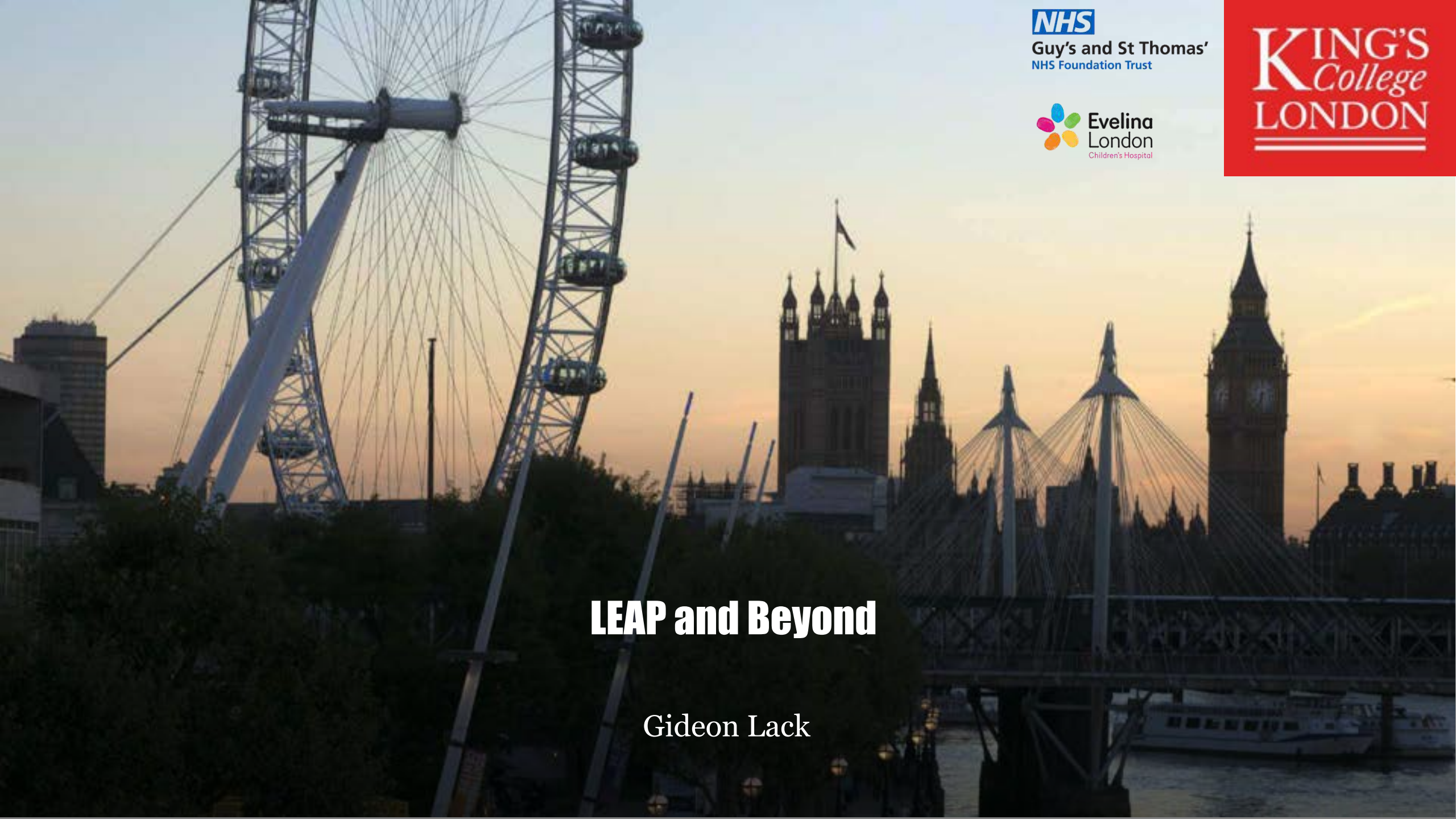


NHS
Guy's and St Thomas'
NHS Foundation Trust

Evelina London
Children's Hospital

King's College London

LEAP and Beyond

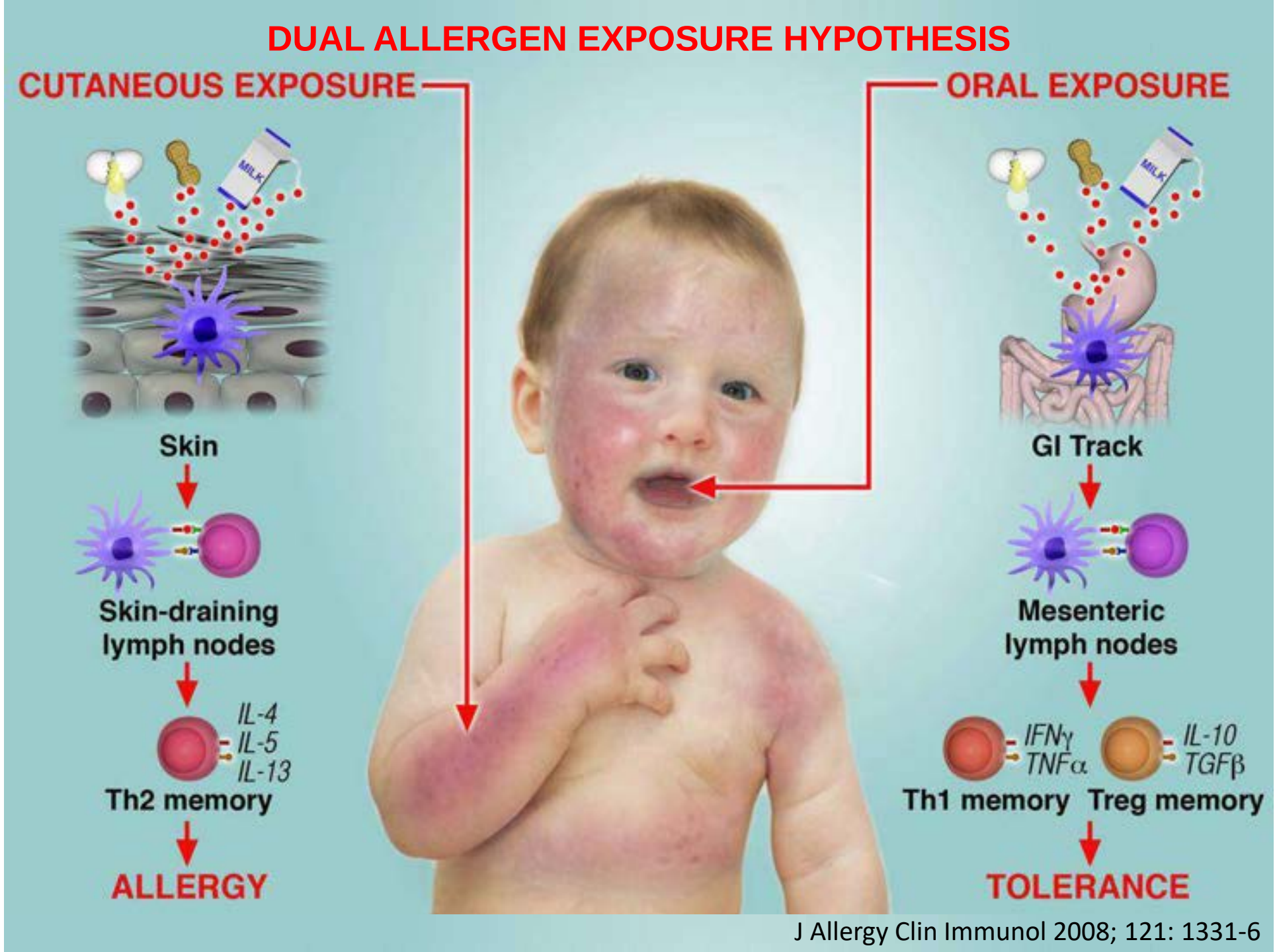
Gideon Lack

Disclosures

- In relation to this presentation I declare that observational studies [but not interventional studies] have benefited from the National Peanut Board Funding [USA]

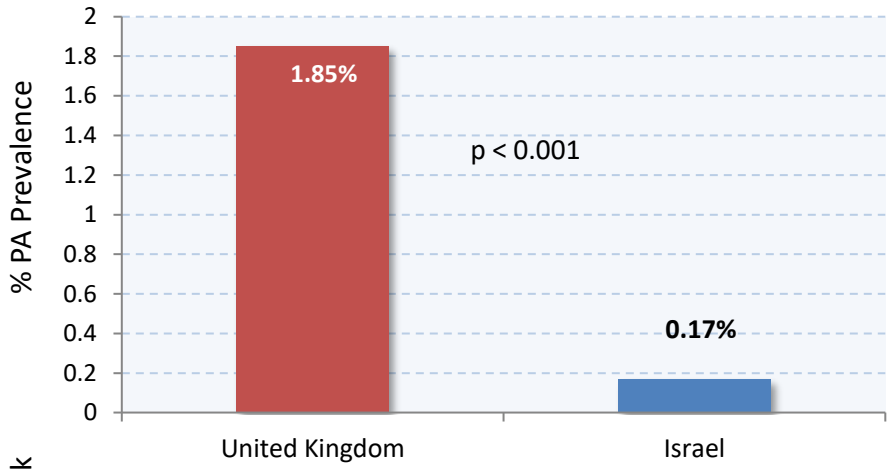
- I am on the Scientific Advisory Board of DBV Technologies and am a shareholder

- I am a shareholder in Mission MightyMe

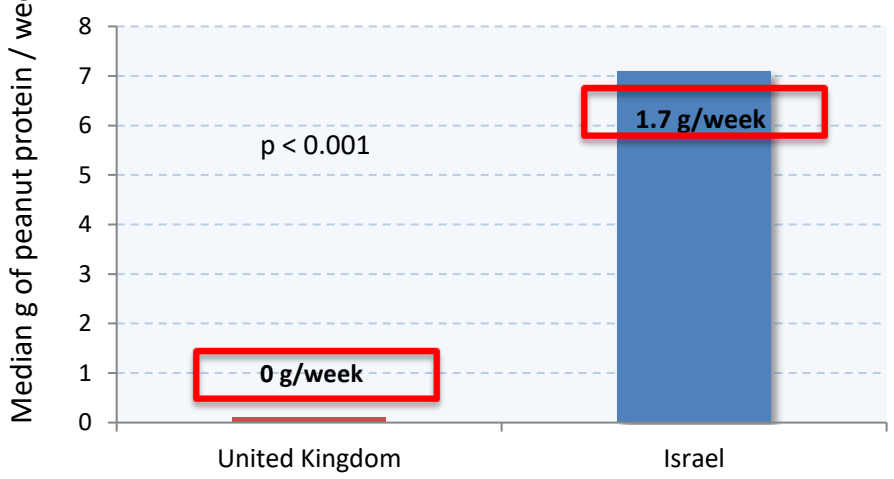


J Allergy Clin Immunol 2008; 121: 1331-6

Early consumption of peanut is associated with a low prevalence of peanut allergy



Prevalence of
Peanut Allergy in
Children 4 – 18 years

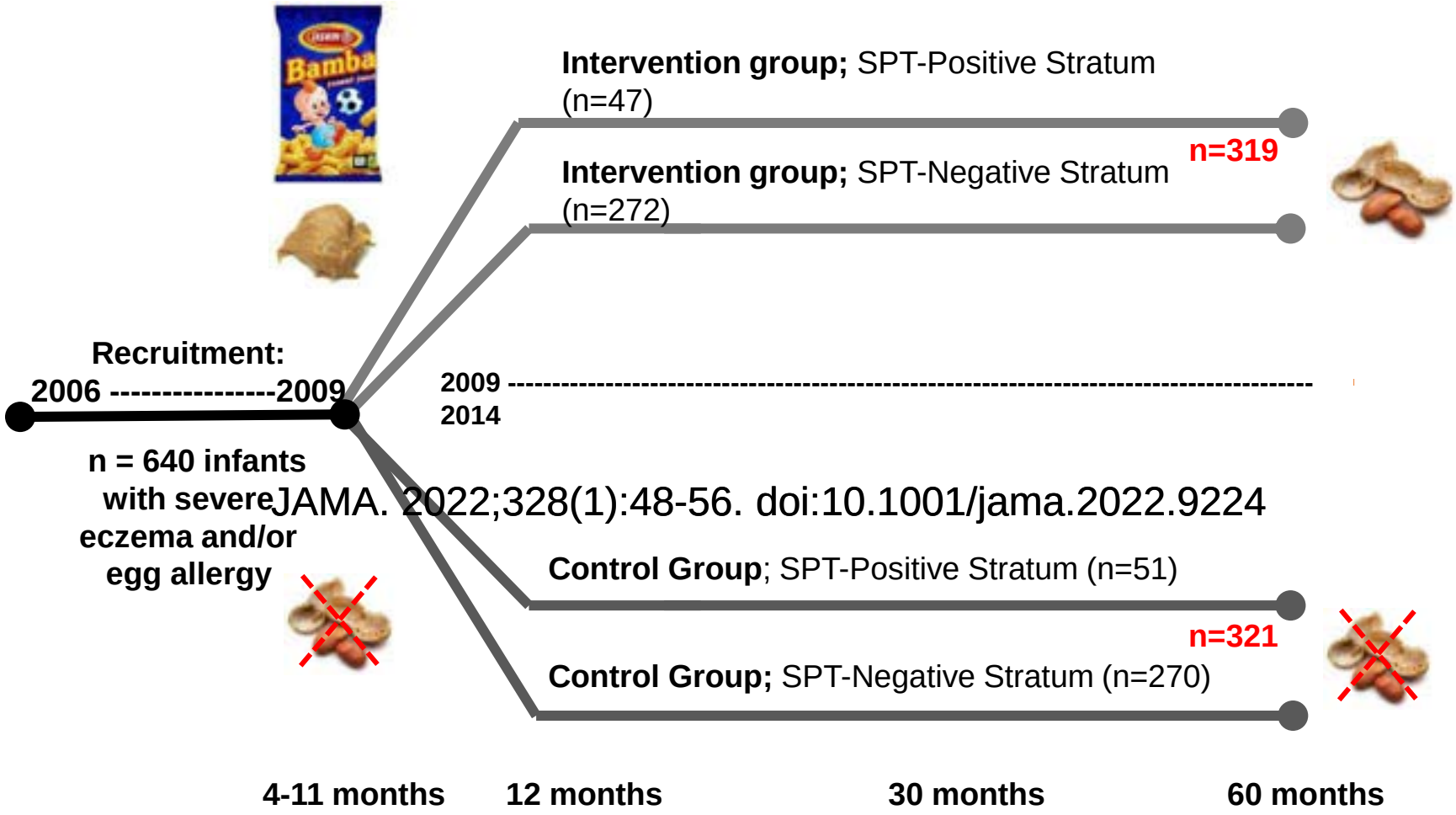


Peanut Protein
Consumption
8 - 14 months

United Kingdom	5171
Israel	5615

Du Toit G, et al. Early Consumption of Peanut in Infancy is Associated with Low Prevalence of Peanut Allergy. JACI 2008; 122: 984-91.

LEAP Study Design



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

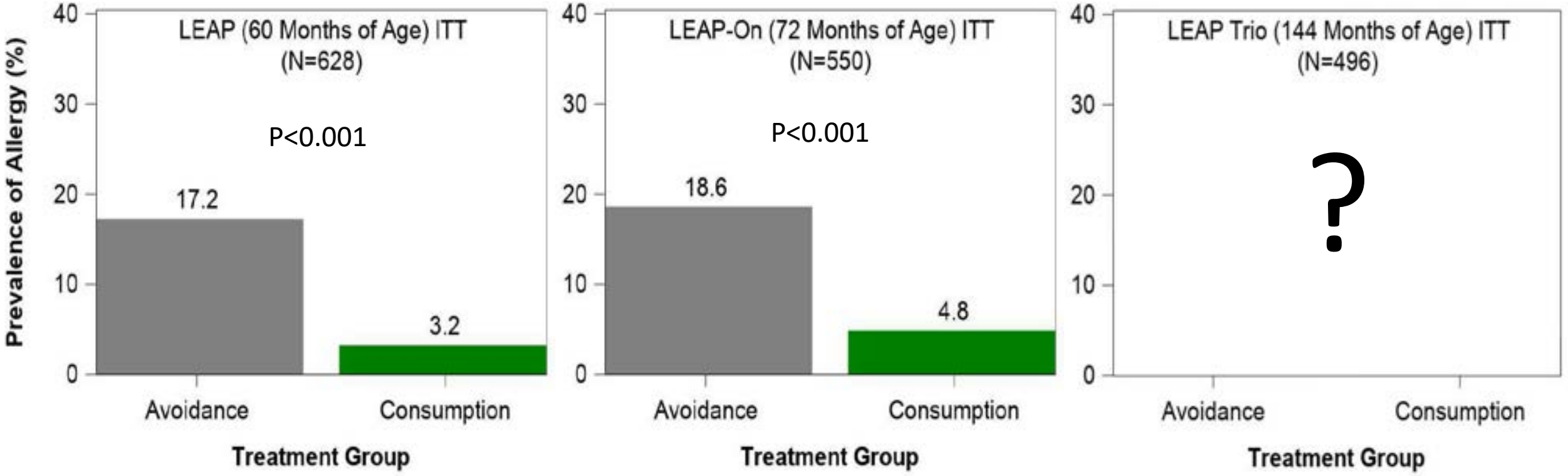
Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

ORIGINAL ARTICLE

Effect of Avoidance on Peanut Allergy after Early Peanut Consumption

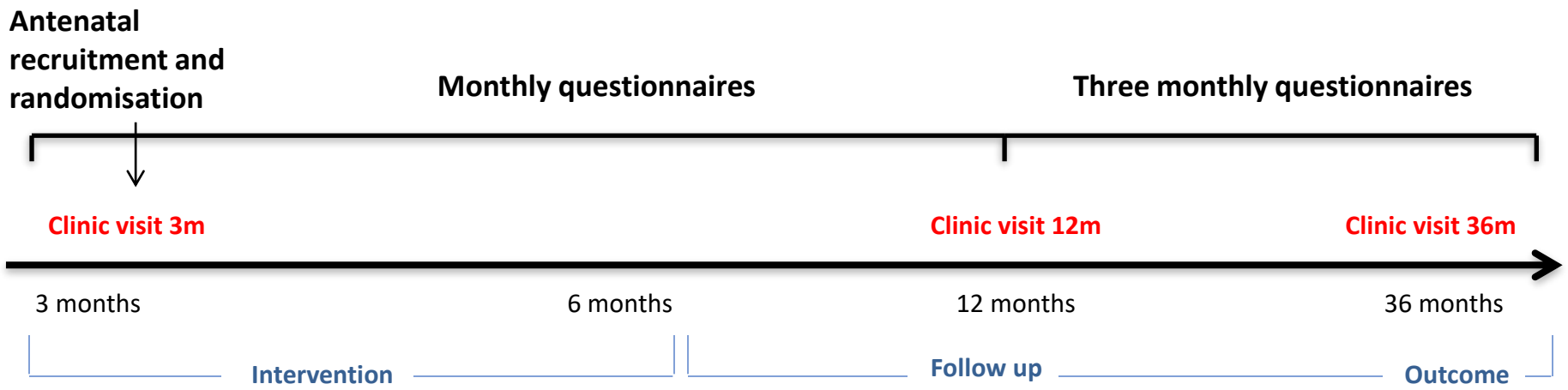
George Du Toit, M.B., B.Ch., Peter H. Sayre, M.D., Ph.D., Graham Roberts, D.M., Michelle L. Sever, M.S.P.H., Ph.D., Kaitie Lawson, M.S., Henry T. Bahnson, M.P.H., Helen A. Brough, M.B., B.S., Ph.D., Alexandra F. Santos, M.D., Ph.D., Kristina M. Harris, Ph.D., Suzana Radulovic, M.D., Monica Basting, M.A., Victor Turcanu, M.D., Ph.D., Marshall Plaut, M.D., and Gideon Lack, M.B., B.Ch., for the Immune Tolerance Network LEAP-On Study Team*

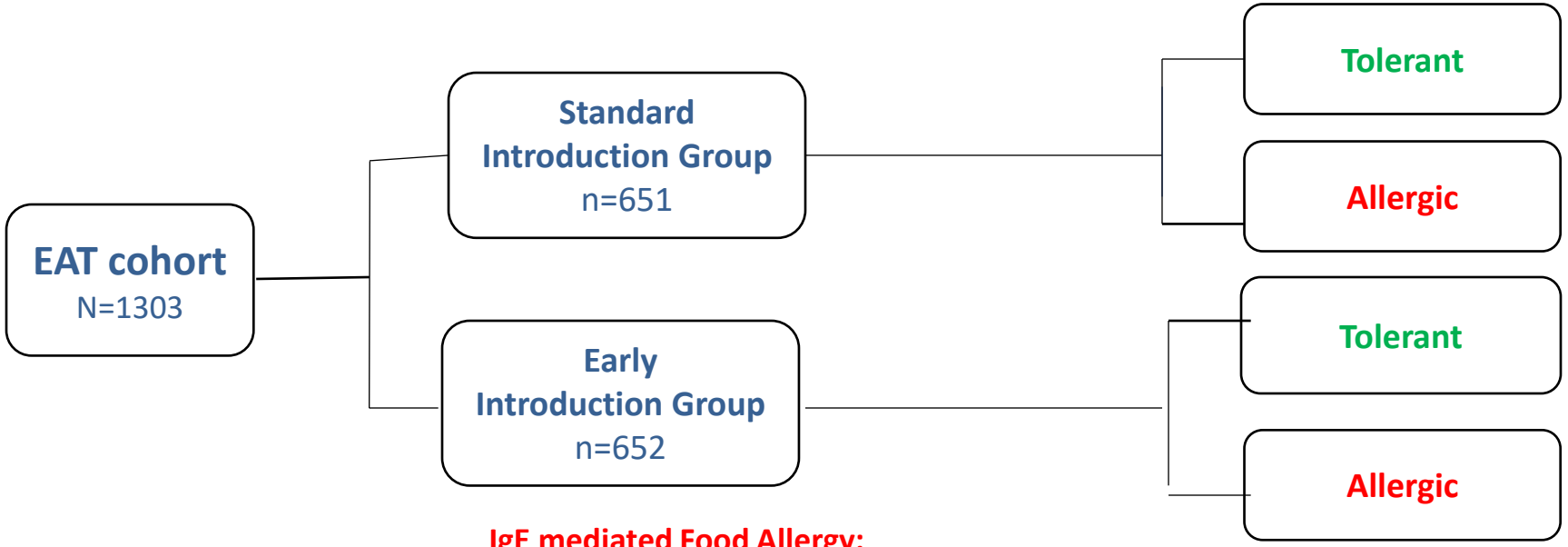
Primary Endpoint LEAP, LEAP-ON, LEAP Trio ITT



Immune Tolerance Network

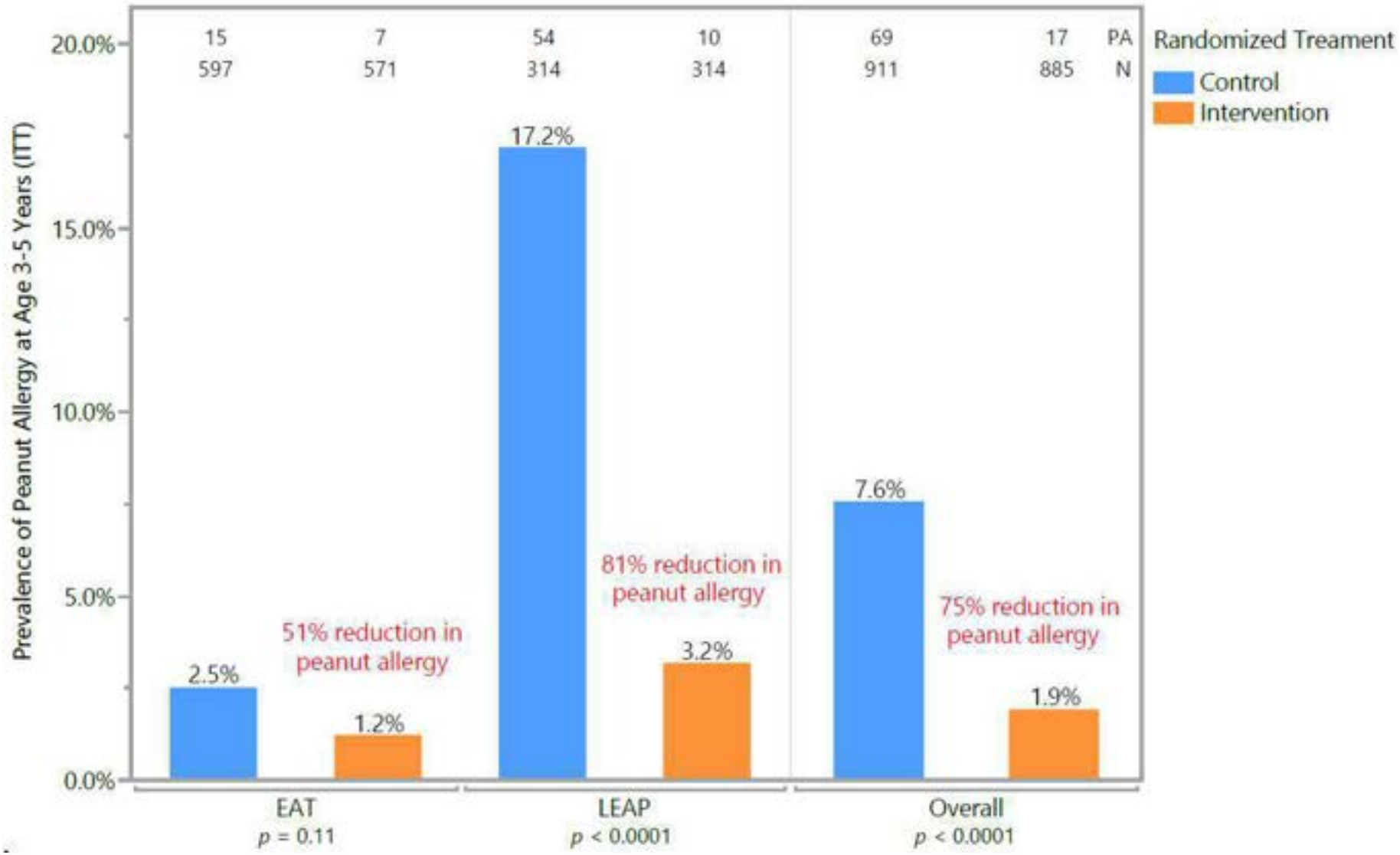
The EAT Study Design





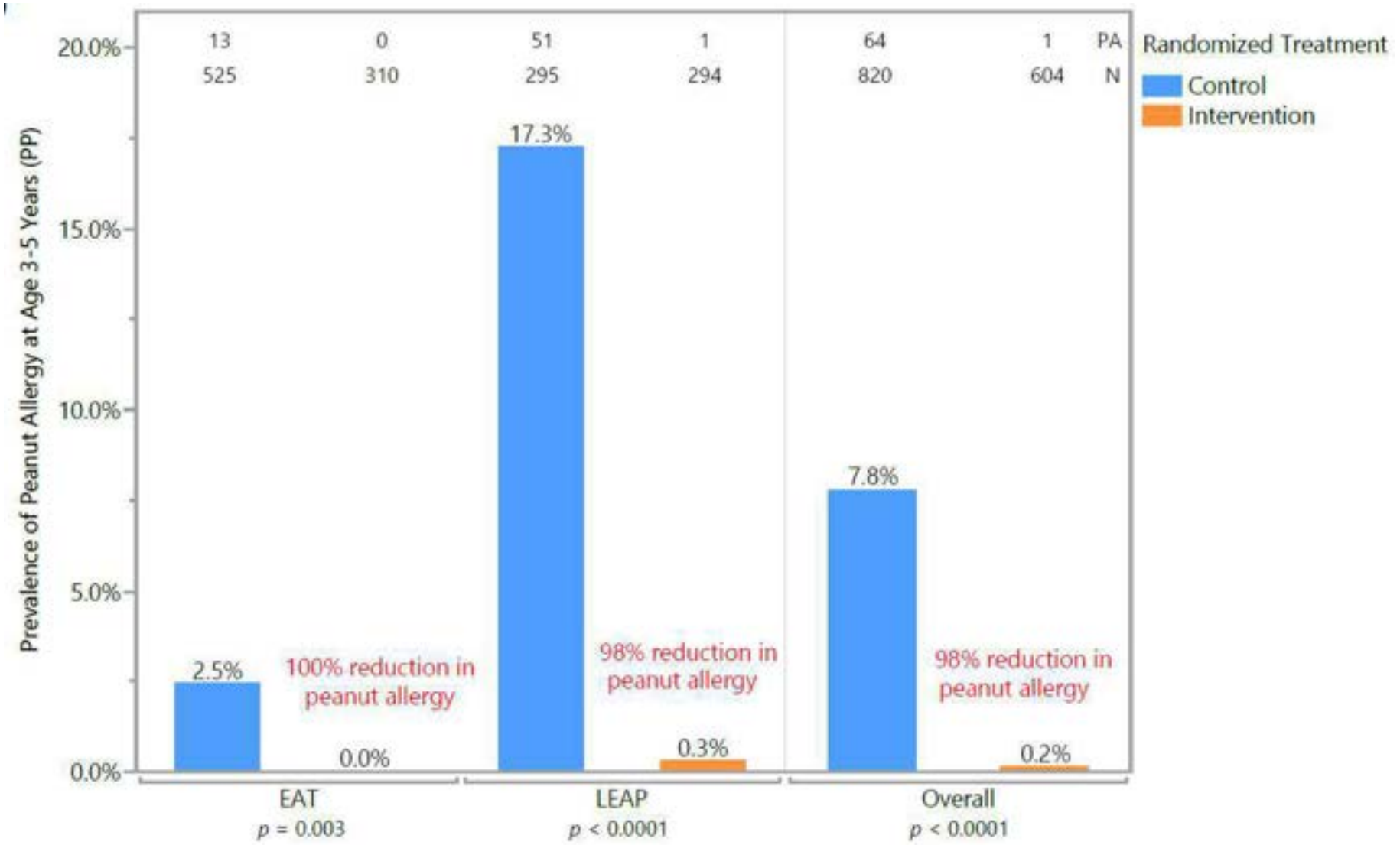
IgE mediated Food Allergy:
SPT >3mm AND positive
DBPCFC to one or more foods

Intention to Treat Population (EAT and LEAP)



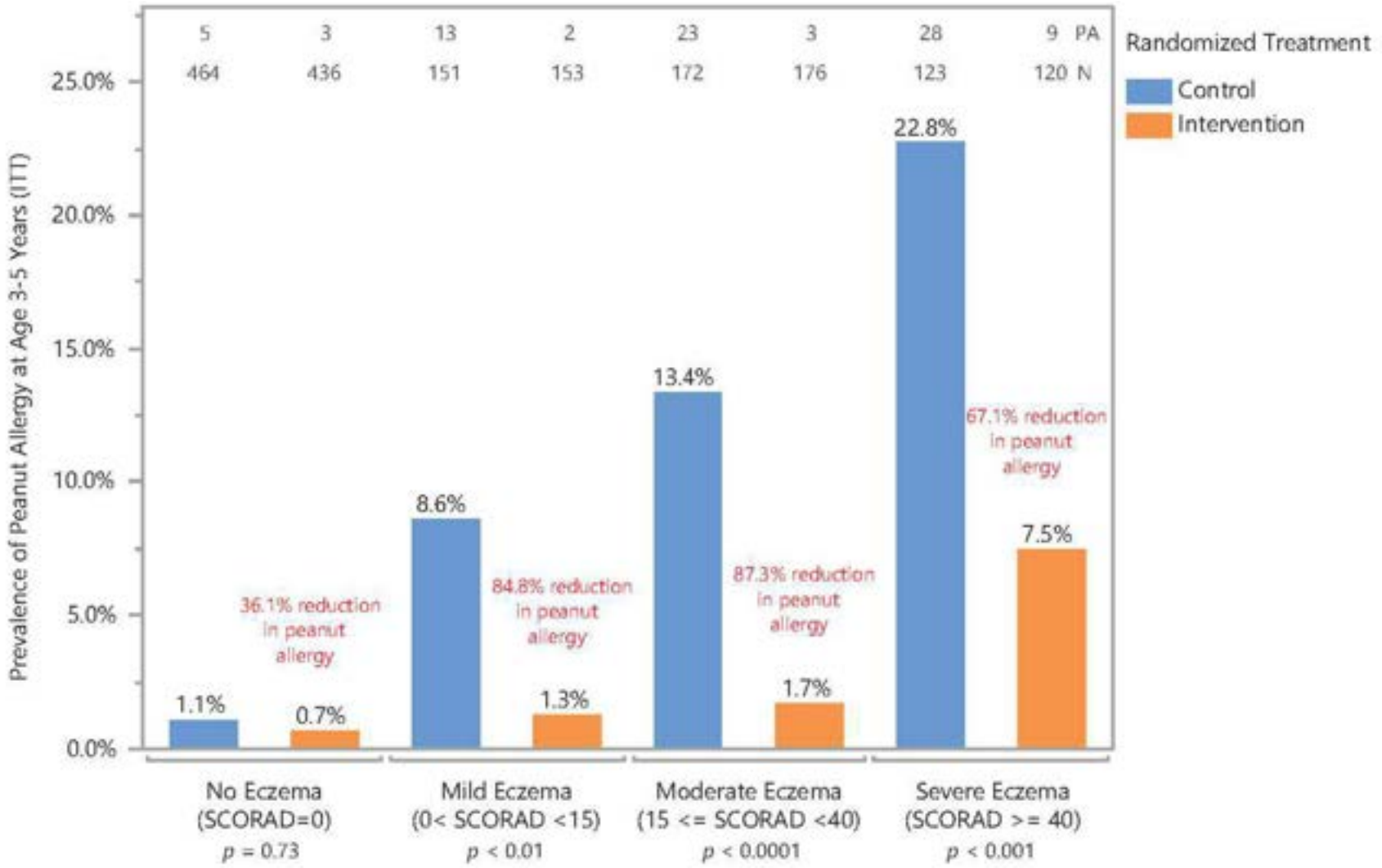
Logan K et al. Allergy. 2022 Nov 27. doi: 10.1111/all.15597. Online ahead of print.

Per-Protocol Population (EAT and LEAP)



Logan K et al. Allergy. 2022 Nov 27. doi: 10.1111/all.15597. Online ahead of print.

Intention to Treat Population (EAT and LEAP) By Eczema Groups



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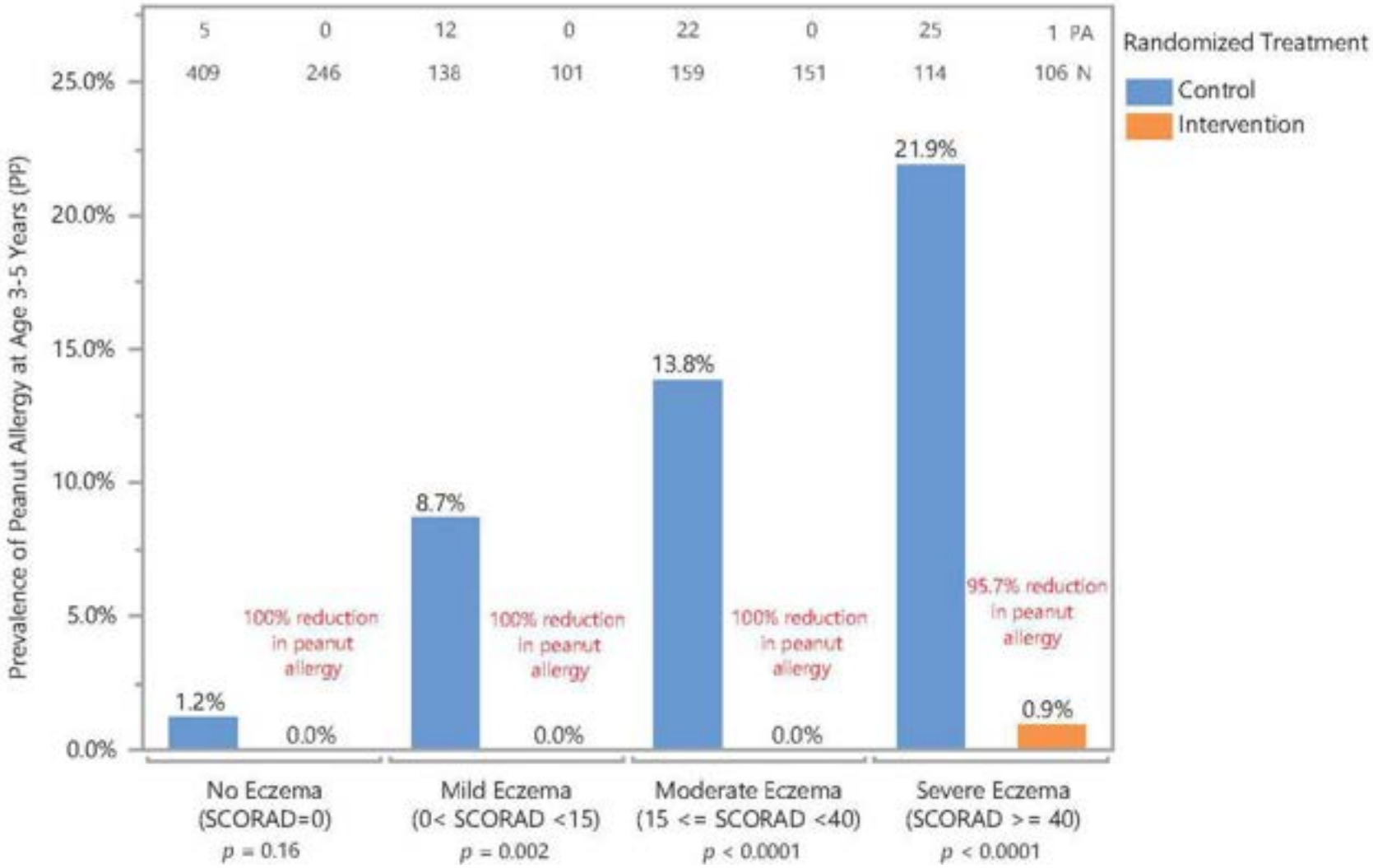
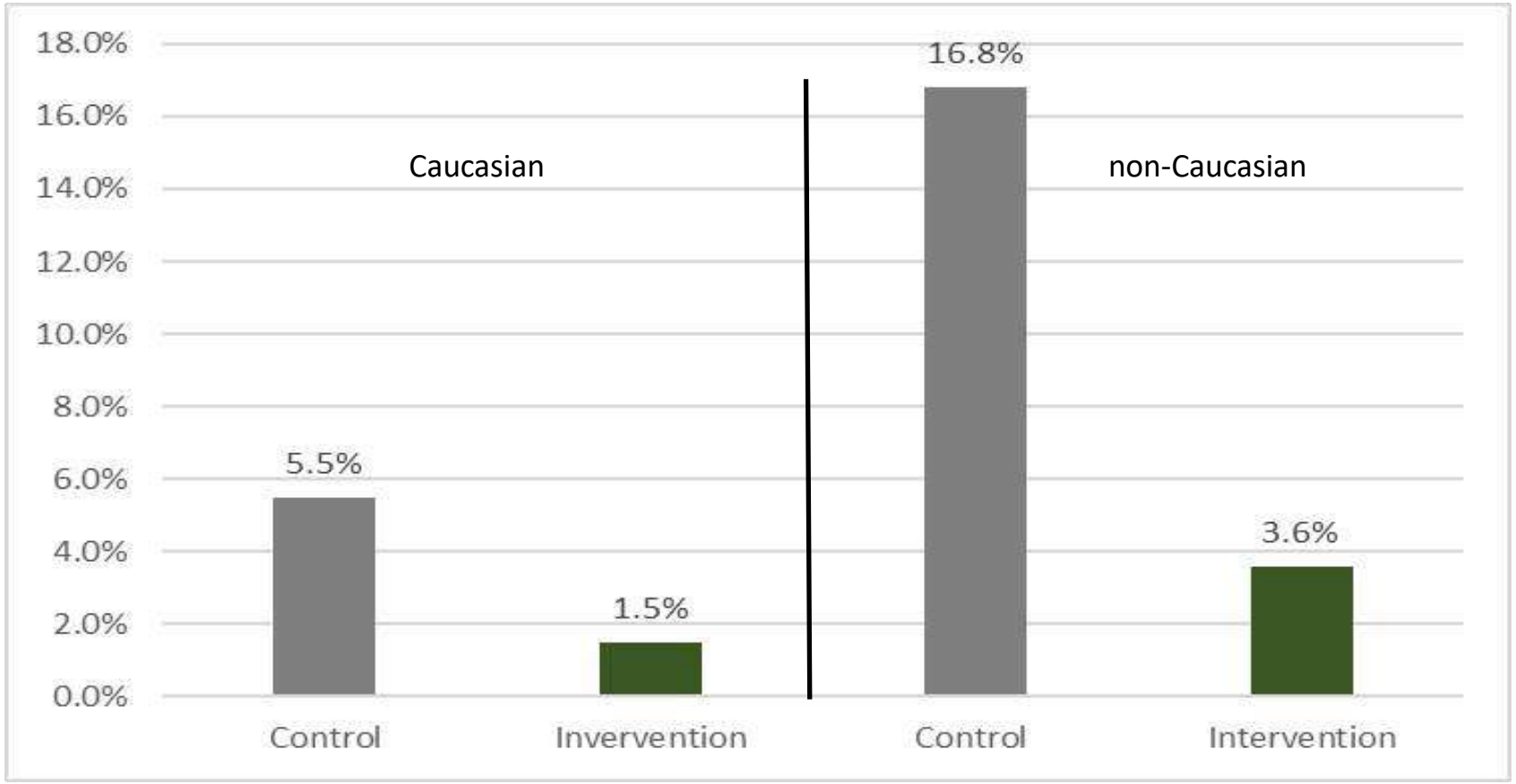
Per Protocol Population (EAT and LEAP) By Eczema Groups



Logan K et al. Allergy. 2022 Nov 27. doi: 10.1111/all.15597. Online ahead of print.

Peanut allergy (EAT and LEAP at 36 and 60 months) in ethnicity groups (ITT)



p<0.001

p<0.001

- Peanut allergy prevalence is significantly higher in non-Caucasian children, p<0.001
- Early introduction significantly reduces peanut allergy prevalence in both Caucasian and non-Caucasian groups in an intention-to-treat analysis

Logan K et al. Allergy. 2022 Nov 27. doi: 10.1111/all.15597. Online ahead of print.

THE LANCET
Volume 399, Issue 10344, 25 June–1 July 2022, Pages 2398-2411

Articles

Early food intervention and skin emollients to prevent food allergy in young children (PreventADALL): a factorial, multicentre, cluster-randomised trial

Håvard Ove Skjerven PhD [a, f] ✉, Anine Lie MD [a, f], Riyas Vettukattil PhD [a, f], Eva Maria Rehbinder PhD [b, f], Marissa LeBlanc PhD [d], Anna Asarnoj PhD [b, i], Prof Kai-Håkon Carlsen DrMed [a, f, g], Åshild Wik Despriee MSc [f, i], Martin Färdig MSc [b, i], Sabina Wärnberg Gerdin MSc [b, i], Berit Granum PhD [e], Hrefna Katrin Gudmundsdóttir MD [a, f], Prof Guttorm Haugen DrMed [c, f], Prof Gunilla Hedlin DrMed [b, i], Geir Håland PhD [a], Prof Christine Monceyron Jonassen PhD [j, k], Linn Landrø PhD [b, f], Caroline-Alekti Olsson Mägi MSc [b, i] ... Prof Karin C Ladrup Carlsen DrMed [a, f]

Abstract

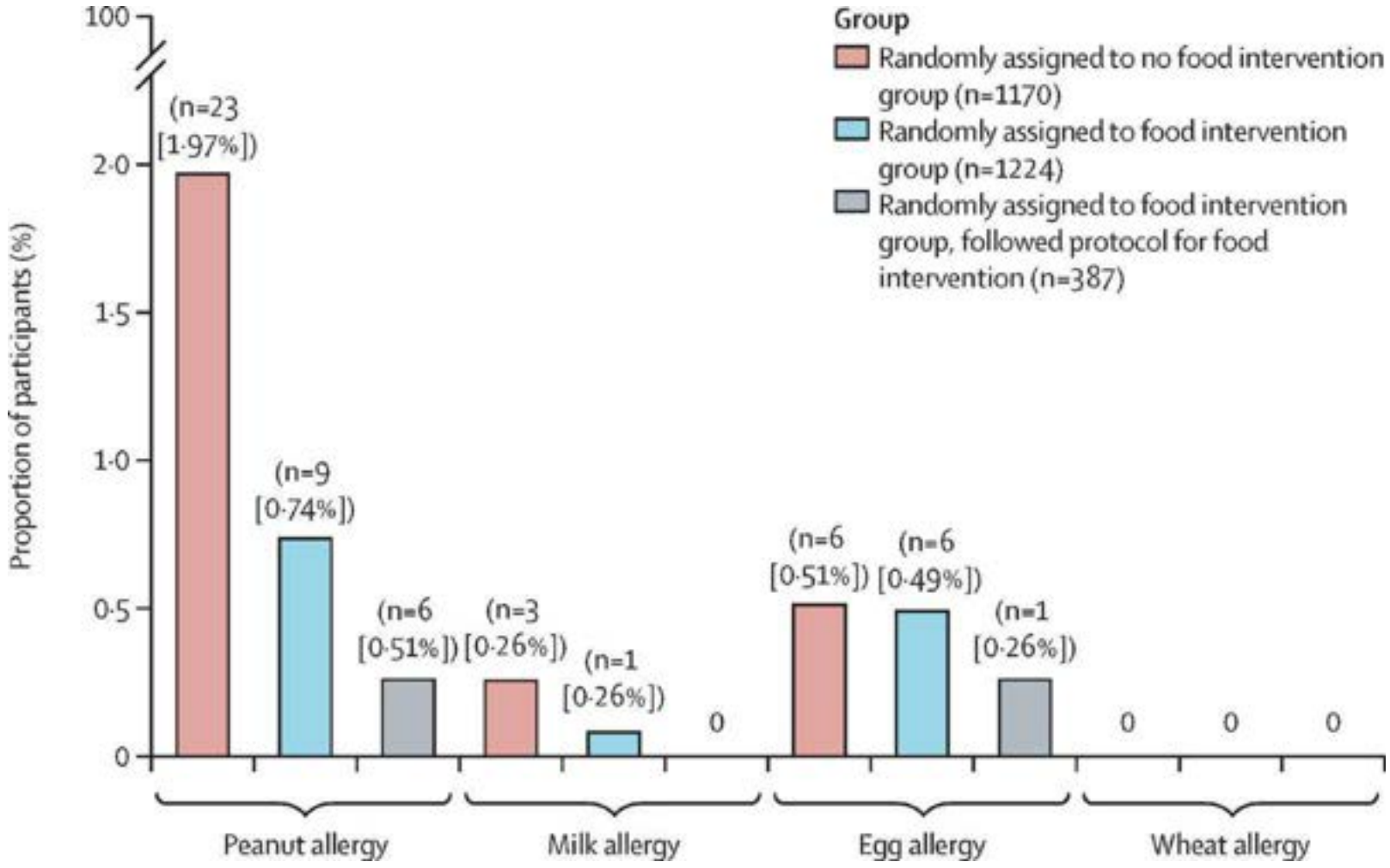
Background: Primary prevention of food allergy by early introduction of allergenic foods seems promising. We aimed to determine whether early food introduction or the application of regular skin emollients in infants from a general population reduced the risk of food allergy.

Methods: This 2 × 2 factorial, cluster-randomised trial was done at Oslo University Hospital and Østfold Hospital Trust, Oslo, Norway, and Karolinska University Hospital, Stockholm, Sweden. Infants of women recruited antenatally at the routine 18-week ultrasound examination were cluster-randomised at birth to the following groups: (1) no intervention group; (2) the skin intervention group (skin emollients; bath additives and facial cream; from age 2 weeks to <9 months, both at least four times per week); (3) the food intervention group (early complementary feeding of peanut, cow's milk, wheat, and egg from age 3 months); or (4) combined intervention group (skin and food interventions). Participants were randomly assigned (1:1:1:1) using computer-generated randomisation based on clusters of 92 geographical areas and eight 3-month time blocks. Study personnel performing clinical assessments were masked to group allocation. The primary outcome was allergy to any interventional food at 36 months of age. The primary efficacy analysis was done by intention-to-treat analysis, which included all participants who were randomly assigned, apart from three individuals who withdrew their consent. This was a study performed within ORAACLE (the Oslo Research Group of Asthma and Allergy in Childhood; the Lung and Environment). This study is registered as ClinicalTrials.gov, NCT02449850.

Findings: We recruited 2697 women with 2701 pregnancies, from whom 2397 newborn infants were enrolled between April 14, 2015, and April 11, 2017. Of these infants, 597 were randomly assigned to the no intervention group, 575 to the skin intervention group, 642 to the food intervention group, and 583 to the combined intervention group. One participant in each of the no intervention, food intervention, and skin intervention groups withdrew consent and were therefore not included in any analyses. Food allergy was diagnosed in 44 children; 14 (2·3%) of 596 infants in the non-intervention group, 17 (3·0%) of 574 infants in the skin intervention group, six (0·9%) of 641 infants in the food intervention group, and seven (1·2%) of 583 infants in the combined intervention group. Peanut allergy was diagnosed in 32 children, egg allergy in 12 children, and milk allergy in four children. None had allergy to wheat. Prevalence of food allergy was reduced in the food intervention group compared with the no food intervention group (risk difference -1·6% [95% CI -2·7 to -0·5]; odds ratio [OR] 0·4 [95% CI 0·2 to 0·8]), but not compared with the skin intervention group (0·4% [95% CI -0·6 to 1· 5%]; OR 1·3 [0·7 to 2·3]), with no significant interaction effect (p=1·0). Preventing food allergy in one child required early exposure to allergenic foods in 63 children. No serious adverse events were observed.

Interpretation: Exposure to allergenic foods from 3 months of age reduced food allergy at 36 months in a general population. Our results support that early introduction of common allergenic foods is a safe and effective strategy to prevent food allergy.

Frequency of food allergy by group allocation and adherence to food intervention



Skjerven et al. Lancet. 2022 Jun 25;399(10344):2398-2411.

Egg Allergy

Milk Allergy

Table. Summary of Key Review Findings for Earlier vs Later Introduction of Allergenic Foods to the Infant Diet

Intervention, outcome	Participants, No. (studies, No.)	RR (95% CI)	Certainty of evidence[a]	Control risk, cases per 1000 population[b]	RD (95% CI), cases per 1000 population	NNTB/H (95% CI)
Earlier introduction of multiple allergenic foods						
Allergy to any food	3295 (4[9,10,37,40])	0.49 (0.33 to 0.74)	Moderate	50	−26 (−34 to −13)	38 (29 to 77)
				200[c]	−102 (−134 to −52)	10 (7 to 19)
Withdrawal from study intervention	4703 (5[9,10,28,37,40])	2.29 (1.45 to 3.63)	Moderate	200	258 (90 to 526)	4 (2 to 11)
Earlier egg introduction						
Allergy to egg	4811 (9[9,10,24,29,36-39,43])	0.60 (0.46 to 0.77)	High	40	−16 (−22 to −9)	63 (45 to 111)
				200[c]	−80 (−108 to −46)	13 (9 to 22)
Withdrawal from study intervention	7442 (13[9,10,24,28,29,33,36-40,42,43])	1.58 (1.12 to 2.22)	Low	200	116 (24 to 244)	9 (4 to 42)
Earlier peanut introduction						
Allergy to peanut	3796 (4[3,9,10,37])	0.31 (0.19 to 0.51)	High	25	−17 (−20 to −12)	59 (50 to 83)
				100[c]	−69 (−81 to −49)	14 (12 to 20)
Withdrawal from study intervention	5343 (6[3,9,10,28,37,40])	1.91 (1.19 to 3.05)	Very low	200	182 (38 to 410)	5 (2 to 26)
Earlier cow's milk introduction						
Allergy to cow's milk	3900 (6[9,10,31,32,37,44])	0.84 (0.38 to 1.87)	Very low	10	−2 (−6 to 9)	500 (110 to ∞)
				50[c]	−8 (−31 to 44)	125 (23 to ∞)
Withdrawal from study intervention	7895 (11[9,10,25,26,28,31,32,37,40,41,44])	1.05 (0.61 to 1.82)	Low	200	10 (−78 to 164)	100 (6 to ∞)

Abbreviations: NNTB/H, number needed to treat for an additional beneficial or harmful outcome; RD, risk difference; RR, risk ratio.

[a] Grading of Recommendations, Assessment, Development, and Evaluation framework.

[b] Control event rate was pooled from the largest included studies.

[c] Population at high risk for developing food allergy.

Scarpone R et al. JAMA Pediatr. 2023 May 1;177(5):489-497.

ascia
australasian society of clinical immunology and allergy

Guide for introduction of peanut to infants (2017)

https://www.allergy.org.au/images/stories/pospapers/ASCIA_HP_guide_introduction_peanut_infants_2017.pdf

- For all infants, peanut and other solid foods should be introduced around 6 months (not before 4 months) and in the first 12 months.

- If there is no allergic reaction, parents should continue to include peanut in their infant's diet in **gradually increasing amounts** at least weekly, as it is important to continue to feed peanut to the infant as a part of a varied diet.

Infant Feeding and Allergy Prevention (2020)

https://www.allergy.org.au/images/pcc/ASCIA_Guidelines_Infant_Feeding_and_Allergy_Prevention_2020.pdf

- When your infant is ready, at around six months, but not before four months, start to introduce a variety of solid foods, starting with iron rich foods, while continuing breastfeeding.

- ASCIA recommends the introduction of solid foods around six months, but not before four months, and preferably whilst breastfeeding. There is some evidence this is protective against the development of allergic disease

- *Comment – no recommendation on dosing*

EAACI guideline: Preventing the development of food allergy in infants and young children (2020 update)

- In populations with a high prevalence of peanut allergy, the EAACI Task Force suggests introducing peanuts in an age-appropriate form as part of complementary feeding in order to prevent peanut allergy in infants and young children
- Certainty of evidence: moderate
- Conditional recommendation made

Practical implications

- Professionals should advocate introducing peanut in an age-appropriate form alongside continued breastfeeding. It appears that the most effective age to introduce is from four to 6 months of life.
- Infants should be given two heaped teaspoons of diluted peanut butter (2g peanut protein) each week
- We suggest that peanut should not be the first solid to be introduced into the infant diet.

Halken et al. Pediatr Allergy Immunol. 2021 Jul;32(5):843-858.

Association Between Earlier Introduction of Peanut and Prevalence of Peanut Allergy in Infants in Australia

Two population studies assessing prevalence of peanut allergy in 5276 one year old infants in 2011 (before new peanut guidelines) and in 1933 one year old infants in 2019 (after new peanut introduction guidelines 2016)

Results on peanut consumption:

- In 2011 - 21.6% of participants in HealthNuts study consumed peanuts before 12 months of age
- In 2019 - 85.6% of participants in EarlyNuts study consumed peanuts before 12 months of age

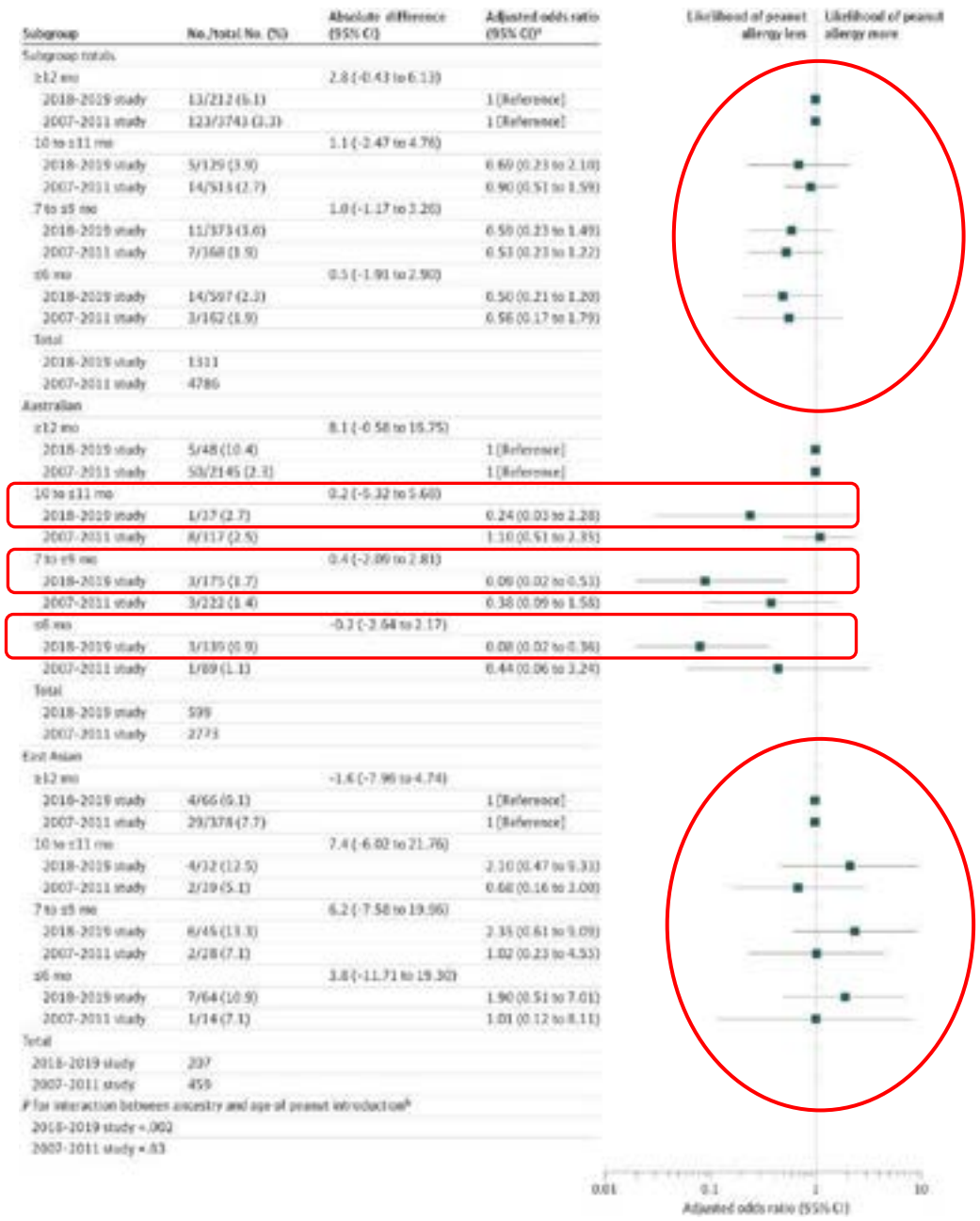
Results on peanut allergy prevalence at 1 year of age:

- In 2011 – 3.1% of participants in HealthNuts study had peanut allergy
- In 2019 – 3.1% of participants in EarlyNuts study had peanut allergy
  (2.6% corrected rate for demographic differences)

Conclusions:
Public health measures to introduce peanut early in the first year of life are successful but not sufficiently successful to prevent peanut allergy

Soriano et al. JAMA. 2022 Jul 5;328(1):48-56.

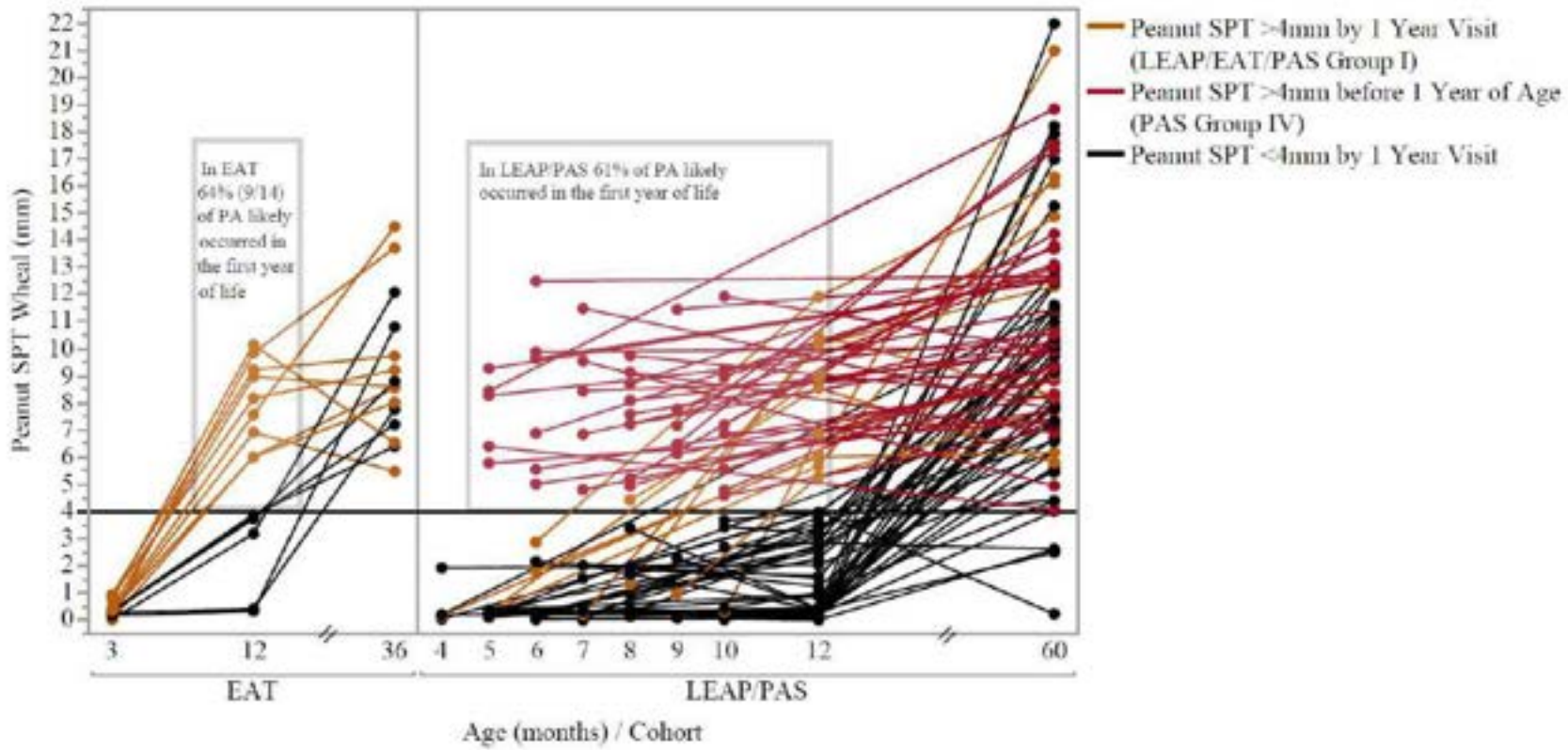
Association Between Age of Peanut Introduction and Peanut Allergy at 1 Year



Introduction of peanut is only associated with reduced peanut allergy in infants of European origin (and only before 6 months of age)

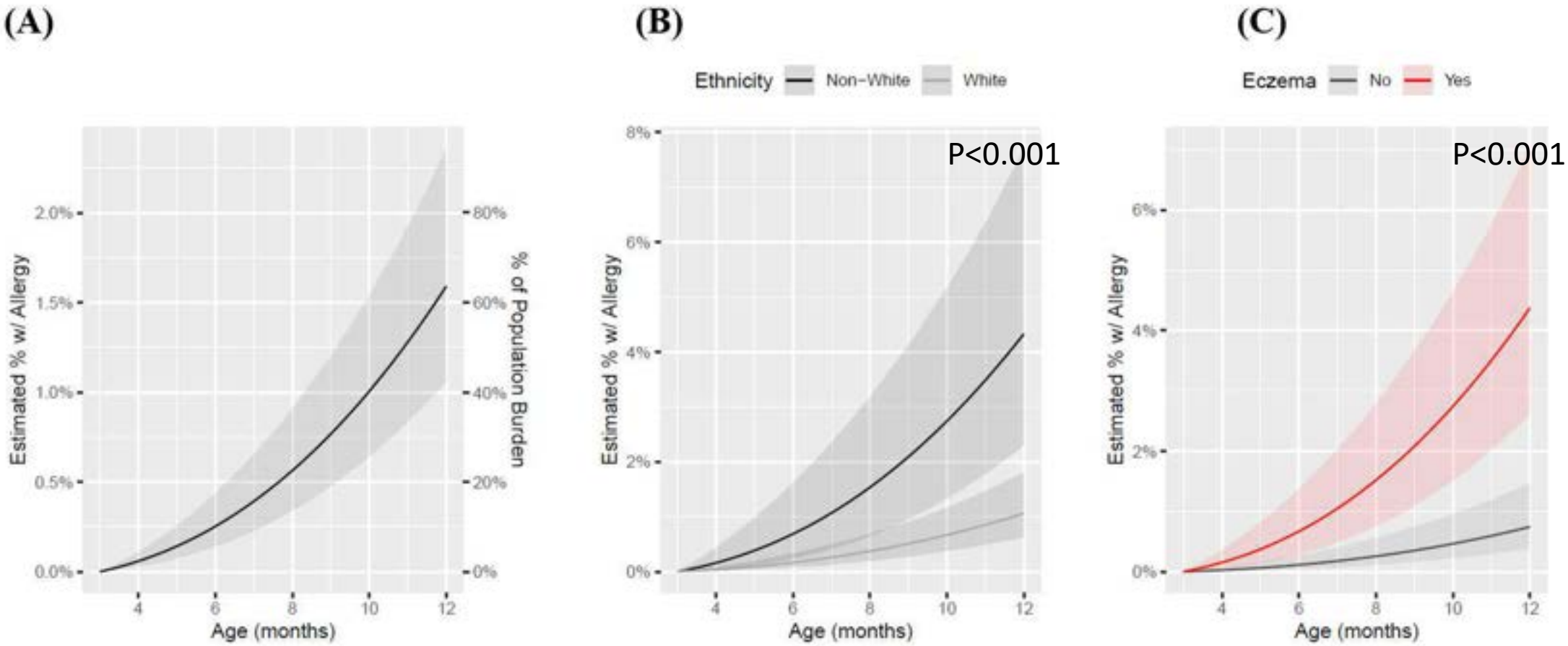
Soriano et al. JAMA. 2022 Jul 5;328(1):48-56.

TRAJECTORY OF PEANUT WHEAL SIZES OF ALLERGIC PARTICIPANTS AT 60 MONTHS FOR LEAP PAS AND EAT PARTICIPANTS



Roberts G et al. J Allergy Clin Immunol. 2022 Dec 12:S0091-6749(22)01656-6

Time to event modeling of the development of allergy in the first year of life in a normal population (based on SPT >4mm)



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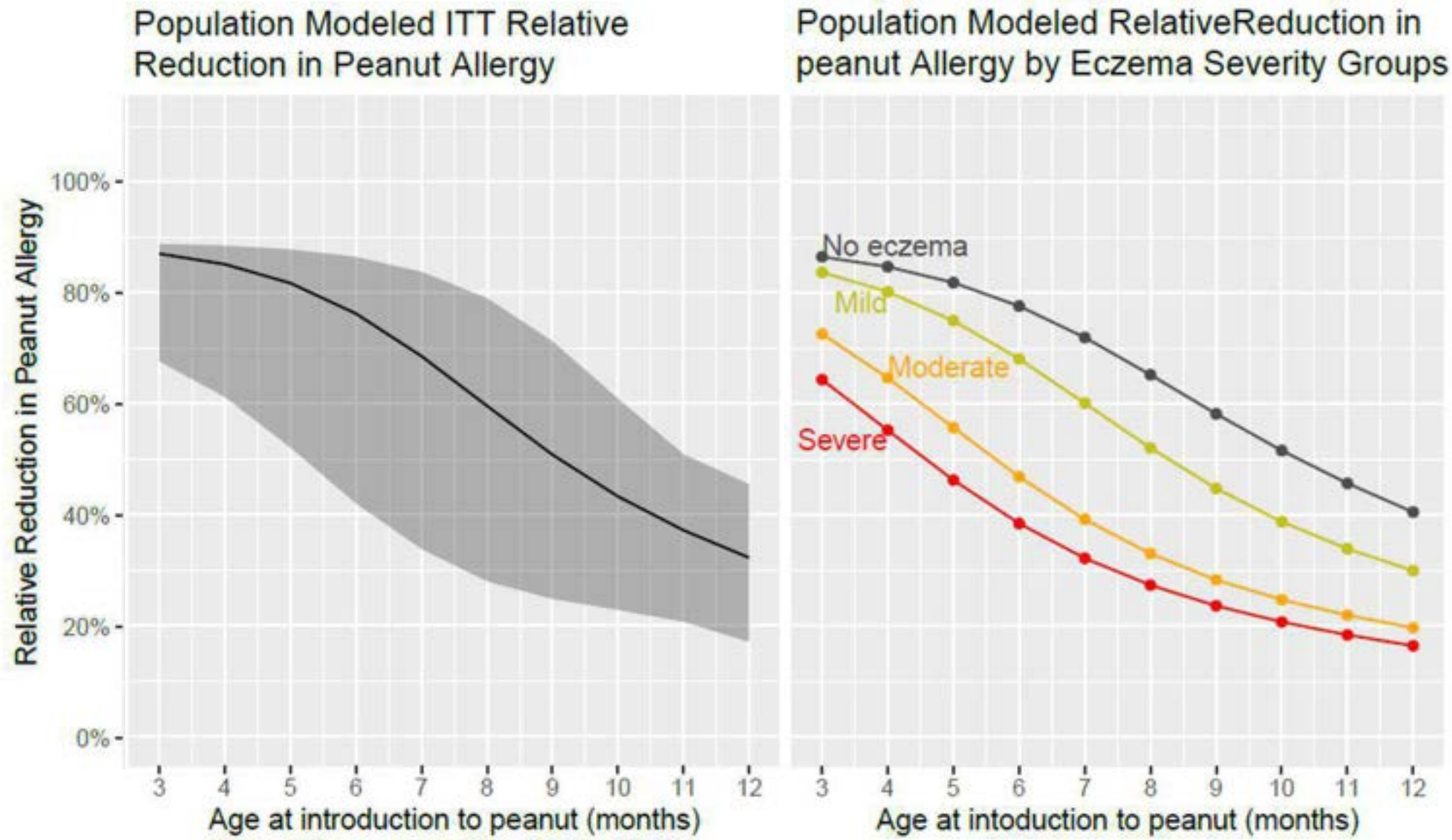
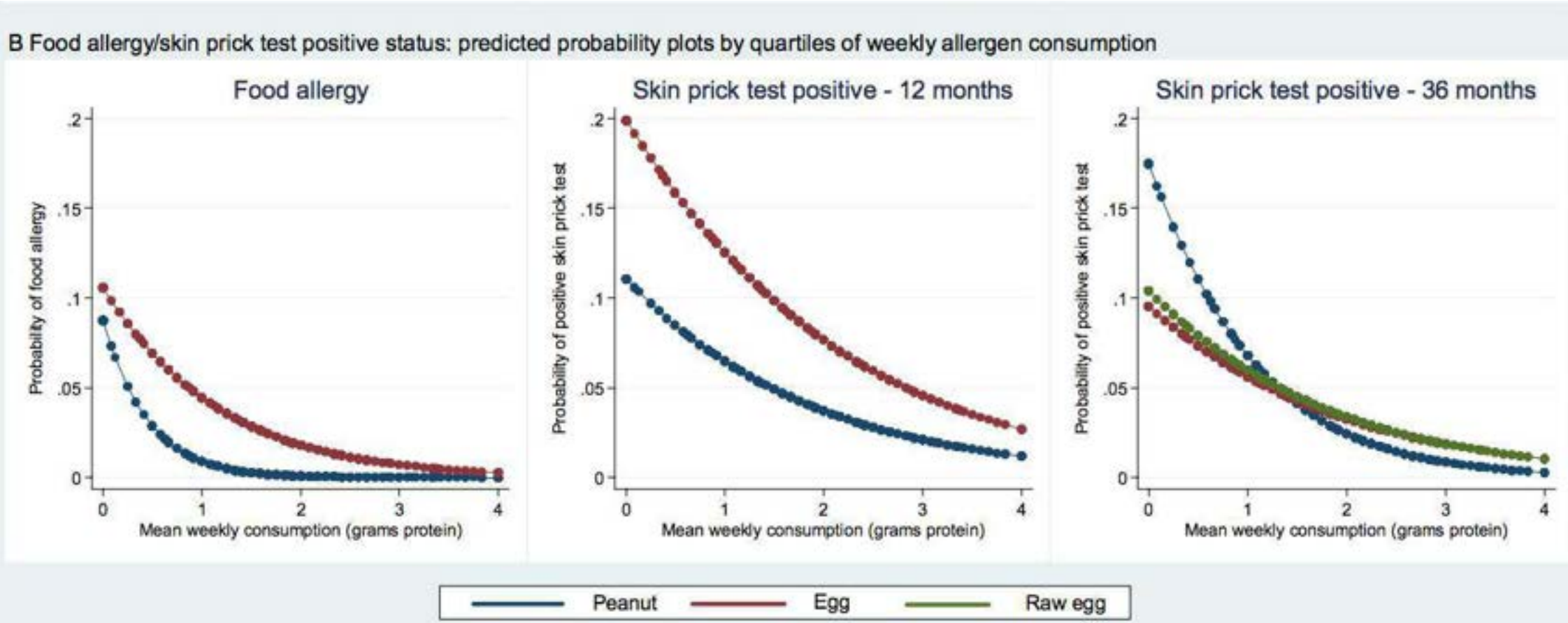


Roberts G et al. J Allergy Clin Immunol. 2022 Dec 12:S0091-6749(22)01656-6

Modelled data demonstrates dose response relationship between amount of peanut and egg eaten and prevention effects - ≥ 2g optimal



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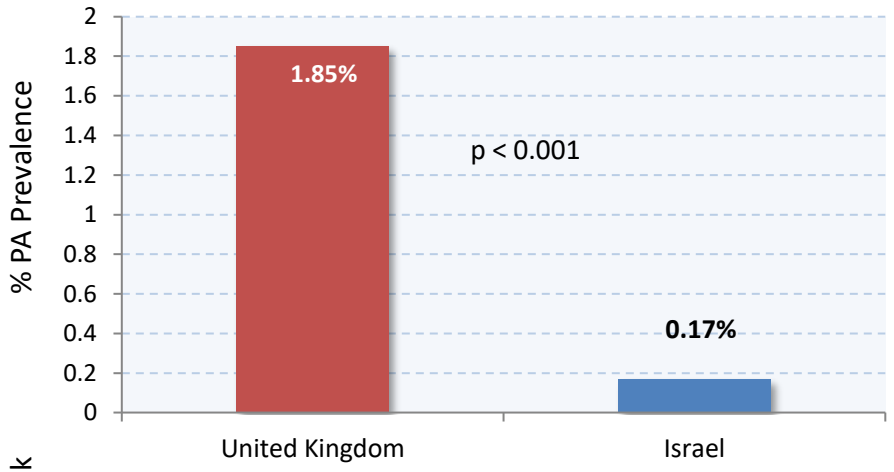

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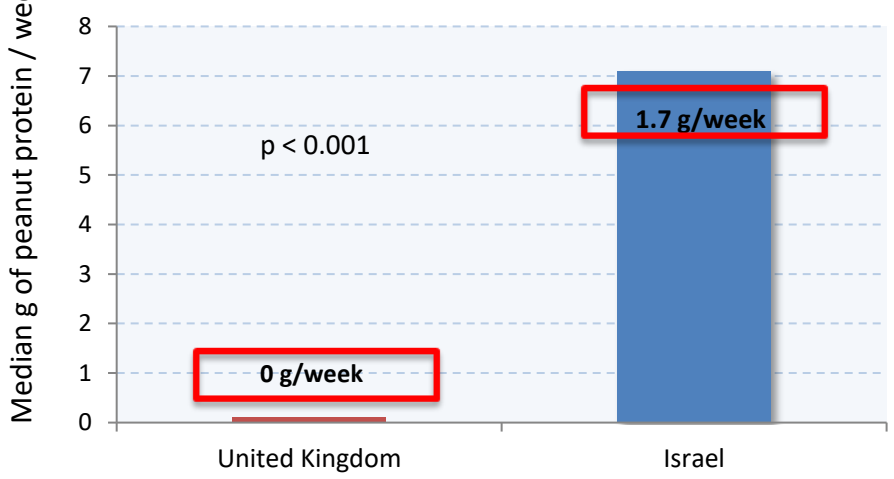


Peanut Protein
Consumption
8 - 14 months

United Kingdom	5171
Israel	5615

Du Toit G, et al. Early Consumption of Peanut in Infancy is Associated with Low Prevalence of Peanut Allergy. JACI 2008; 122: 984-91.

Conclusions

1. **RCTs with early introduction of food allergens demonstrate:**
    - Successful prevention of peanut allergy - high level of evidence – long term protection
    - Successful prevention of egg allergy – high level of evidence
    - Successful prevention of cow's milk allergy – low level of evidence
    - Opportunity to prevent all IgE mediated food allergies but protection is allergen specific

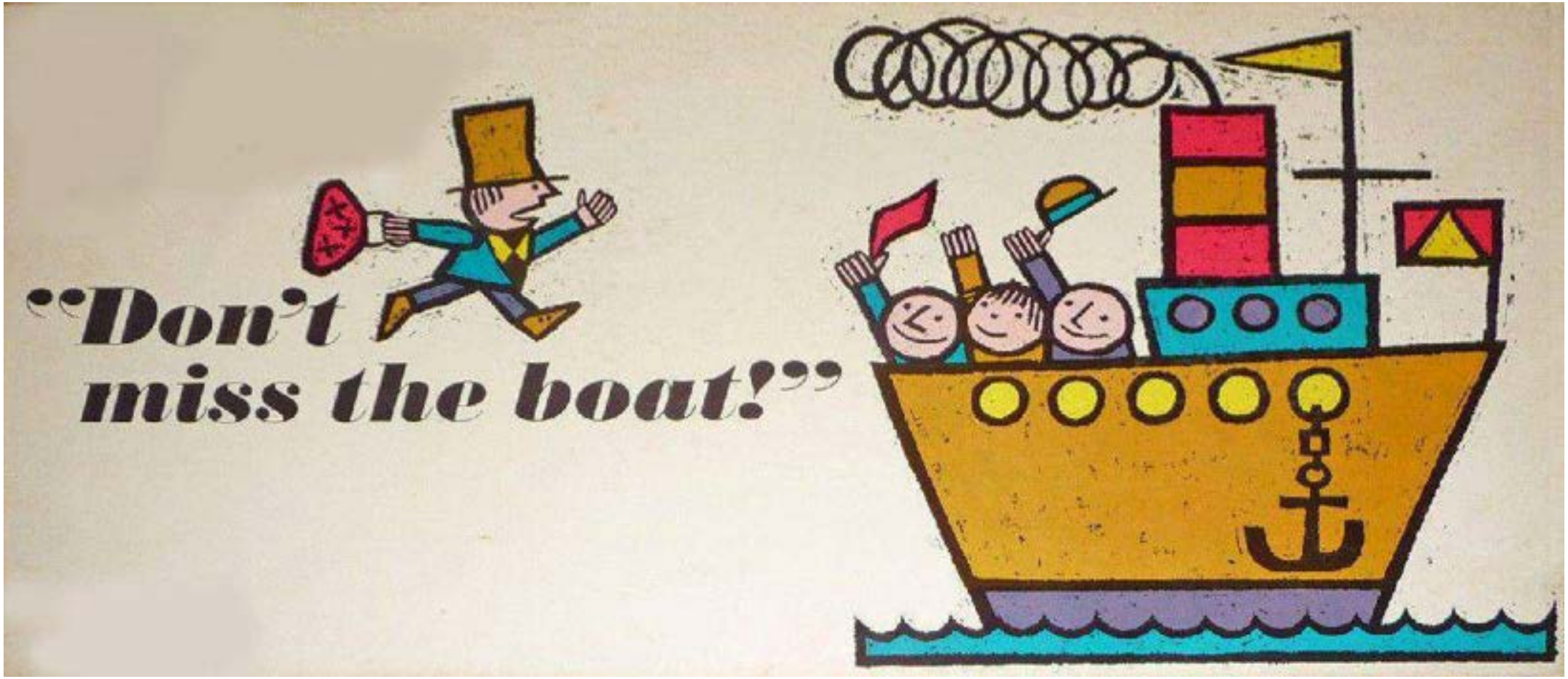
2. **Guidelines in Australia since 2016 have resulted in a marked increase in percentage of infants eating peanuts in the first year of life but no reduction in peanut allergy**

3. **Guidelines appear not to be working**

4. **Infants are receiving too little peanut and too late (after 6 months of age)**

5. **High risk infants (non Caucasian minorities and/or eczema) show the highest burden of food allergy and of benefitting the least from the guidelines**

6. **New guidelines should be more proactive and more prescriptive with emphasis on high risk minorities, high level consumption and early exposure**


"Don't
miss the boat!"

LEAP and LEAP-On Acknowledgements

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National Institute of Allergy and Infectious Diseases

Food Allergy Research & Education

Food Standards Agency UK

Rho Federal Systems Division

MRC & Asthma UK Centre in Allergic Mechanisms of Asthma;
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Food Standards Agency UK

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King's College London

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- Charlotte Stedman
- Mary Feeney
- Susan Chan
- Marshall Plaut
- Peter Sayre
- Suzana Radulovic
- Monica Basting
- Ronald van Ree
- Kirsten Beyer
- Johanna Bellach
- Dianne Campbell
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- Philippe Eigenmann
- Kate Grimshaw
- Arne Hoest
- Carla Jones
- Kari Nadeau
- Liam O'Mahony
- Hania Szajewska
- Carina Venter
- Valérie Verhasselt
- Gary W. K. Wong
- European Academy of Allergy and Clinical Immunology Food Allergy and Anaphylaxis Guidelines Group

- Immune Tolerance Network and Benaroya Research Institute
- Food Standards Agency
- Food Allergy Research & Education
- MRC & Asthma UK Centre in Allergic Mechanisms of Asthma
- National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre
- National Peanut Board
- Davis Foundation

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