

Early Intervention and Prevention of Allergic Disease: Where do we stand?

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Guy's and St Thomas'

KING'S
College
LONDON

Declaration

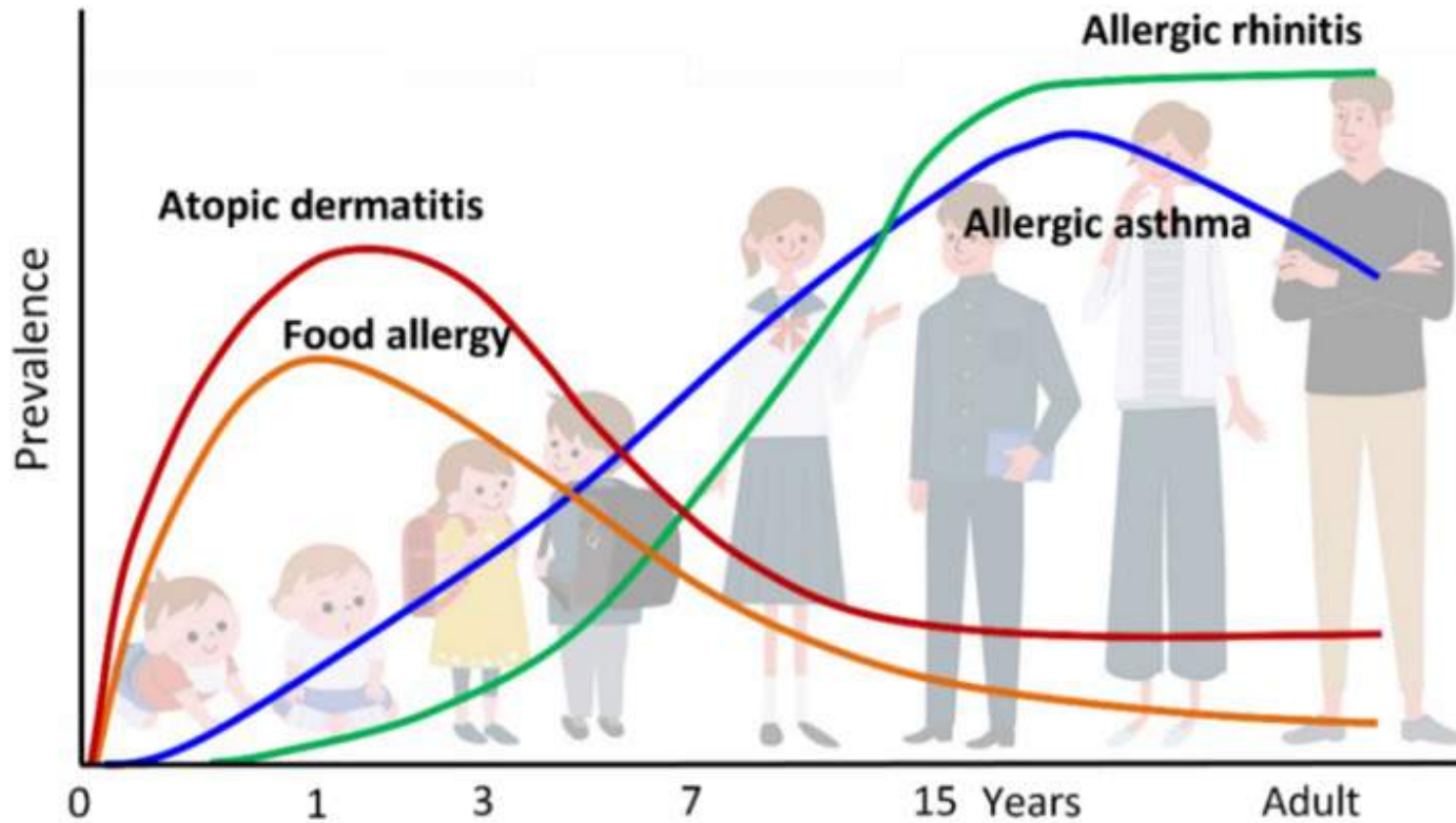
- I have no conflicts of interest.
- I would like to thank my colleagues who have shared some of these slides with me – Professor George du Toit, Professor Alexandra Santos, Rebecca Batt (Nurse consultant), James Gardner (Nurse consultant)

Outline

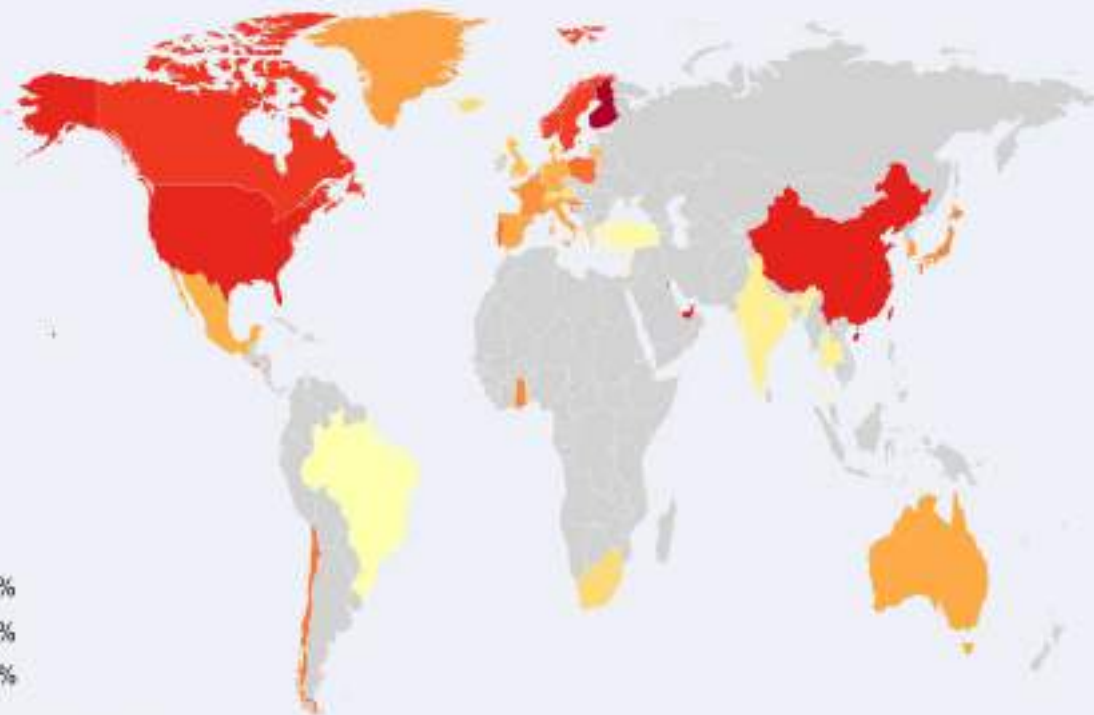
- Food allergy epidemiology
- Risk factors for food allergy development
- Food allergy prevention
 - Early introduction of allergens
- Food allergy interventions
 - Food Immunotherapy
 - Biologics



The Atopic March



Prevalence of paediatric food allergy



North America

Canada	7.1%	▶ Soller 2012	(0-17 yr)
Mexico	3.5%	▶ Ontiveros 2016	(5-13 yr)
USA	7.6%	▶ Gupta 2018	(0-17 yr)

Central America & South America

Brazil	0.6%	▶ Goncalves 2016	(4-59 mo)
Chile	5.5%	▶ Hoyos-Bachilloglu 2014	(5-15 yr)
El Salvador	5.3%	▶ Cabrera-Chavez 2018	(4-12 yr)

Middle East

Israel	3.6%	▶ Graif 2012	(13-14 yr)
Kuwait	5.4%	▶ Ali 2017	(17-30 yr)
Lebanon	4.1%	▶ Irani 2015	(0-17 yr)
Turkey	0.8%	▶ Orhan 2009	(6-9 yr)
UAE	8.0%	▶ Al Hammadi 2010	(6-9 yr)

Asia & Oceania

Australia	3.8%	▶ Peters 2017	(4 yr)
China	7.7%	▶ Hu 2010	(0-2 yr)
Hong Kong	4.8%	▶ Ho 2012	(0-14 yr)
Japan	5.1%	▶ Ebisawa 2017	(0-17 yr)
Singapore	5.4%	▶ Lee 2014	(11-30 mo)
South Korea	4.1%	▶ Kim 2017	(6-16 yr)
Taiwan	7.4%	▶ Wu 2012	(0-18 yr)
Thailand	1.1%	▶ Lao-Aranya 2011	(3-7 yr)

Europe

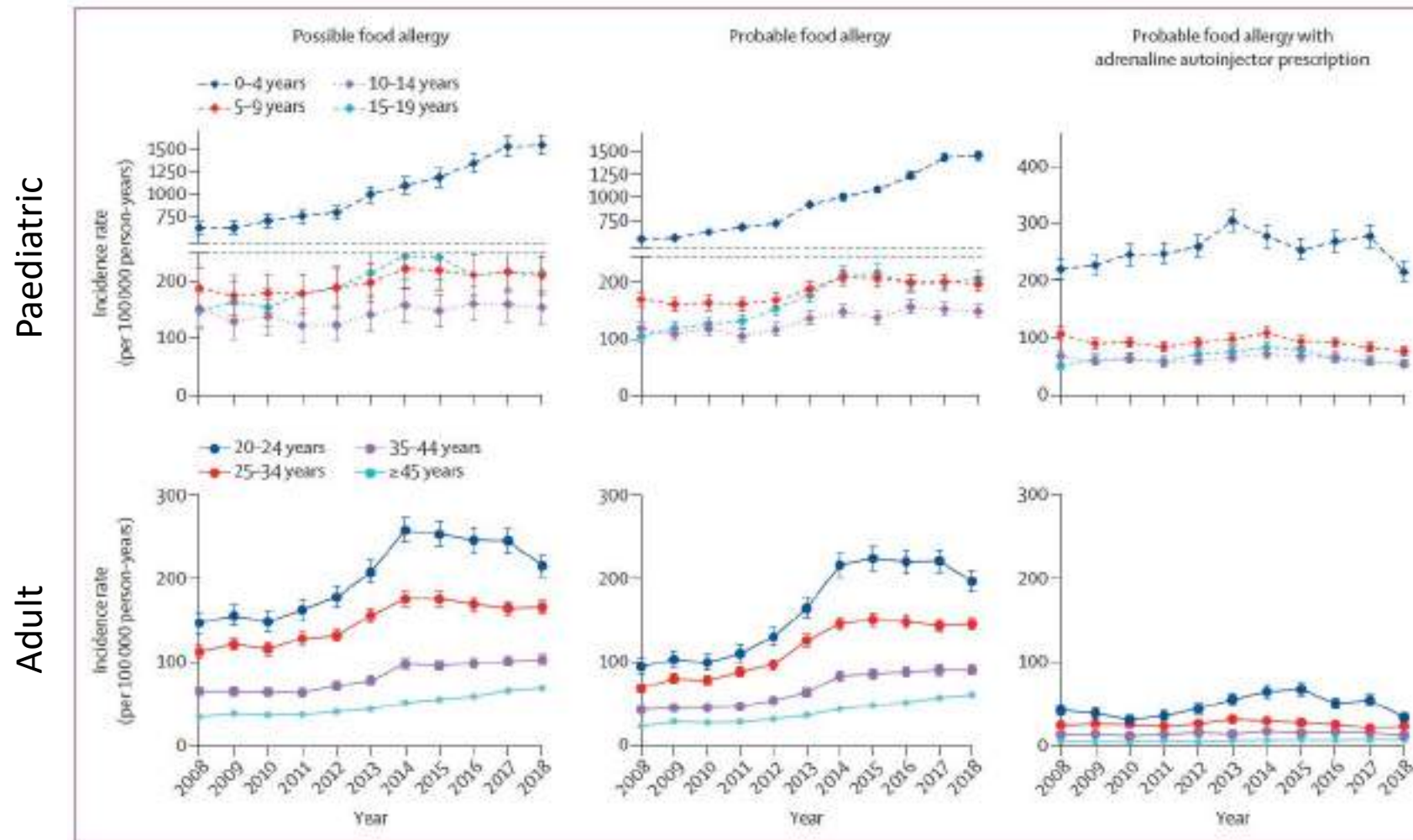
Austria	1.7%	▶ Steinke 2007	(0-17 yr)
Belgium	4.9%	▶ Steinke 2007	(0-17 yr)
Croatia	5.4%	▶ Pavlović 2015	(8 yr)
Denmark	3.6%	▶ Steinke 2009	(0-6 yr)
Finland	9.3%	▶ Pyrhonen 2009	(1-4 yr)
France	4.7%	▶ Rance 2005	(2-14 yr)
Germany	3.5%	▶ Roehr 2004	(0-17 yr)
Greece	2.0%	▶ Lyons 2020	(7-10 yr)
Greenland	4.1%	▶ Krause 2002	(5-18 yr)
Iceland	1.9%	▶ Lyons 2020	(7-10 yr)
Italy	3.9%	▶ Steinke 2007	(0-17 yr)
Lithuania	3.0%	▶ Lyons 2020	(7-10 yr)
Malta	2.5%	▶ Abdilla 2016	(5-6 yr)
Netherlands	3.0%	▶ Lyons 2020	(7-10 yr)
Norway	6.8%	▶ Kvenshagen 2008	(2 yr)
Poland	5.6%	▶ Lyons 2010	(7-10 yr)
Portugal	5.7%	▶ Gaspar-Marques 2014	(0-6 yr)
Slovenia	4.6%	▶ Steinke 2007	(0-17 yr)
Spain	3.9%	▶ Lyons 2020	(7-10 yr)
Sweden	6.8%	▶ Protudger 2016	(16 yr)
Switzerland	2.3%	▶ Lyons 2020	(7-10 yr)
UK	3.0%	▶ Venter 2008	(3 yr)

Africa

Ghana	5.0%	▶ Obeng 2011	(5-16 yr)
South Africa	1.8%	▶ Botha 2019	(1-3 yr)

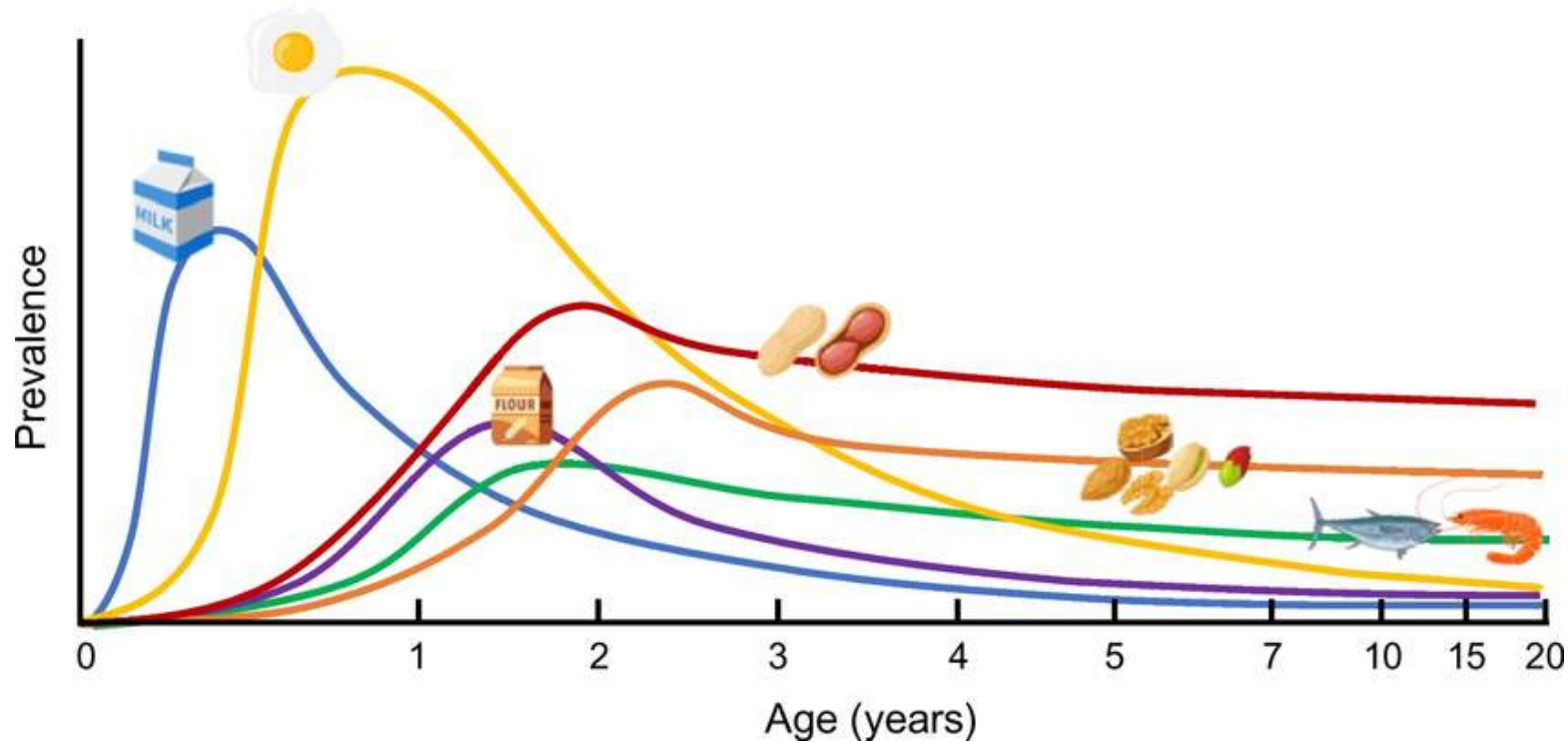
(range of ages comprising study sample)

Food allergy is becoming more prevalent



Changing patterns of food allergies

Natural history of food allergy by common food type



Prevalence rates:

- Peanut allergy: 1-2%
- Sesame seed allergy: 0.1-0.9%
- Egg allergy: 1-2%
- Cow's milk: 1-3%

Resolution rates:

- Peanut allergy: 20%
- Sesame seed allergy: 20%
- Egg allergy: 50-60%
- Milk allergy: 50-60%

Risk factors

Ethnicity

Early onset atopic
dermatitis/eczema

Genetic
predispositions

Changes in
environmental
exposures

Ethnicity

- Food allergy disproportionately affects children from ethnic minorities
 - In Western countries, children of Afro-Caribbean descent
 - Risk of peanut allergy and other food allergies of infants born in Australia to Asian-born parents is higher compared to those born in Australia to Australian-born parents

Genetics



Filaggrin loss of function mutation more likely to have eczema at 3 months



FLG mutations - Strongest genetic risk factor for eczema



Causes increased water loss, higher risk of sensitisation and staph aureus susceptibility

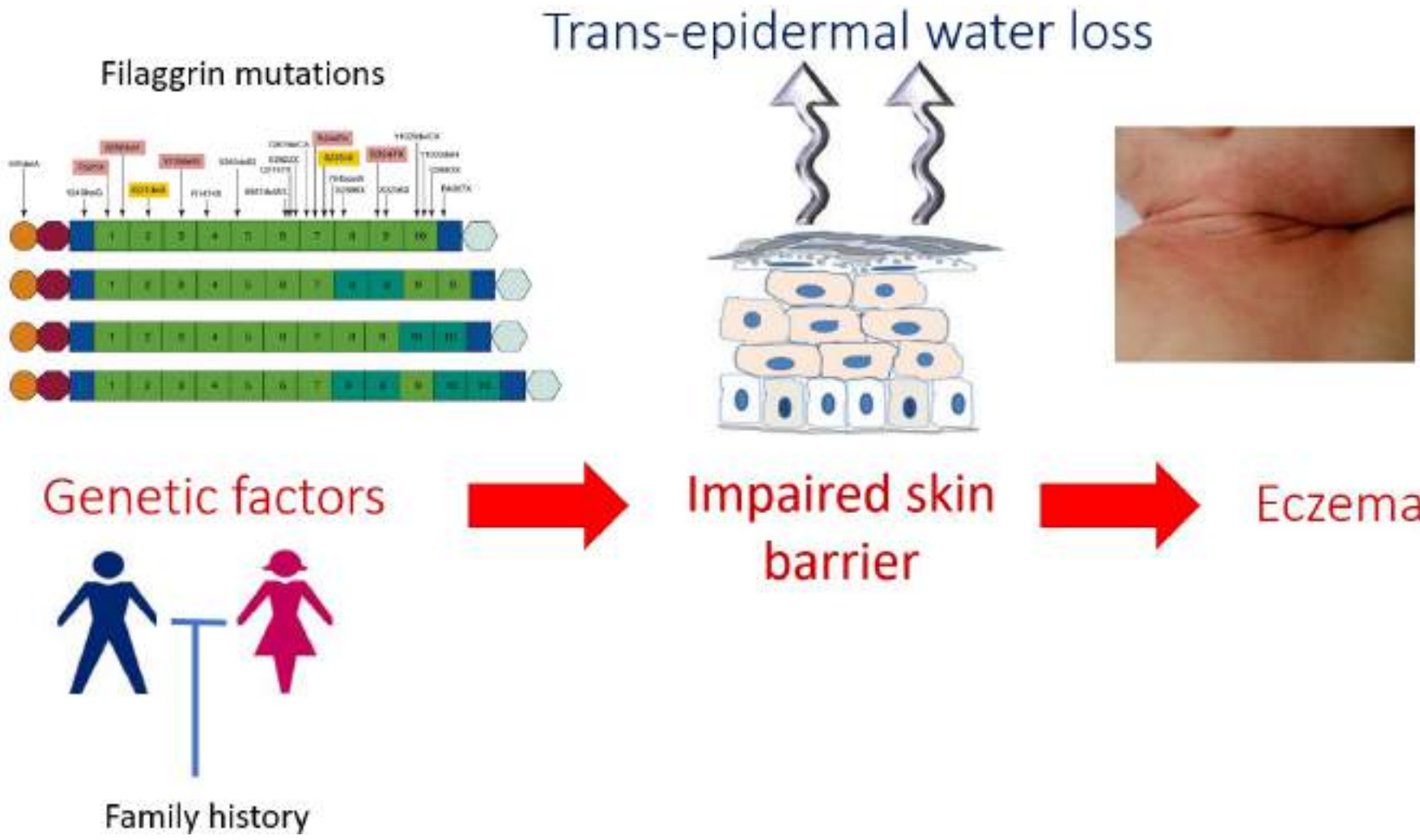


More likely to have clinically dry skin and increased trans epidermal water loss even without diagnosed eczema

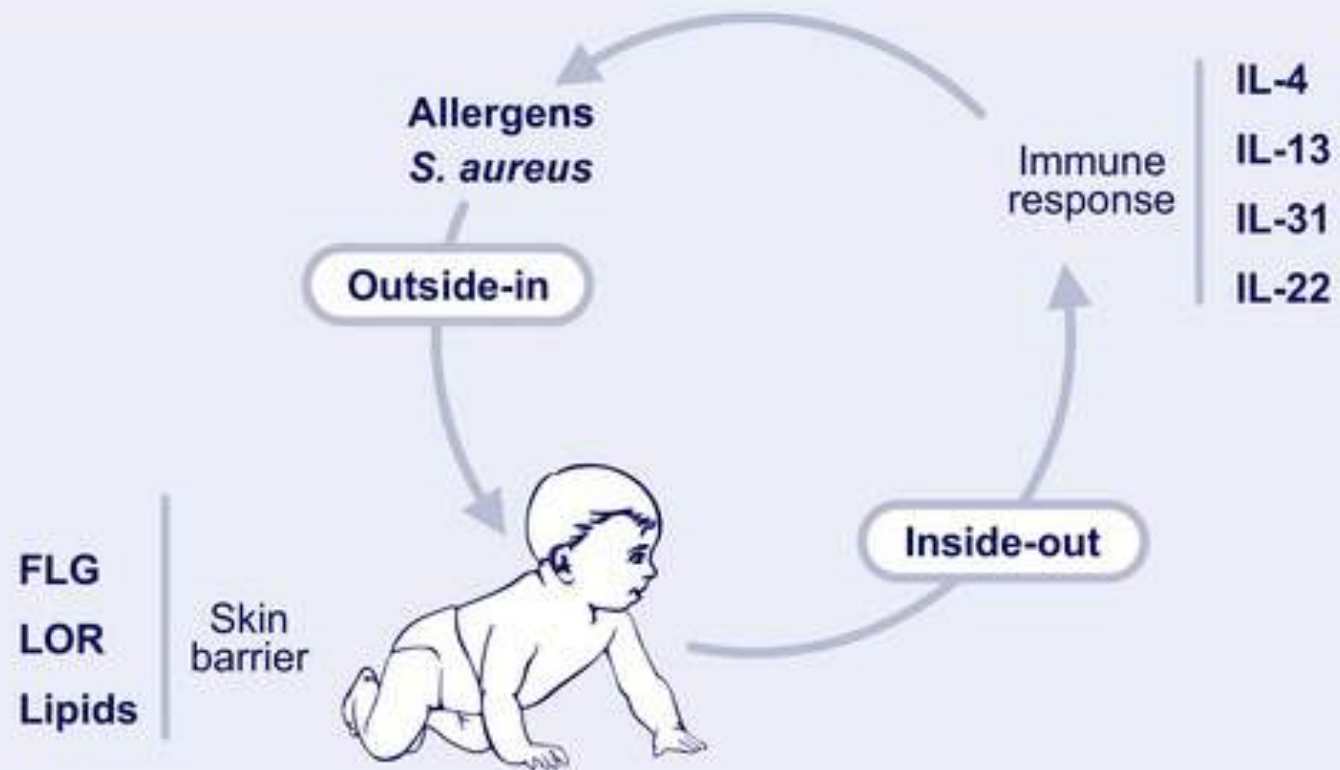


Genetic component –atopic parents matter!

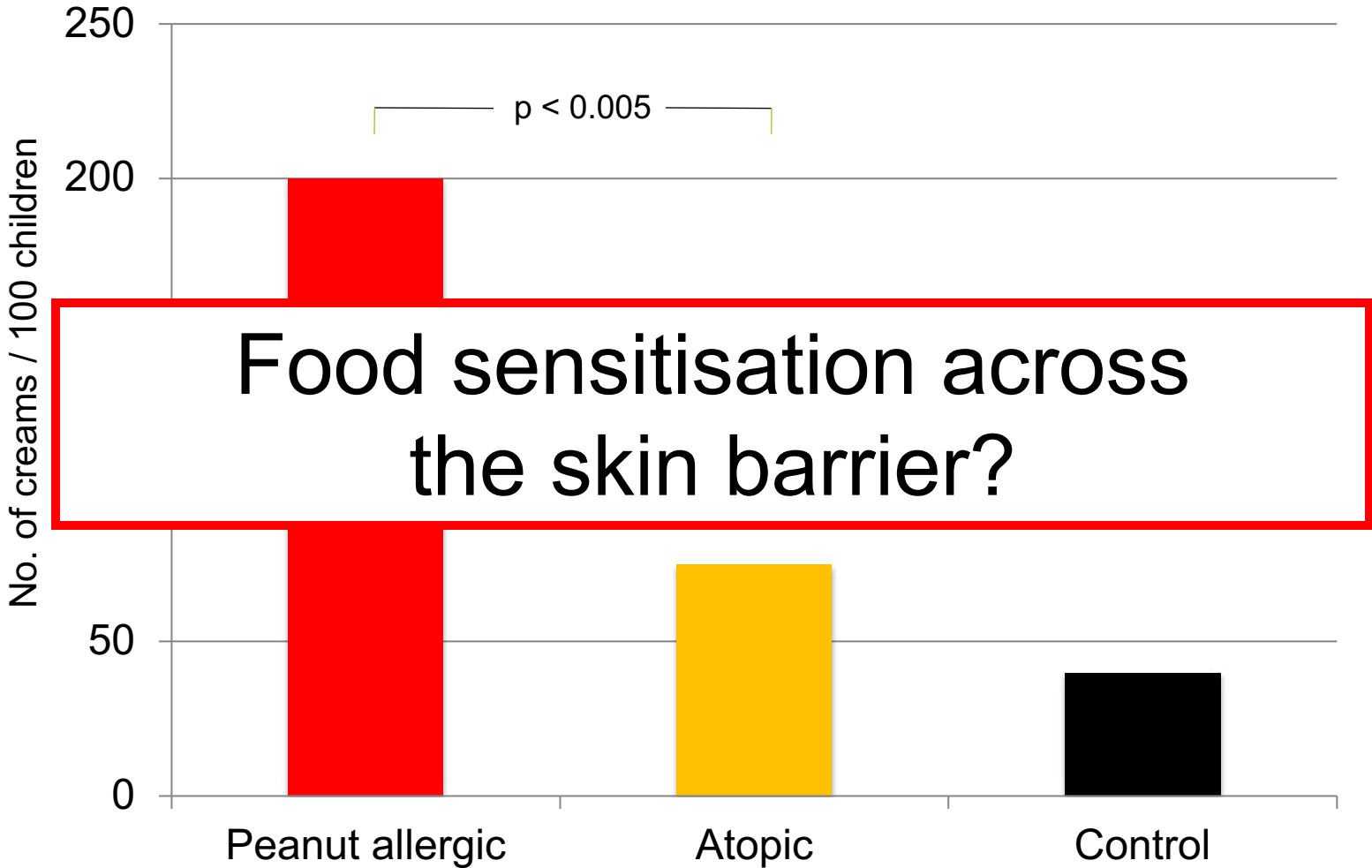
Pathogenesis of eczema



Inside-out vs outside-in hypothesis

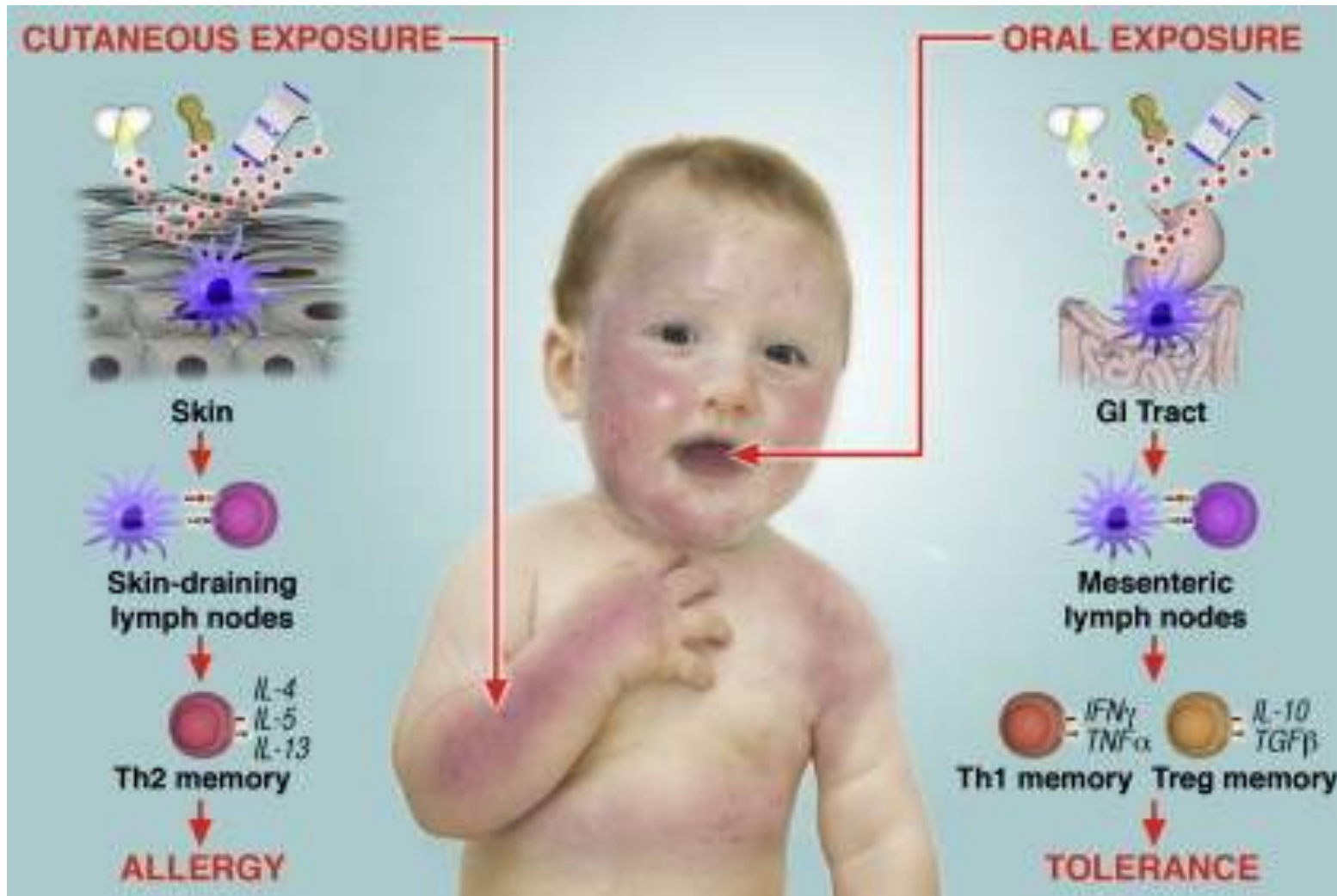


Arachis oil-based cream use ↑ in infants who develop peanut allergy



Food sensitisation across the skin barrier?

Lack Dual Allergen Exposure Hypothesis



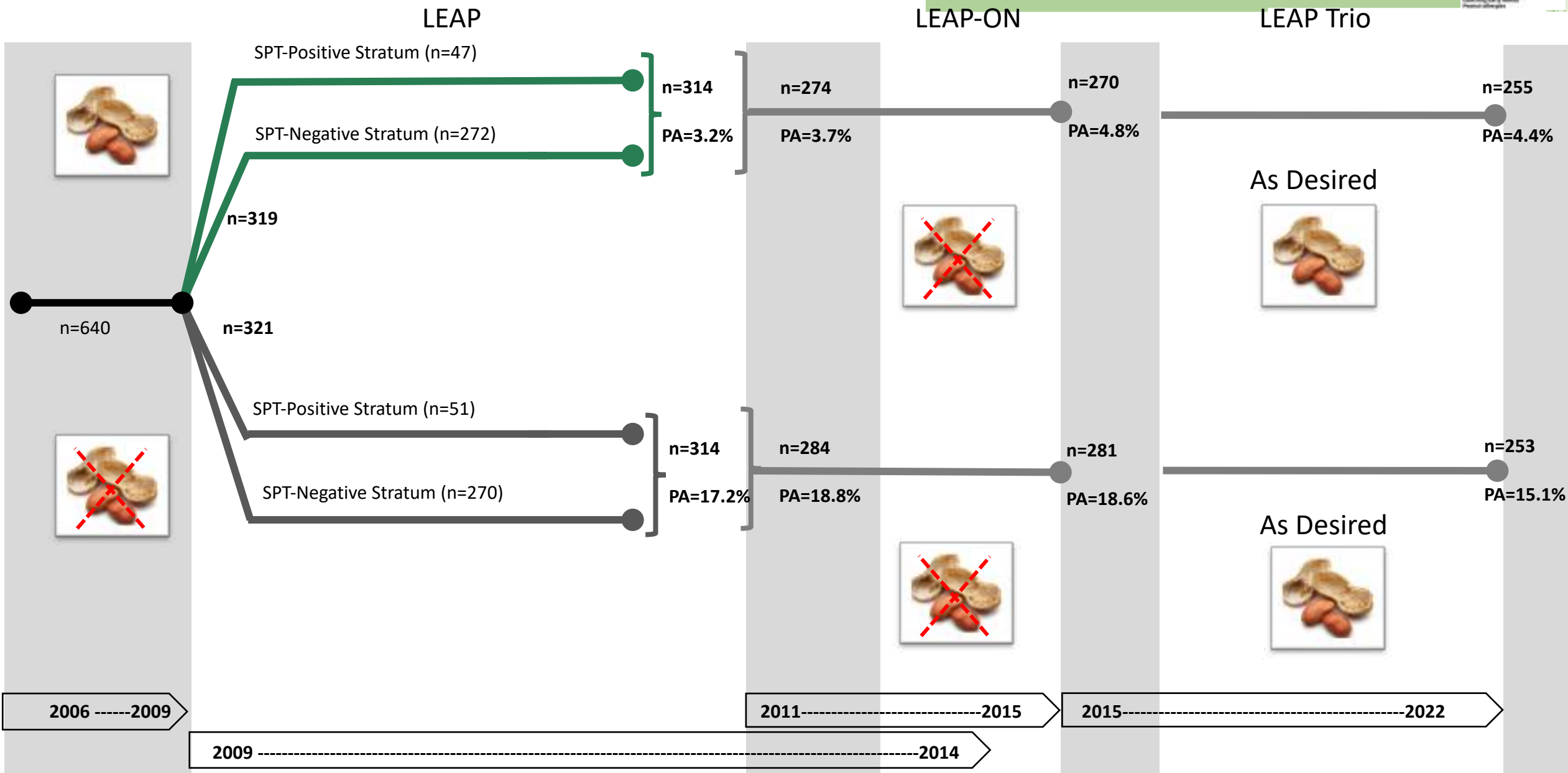
Eczema

- Strongest known risk factor for food allergies especially if it starts earlier in life and is more severe
- Damaged skin barrier allows absorption of food allergens through the skin leading to food sensitisation and allergy in the absence of pre-existing oral tolerance
- 1:5 infants with eczema allergic to peanut/egg/sesame compared to 1:25 without eczema (OR 6.2, 95% CI 4.9, 7.9, $p < 0.001$)

Environmental exposures

- Environmental allergens
- Urbanisation
- Climate change
- Warmer temperatures
- Prolonged hayfever seasons
- Air pollution
- Increased nitrogen dioxide
- Reduced exposure to microbes and infectious agents in early childhood
- Change in dietary habits
- Increased exposure to allergenic foods
- Changes in immune function
- Siblings
- Pets in the household

Learning Early About Peanut (LEAP) Studies

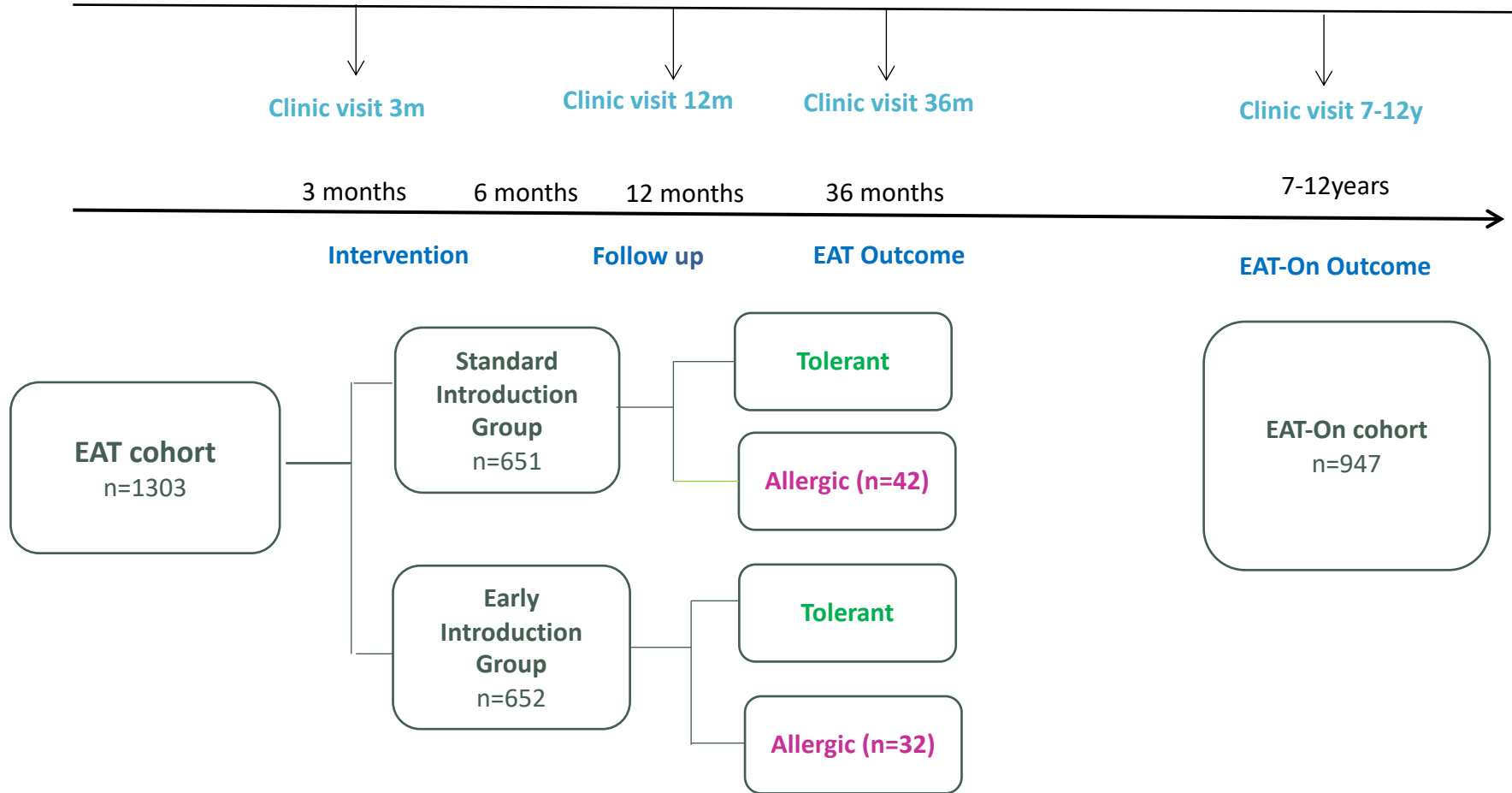


98.1% retention rate in the LEAP Study. 89% of families chose to continue in the LEAP-On Study. 98% completed the LEAP-On Study. 79.4% of original LEAP families completed LEAP Trio

The EAT & EAT-On Studies

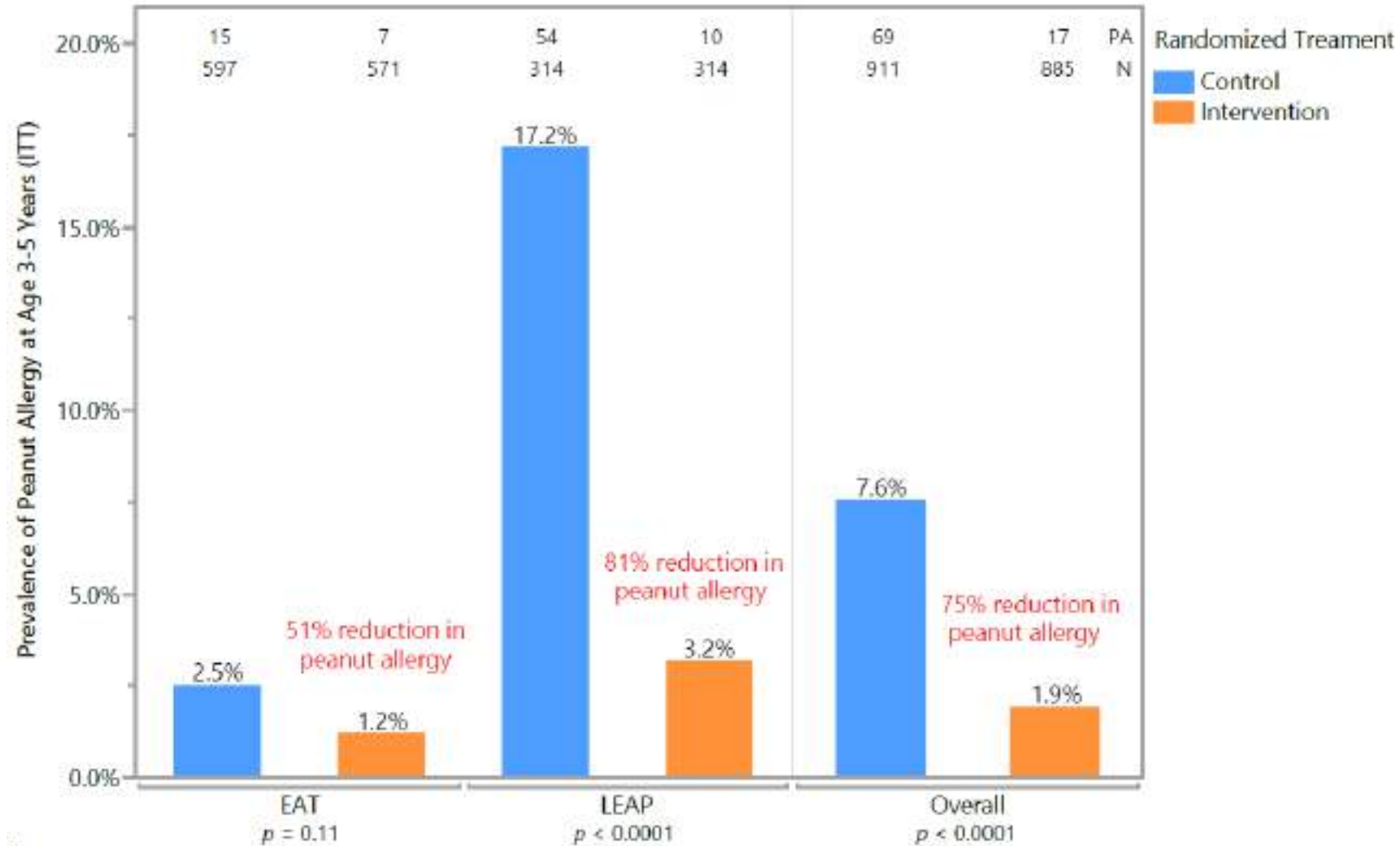


Antenatal recruitment and randomisation

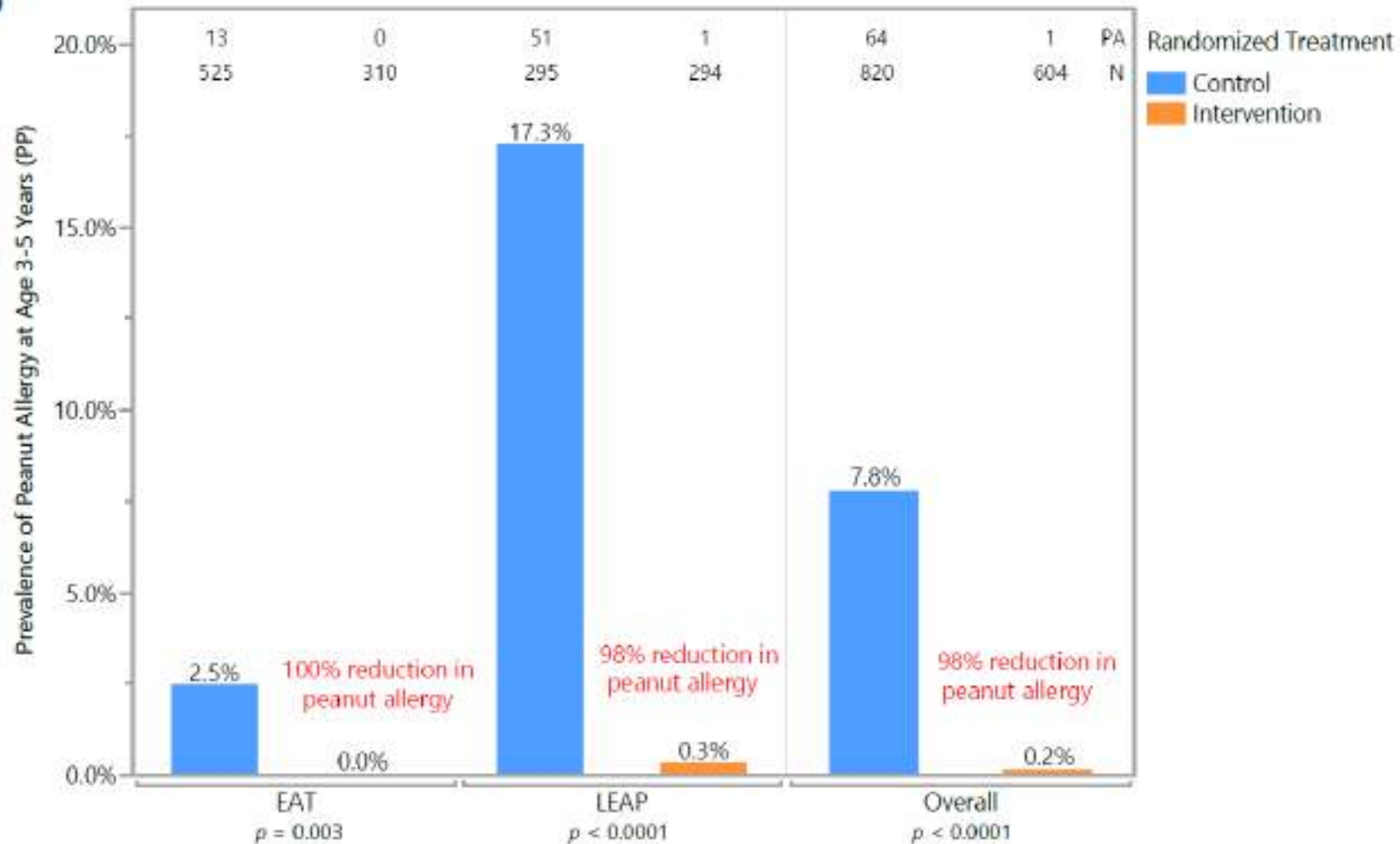


6 foods: Peanut Sesame Cow's milk Egg Wheat Fish

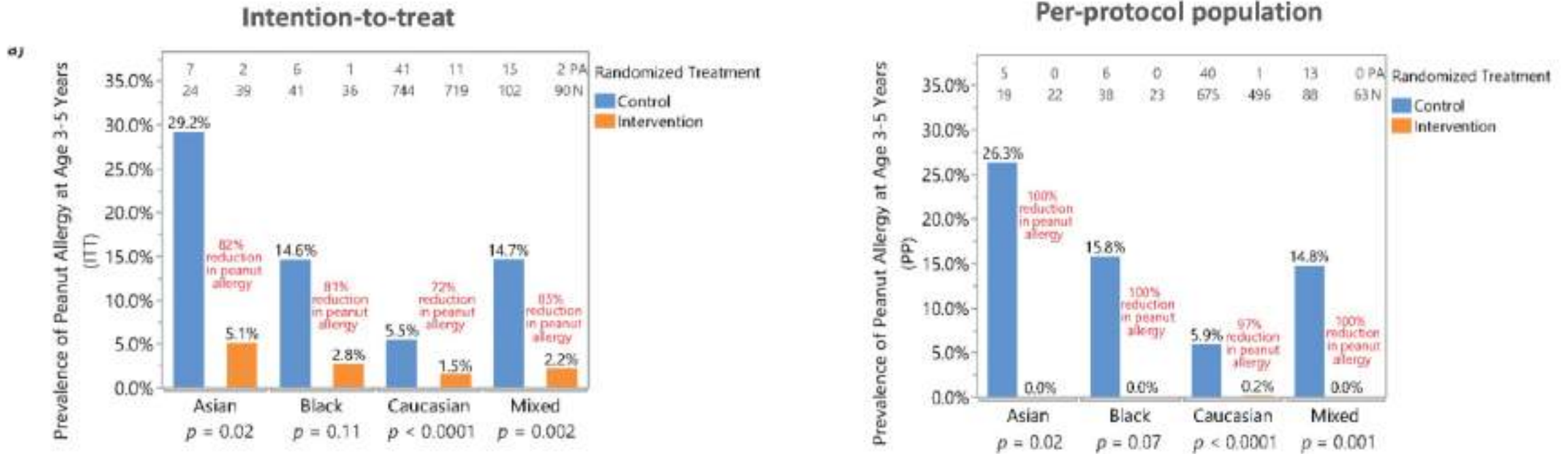
Intention to Treat Population (EAT and LEAP)

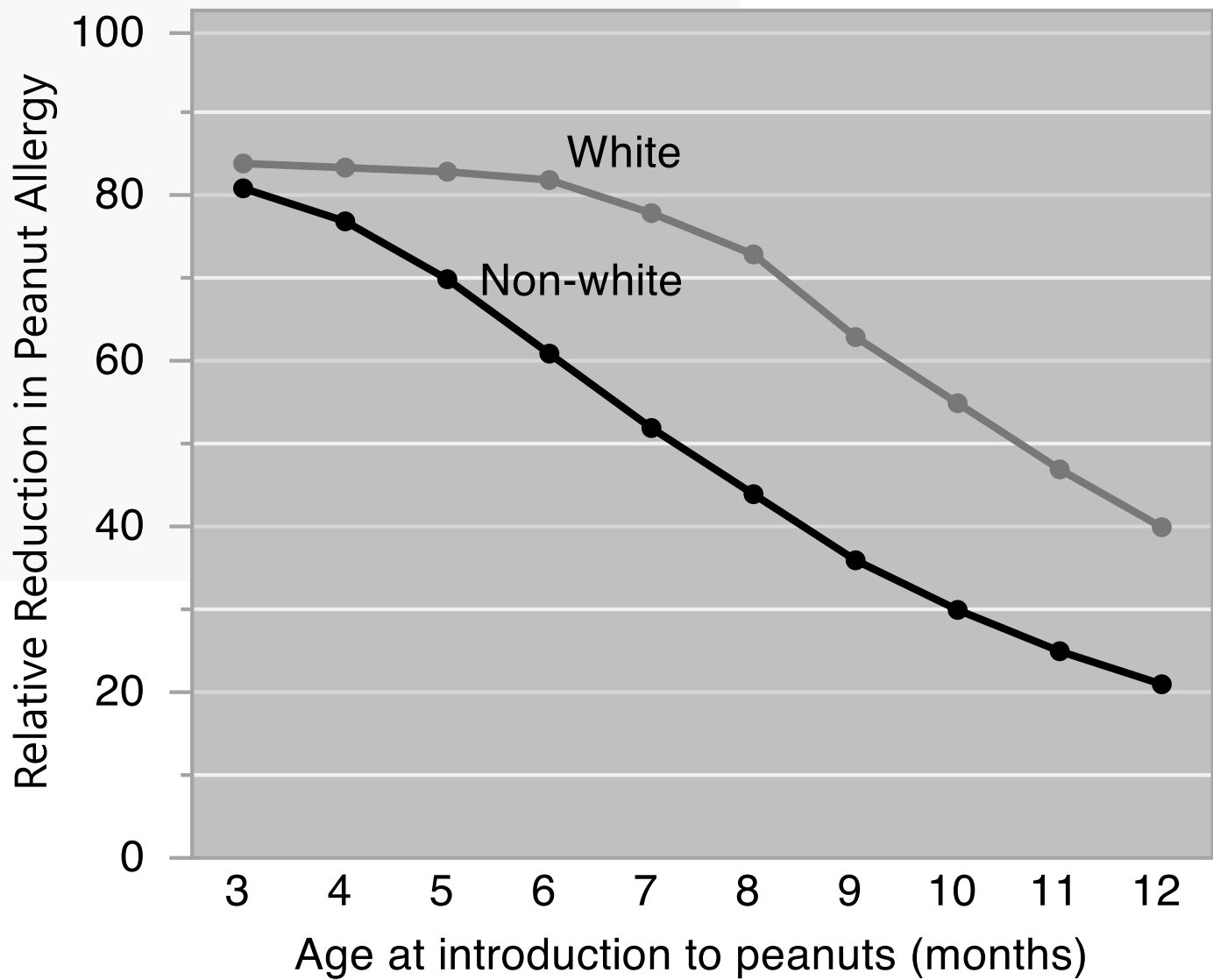


Per-Protocol Population (EAT and LEAP)



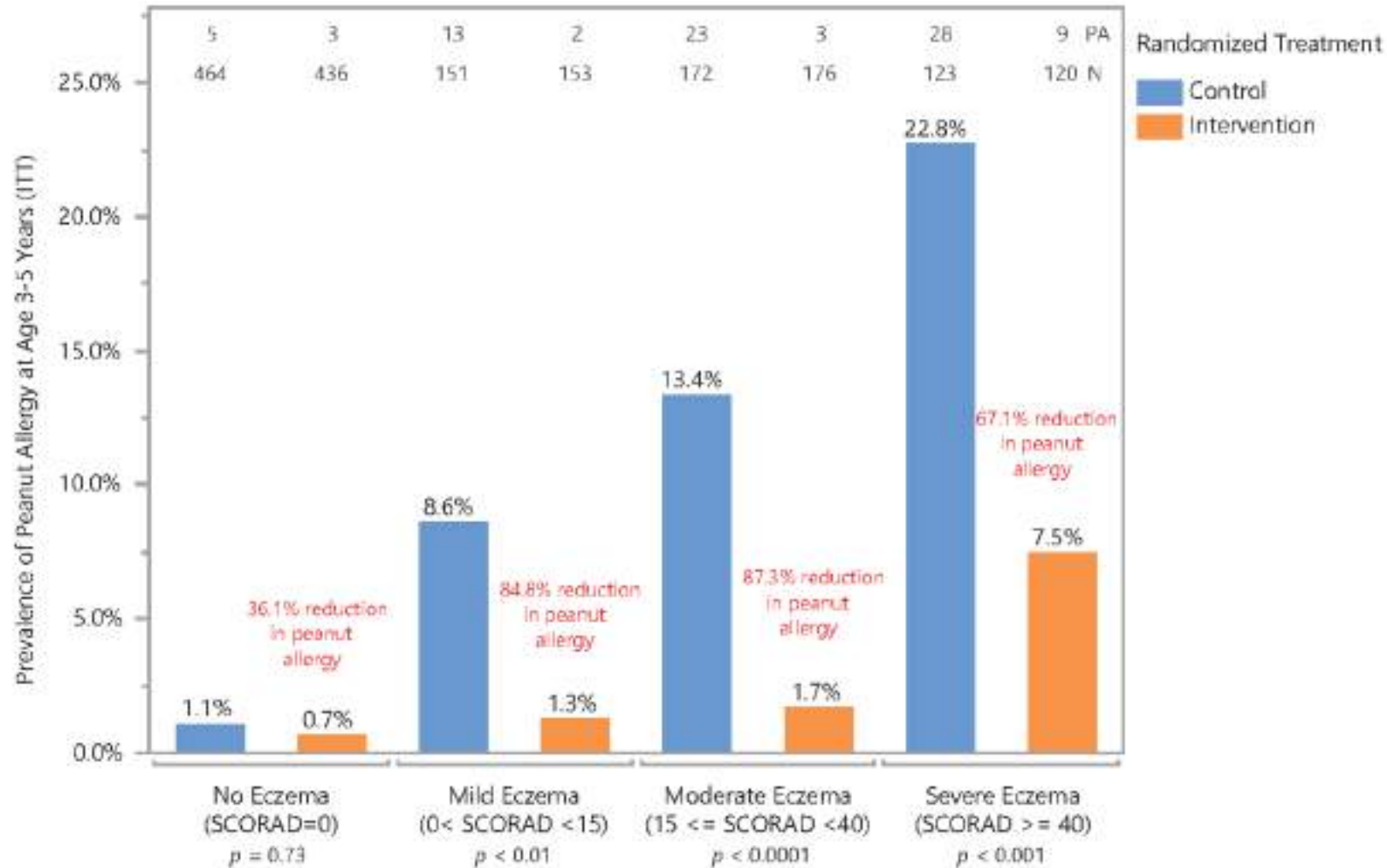
Peanut allergy prevalence in ethnicity groups



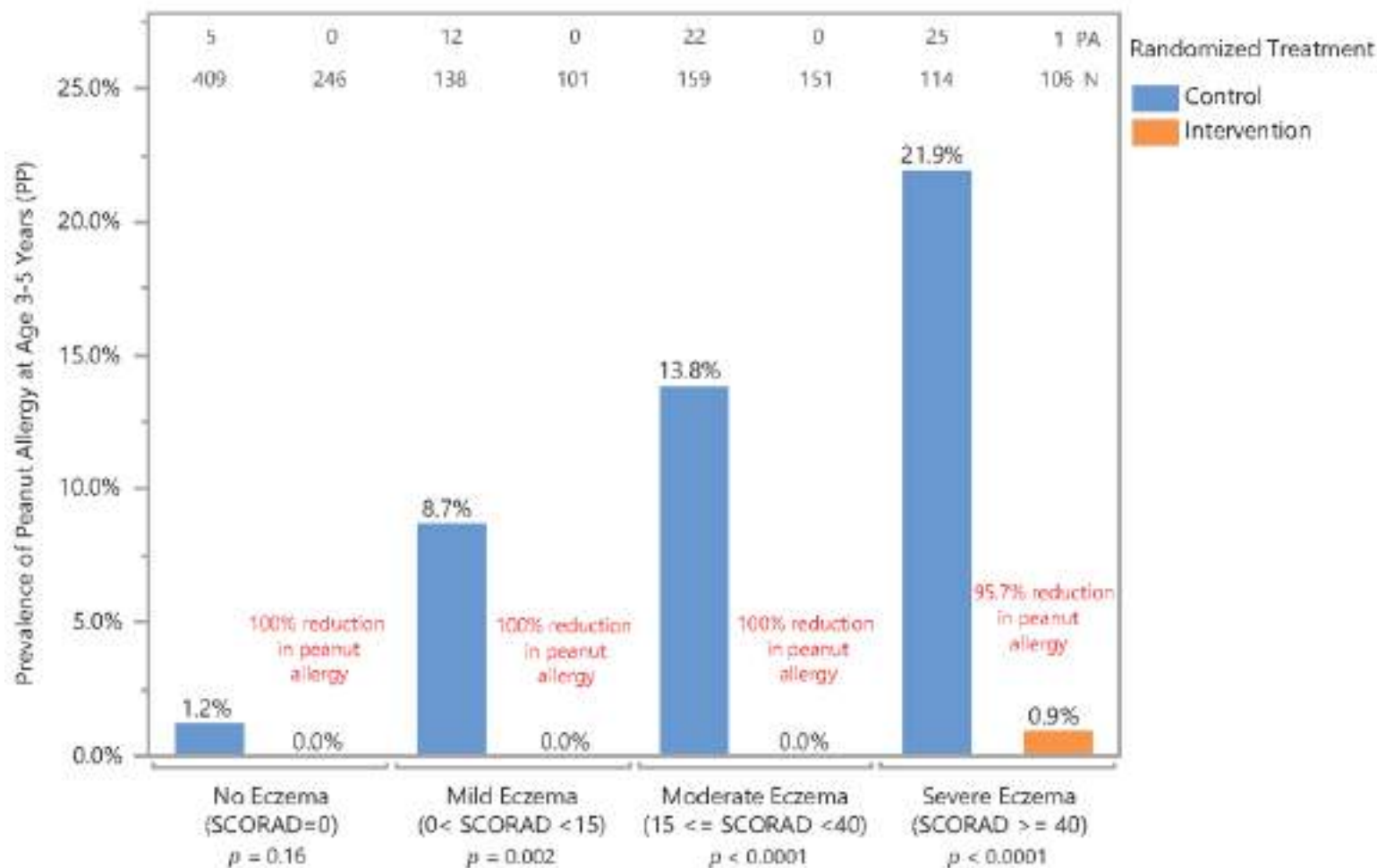


Unpublished data

ITT Population (EAT and LEAP) By Eczema Groups



PP Population (EAT and LEAP) By Eczema Groups

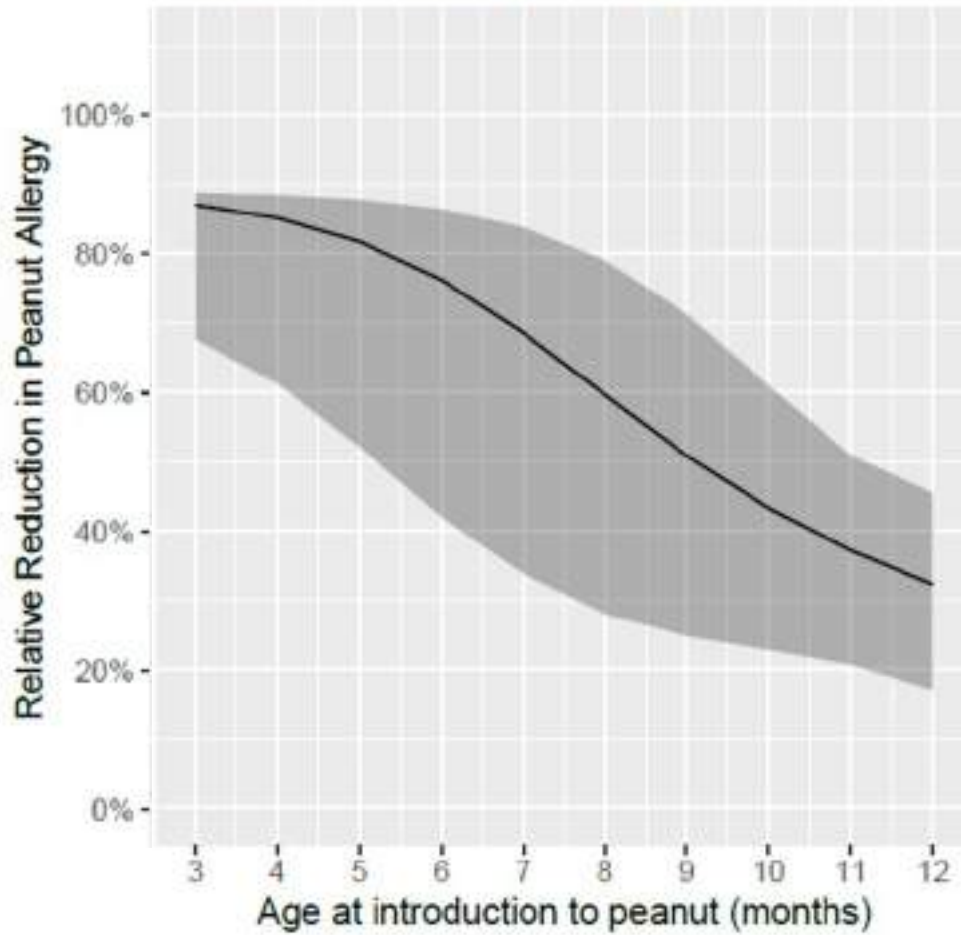


Reducing the burden of peanut allergy in different risk groups - EAT

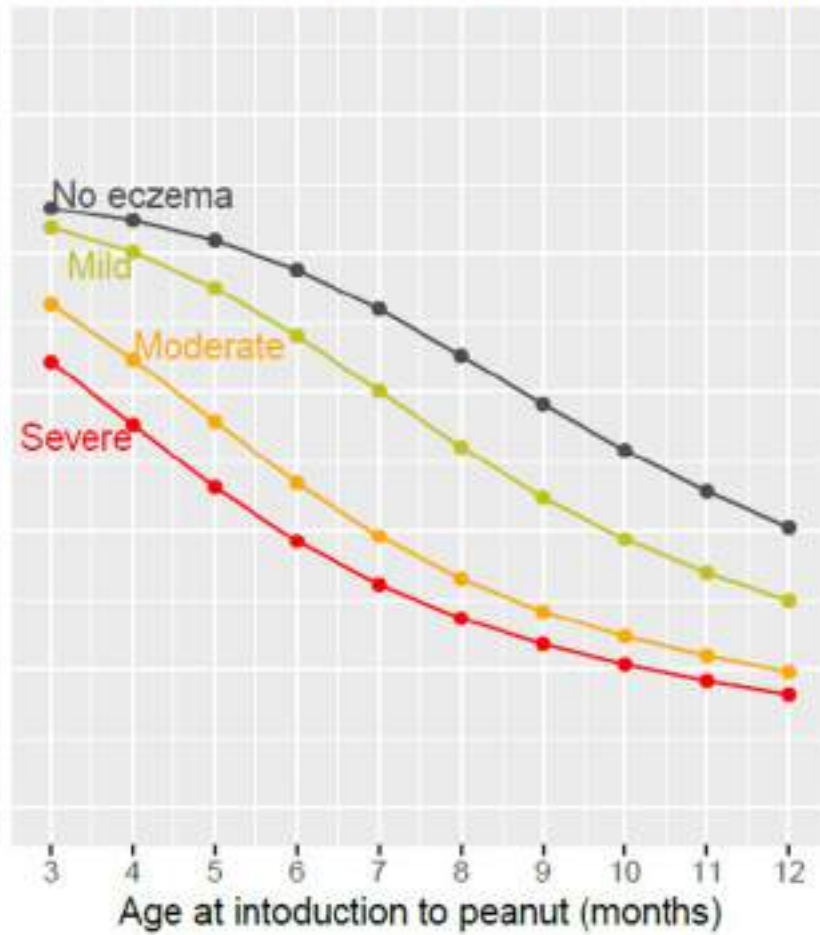


Eczema risk groups by SCORAD	Proportion of EAT avoidance group (n)	Peanut allergy at 36 months		Peanut allergy burden (proportion of total allergy in avoidance group by stratum)	Reduction of burden applying intervention in each group
		Avoidance group (observed data from EAT)	Early introduction group		
>40	0.5% (3)	33.3%	10.32%	6.64%	4.55%
15-40	4.9% (29)	13.8%	0.69%	25.58%	25.43%
1-14	18.5% (110)	4.6%	0.55%	33.61%	29.65%
0	76.2% (454)	1.1%	0.13%	33.17%	29.20%
All	100% (596)	2.5%	0.29%		88.80%

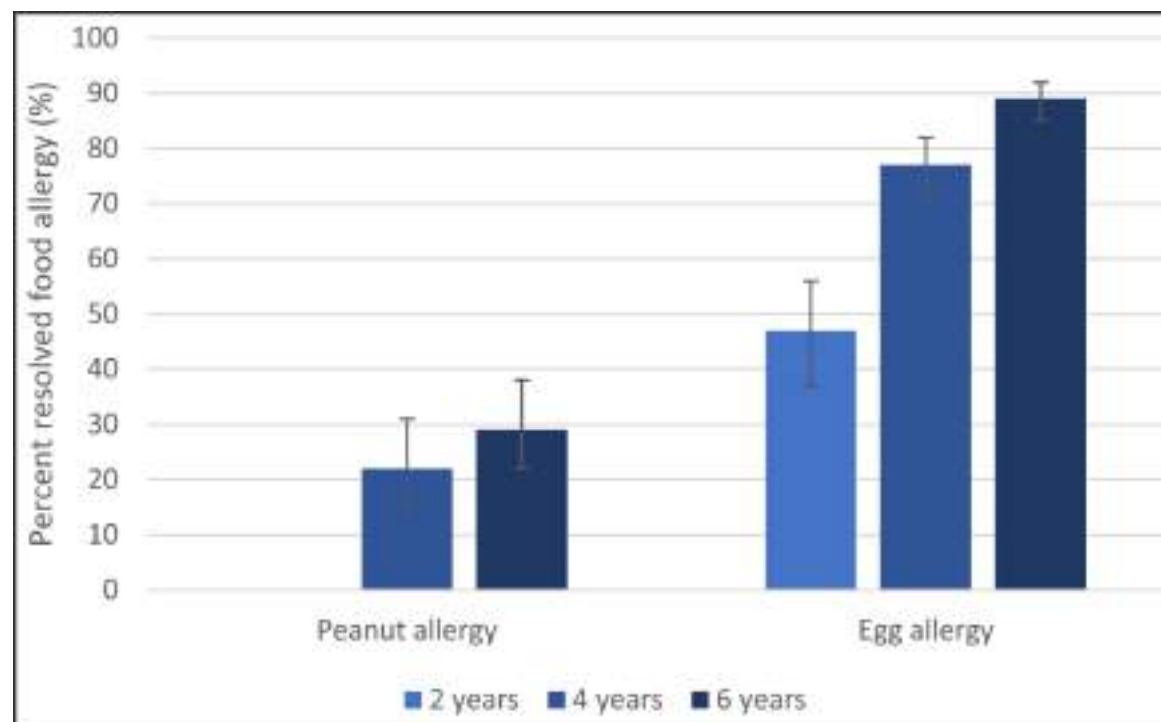
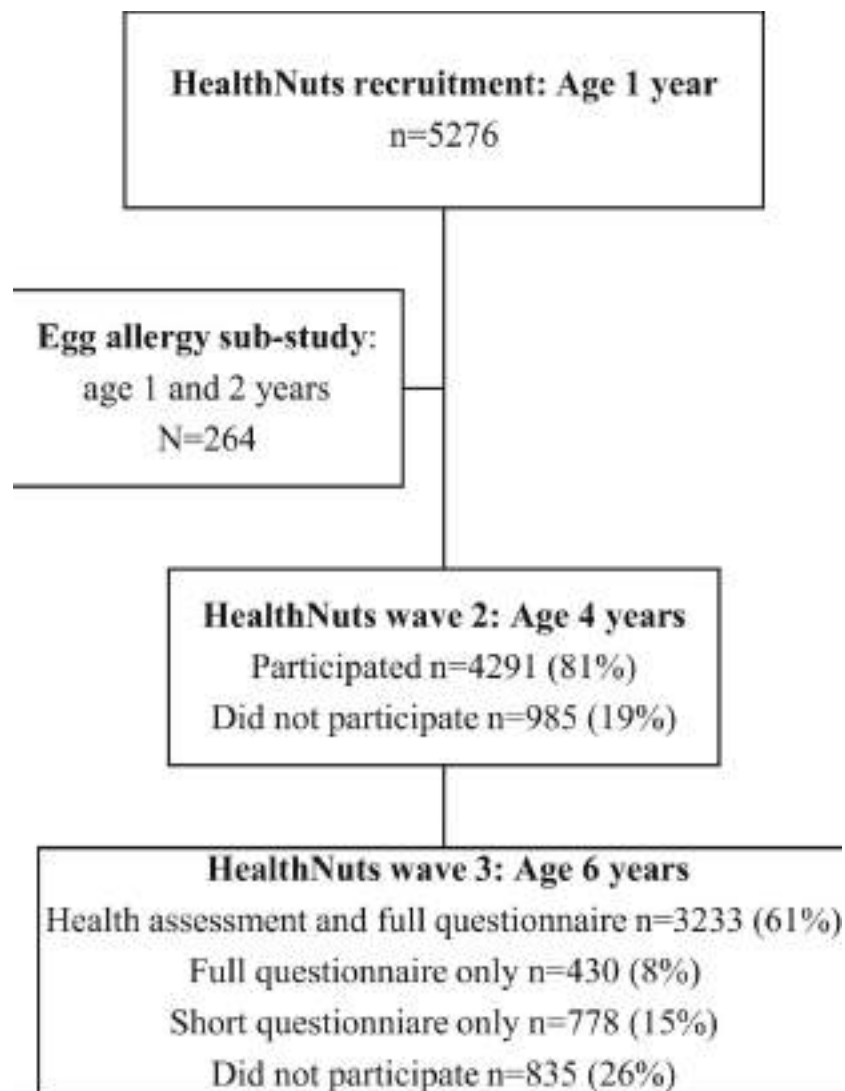
Population Modeled ITT Relative Reduction in Peanut Allergy



Population Modeled Relative Reduction in peanut Allergy by Eczema Severity Groups

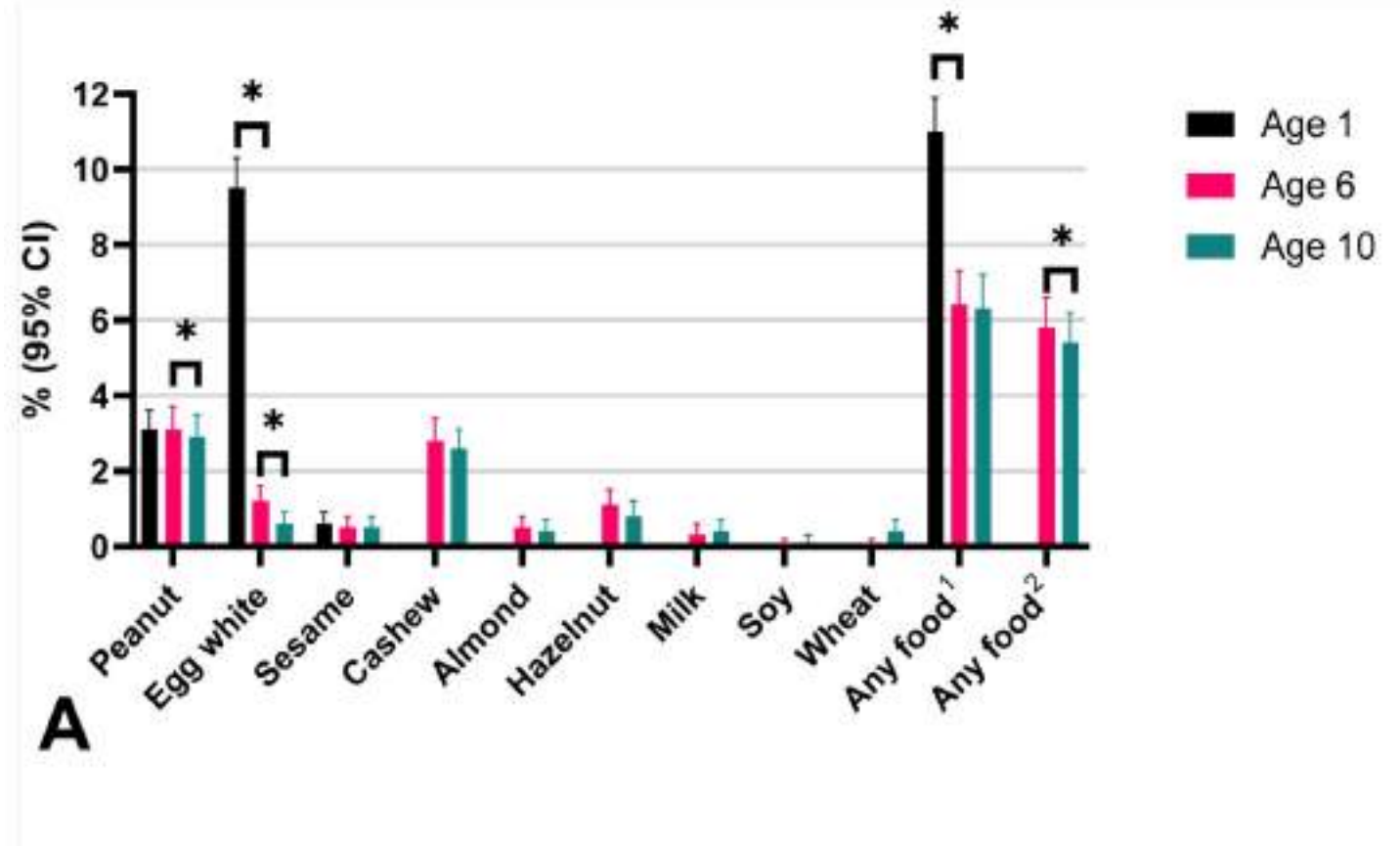


HEALTHNUTS study



HealthNuts longitudinal data

- Food allergy prevalence rates:
 - 6.4% in 6-year olds
 - 6.3% in 10-year olds
- 45% had persistence of challenge-confirmed food allergy at age 10-years



Feasibility of early food allergen introduction



Can we get all these food allergens in at high enough doses to prevent food allergy?



Professional Body	Publication Year	Recommendations
American Academy of Pediatrics (AAP)	2019	<p>High risk infants (severe eczema and/or egg allergy) – introduce peanut 4-6m</p> <p>Infants (mild-mod eczema) – introduce peanut around 6m</p> <p>Infants (ow risk) no eczema or food allergy – peanut freely when parents want</p>
Asia Pacific Association of Pediatric Allergy, Respiratory & Immunology APAPARI	2017	<p>Healthy infants – introduce complementary foods at 6m of age</p> <p>At risk infants (FH atopy) – no delay in introduction foods (sensible manner)</p> <p>High risk infants with eczema – Allergy test to egg (and peanut if country has high peanut allergy prevalence). Supervised OFC in sensitized infants followed by introduction into infant’s regular diet if OFC negative. Introduction all allergenic foods should not be delayed. Aggressive control of eczema</p>
Australian Society of Clinical Immunology and Allergy (ASCIA)	2020	<p>6months (not before 4m) start to introduce solids whilst continuing breast feeding</p> <p>All infants should be given allergenic solids (peanut butter, cooked egg, dairy, wheat) in 1st year of life. Includes infants at high risk of allergy</p>

Professional Body	Publication Year	Recommendations
Canadian Paediatric Society (CPS)	2021	<p>High risk – encourage introduction allergenic foods (cooked egg, peanut) early at around 6m but not before 4m at home.</p> <p>Low risk infants – allergenic foods can also be introduced at around 6m</p> <p>Once allergenic foods introduced make sure ongoing ingestion of age-appropriate serving sizes is regular to maintain tolerance (ie few times a week)</p>
European Academy of Allergy and Clinical Immunology (EAACI)	2020	<p>Introduce well cooked egg but not raw/unpasteurized egg into diet as apart of complementary feeding to prevent egg allergy</p> <p>In populations high prevalence of peanut allergy, introduce peanut in an age-appropriate form as a part of complementary feeding</p> <p>Avoid supplementing with cow’s milk formula in breast fed infants in first week of life to prevent cow’s milk allergy in infants and young children (low quality evidence)</p>

Professional Body	Publication Year	Recommendations
German Society for Allergology and Clinical Immunology (DGAKI)	2014	<p>Introduce solid foods to infants over 4m of age (should not be delayed as means of allergy prevention)</p> <p>No evidence to suggest dietary restriction in the form of avoiding potent food allergens in 1st year of life (Not recommended)</p> <p>No reliable evidence to introduce potential food allergens during first 4m of life has preventive effect</p> <p>Child's consumption of fish in 1st year of life has protective effect against development of atopic diseases. Fish should be introduced in solid foods</p>
National Institute of Allergy and Infectious Diseases (NIAID)	2017	<p>Infants with severe eczema, egg allergy or both – strongly consider sIgE and/or SPT and if necessary OFC and based on test results introduce peanut containing foods as early as 4-6m to reduce risk of peanut allergy</p> <p>Infants with mild to moderate eczema – introduce age-appropriate peanut containing food around 6m</p> <p>For infants without eczema or food allergy – introduce age-appropriate peanut containing foods freely together with other solids (family preference)</p>

Professional Body	Publication Year	Recommendations
UK SACN (Scientific Advisory Committee on Nutrition)	2018	<p>For healthy babies: exclusively breastfeed for 6m</p> <p>From 6m (not before 4m) introduce complementary solids and include egg and peanut before 1 year of age</p> <p>Research shows higher risk of developing food allergy infants may benefit from early introduction (from 4m) of solids including allergens like egg and peanut but only introduce once baby is eating solid foods</p>
Latin American Society of Allergy and Immunology	2020	<p>No specific food allergy guidelines</p> <p>Atopic dermatitis guidelines – introduce all common allergenic foods (peanut, egg) at 4-6 months of age, rather than delaying them</p> <p>*High risk infants with severe atopic dermatitis or known food allergy should seek medical consultation to assess for pre-existing sensitization</p>

Barriers to adherence

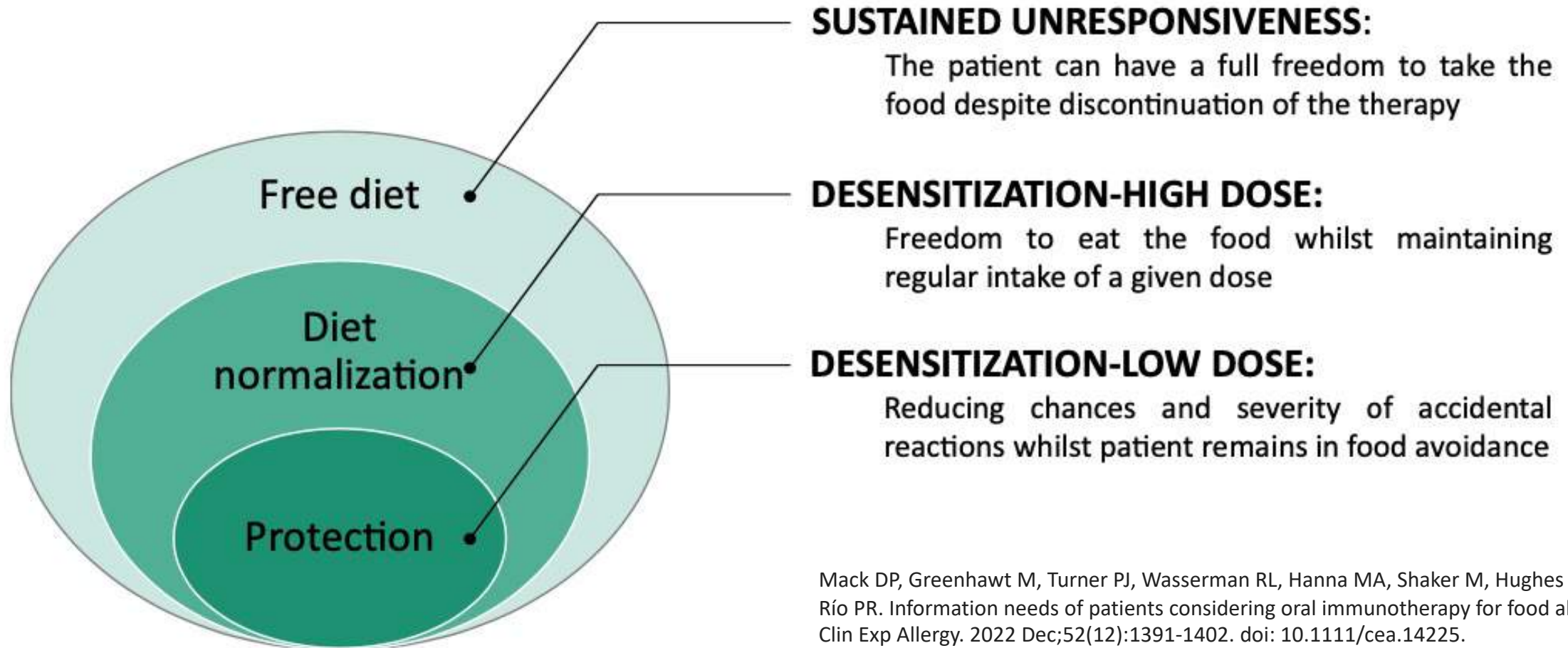
- Patient education
- Access to health services – racial and ethnic disparities
- Child cooperation
- Parental fears/beliefs
- Practical difficulties of adhering to complicated or long-term treatment plans

- EAT study – non-White ethnicity, increased maternal age, infants with feeding difficulties, early onset eczema all associated with decreased protocol adherence



**And...what about for the children with
confirmed allergy diagnosis?**

Expectations for oral food immunotherapy



Mack DP, Greenhawt M, Turner PJ, Wasserman RL, Hanna MA, Shaker M, Hughes SW, Del Río PR. Information needs of patients considering oral immunotherapy for food allergy. Clin Exp Allergy. 2022 Dec;52(12):1391-1402. doi: 10.1111/cea.14225.



ORIGINAL ARTICLE



AR101 Oral Immunotherapy for Peanut Allergy

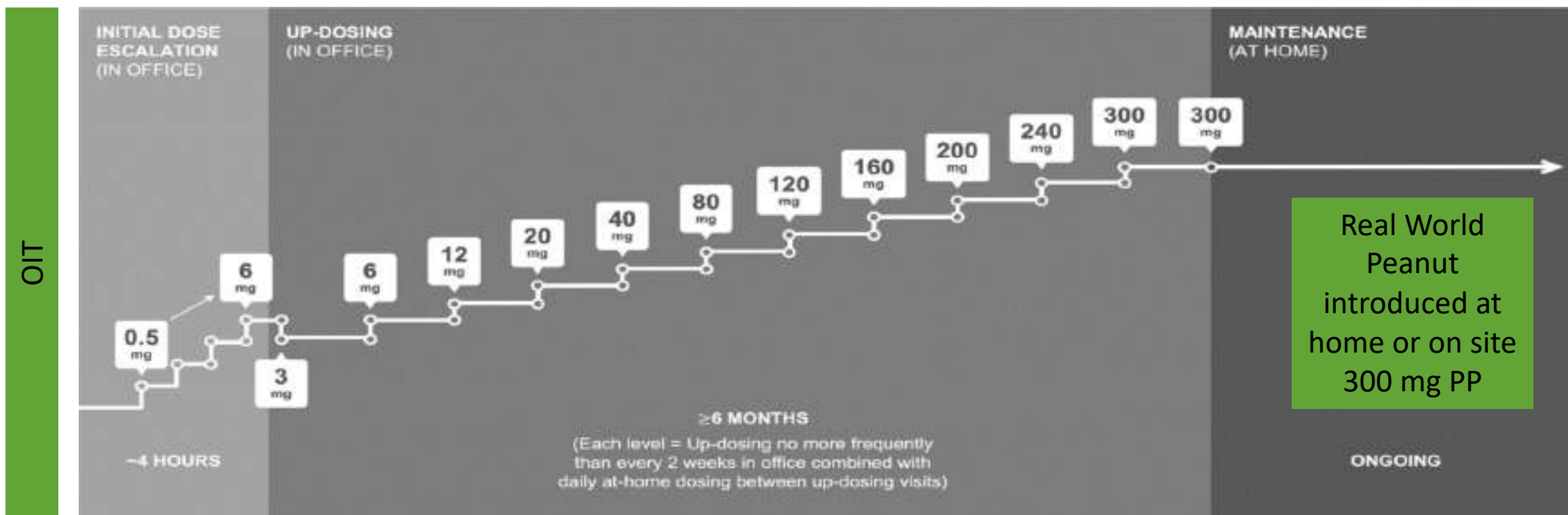
Author: The PALISADE Group of Clinical Investigators* [Author Info & Affiliations](#)

Published November 18, 2018 | N Engl J Med 2018;379:1991-2001 | DOI: 10.1056/NEJMoa1812856

VOL. 379 NO. 21 | Copyright © 2018

67.2% in active group able to ingest single dose of ≥ 600 mg peanut protein during DBPCFC with no more than mild symptoms compared to 4% in placebo group ($p < 0.001$)

PEANUT ORAL IMMUNOTHERAPY PROCESS



Adapted from: Portnoy, J., Ciaccio, C.E., Beausoleil, J. *et al.* Eight tips for the implementation of the first licenced peanut allergy oral immunotherapy into clinical practice. *Allergy Asthma Clin Immunol* **18**, 37 (2022). <https://doi.org/10.1186/s13223-022-00671-5>

Special thanks to Dr Andreina Marques-Mejias for sharing this slide

ORIGINAL ARTICLE

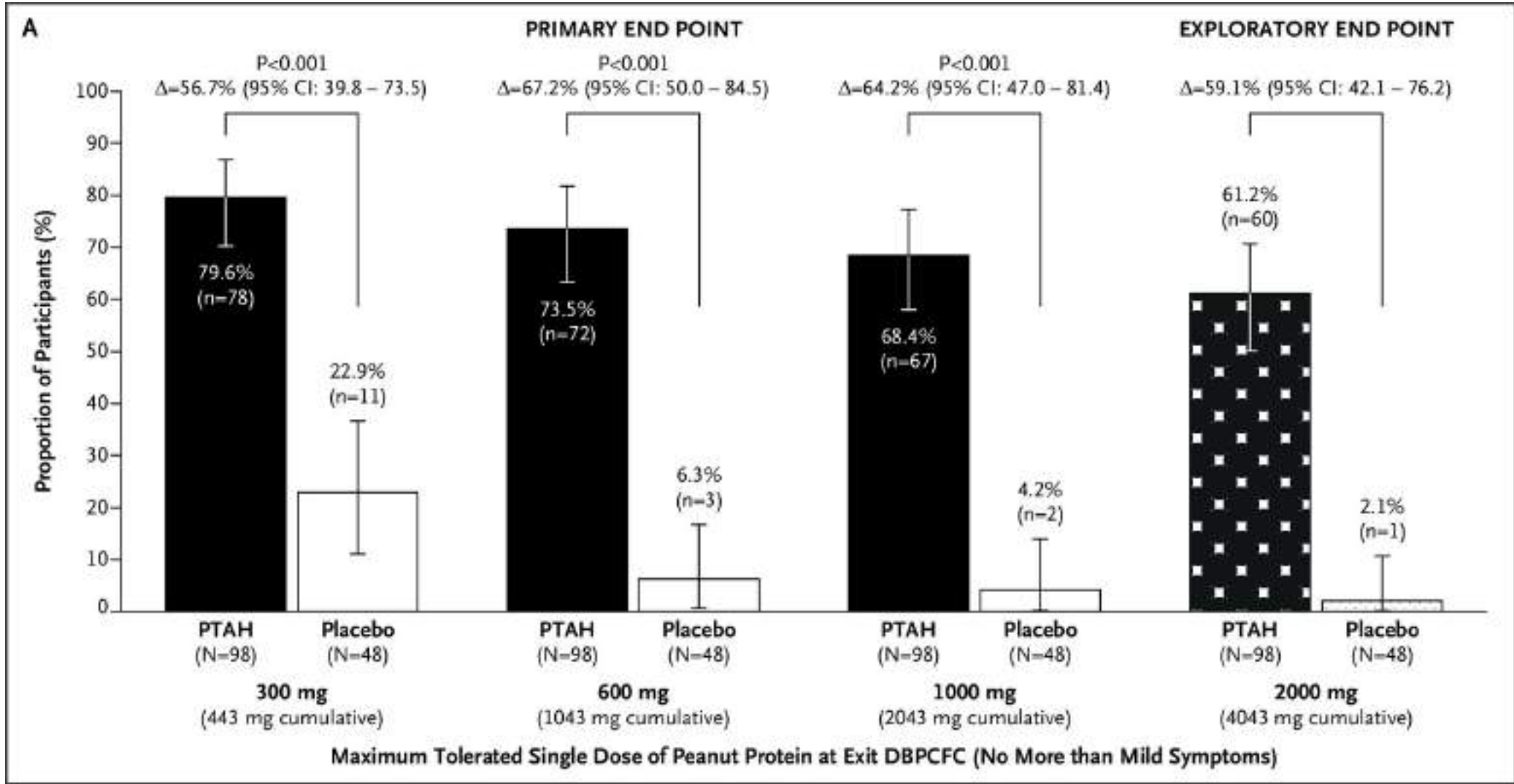


Oral Immunotherapy for Peanut Allergy in Children 1 to Less Than 4 Years of Age

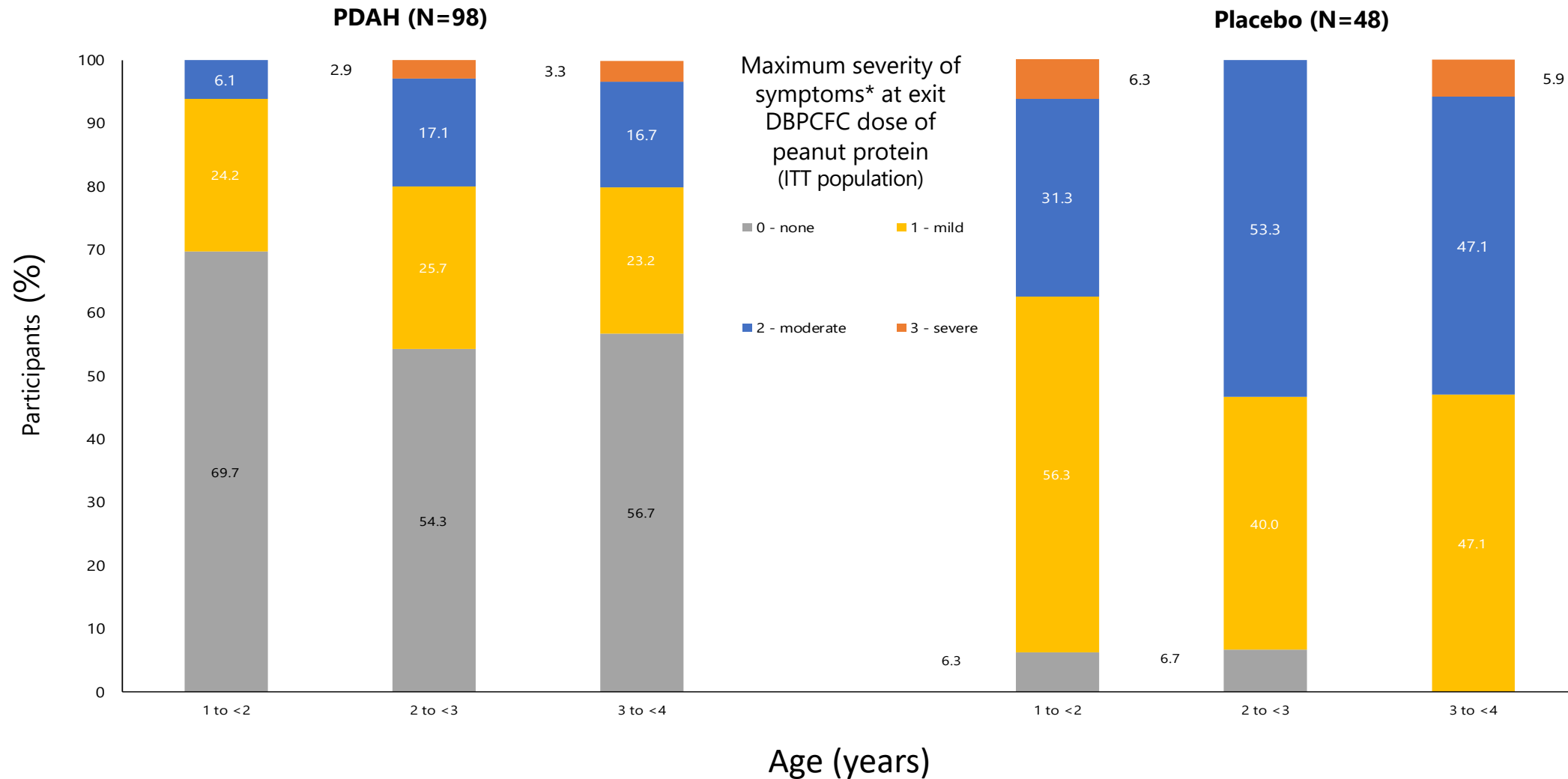
Authors: George Du Toit, M.B., B.Ch., Kari R. Brown, M.D., Andrea Vereda, M.D., Ph.D., Anne-Marie Irani, M.D., Stephen Tilles, M.D., Anoshie Ratnayake, M.D., Stacie M. Jones, M.D., and Brian P. Vickery, M.D., for POSEIDON Study Group* [Author Info & Affiliations](#)

Published October 23, 2023 | NEJM Evid 2023;2(11) | DOI: 10.1056/EVIDoa2300145 | [VOL. 2 NO. 11](#)

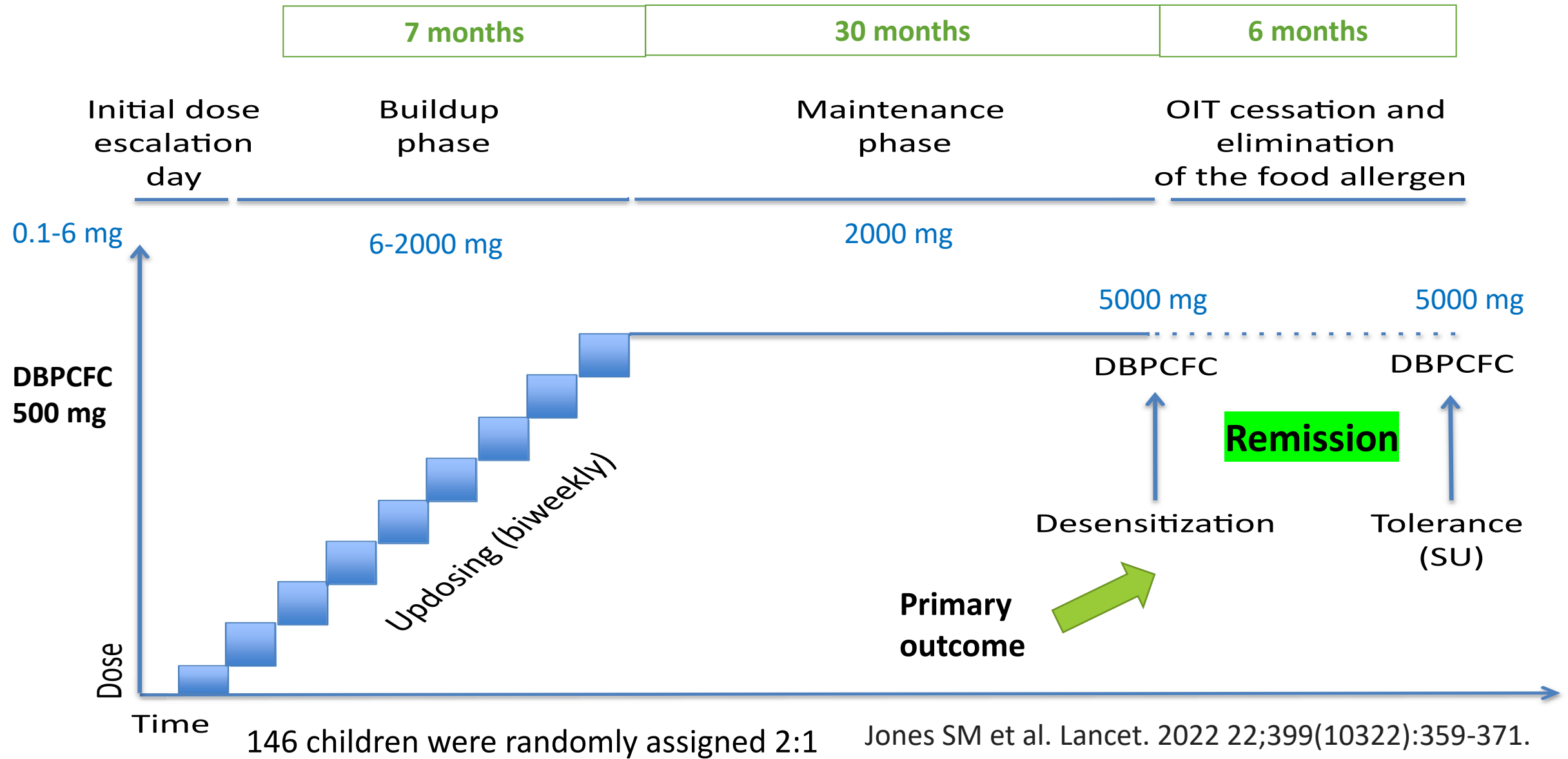
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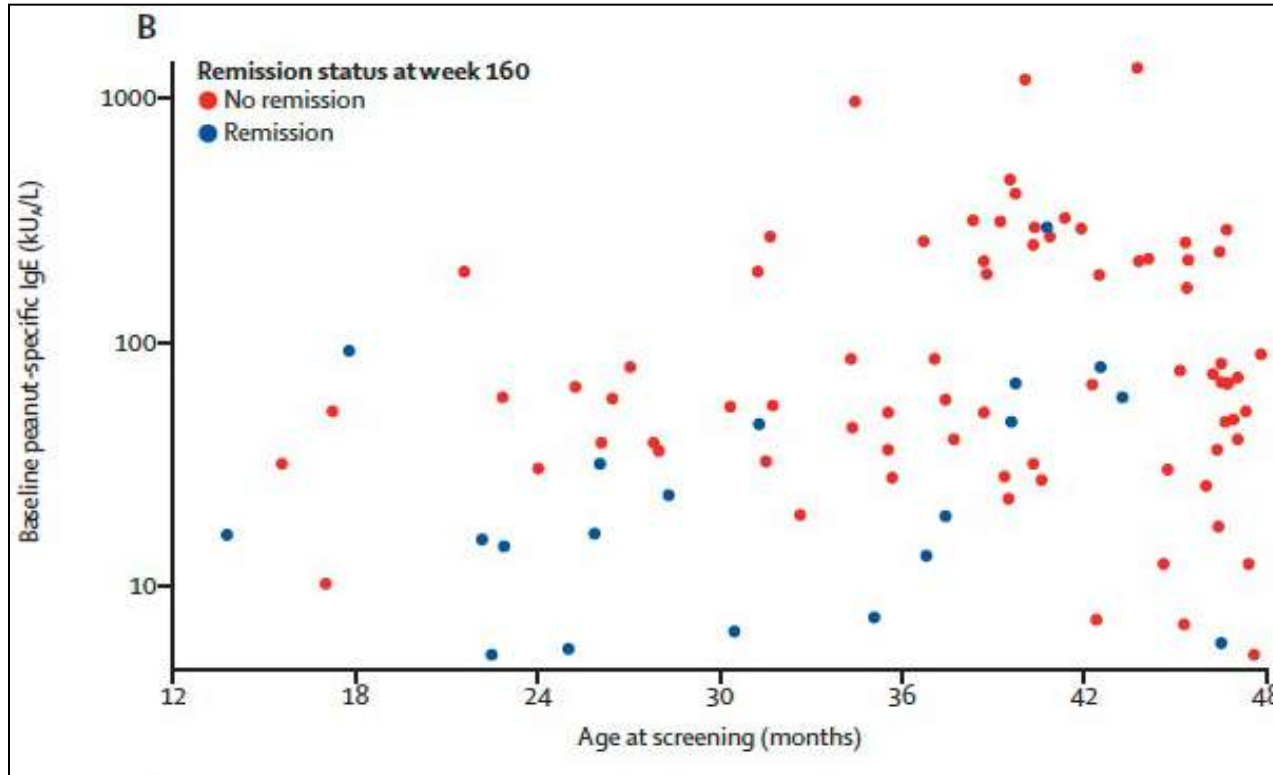
Post hoc analyses suggest potential advantages in the youngest, <2-year age group (up to 1000 mg)



IMPACT study



INCREASED probability of remission associated with younger age and lower sIgE to peanut



Blue: probability of remission > 50%
Red: probability of remission < 50%.

- For every 10-fold increase in baseline peanut-specific IgE, the odds of remission ↓ 88%
- For every month increase in age at screening, the odds of remission ↓ 7%

Per protocol

5/7 (71%)

12.0–23.9 months

7/20 (35%)

24.0–35.9 months

8/43 (19%)

36.0–47.9 months

Jones SM et al. (ITN
IMPACT trial) Lancet.
2022
22;399(10322):359-
371.

Improved safety in doing preschool peanut OIT

- Systematic review of peanut OIT in children (average 9 years old):
 - 16.5% had a severe allergic reaction

	PALISADE (4-17 years)	POSEIDON (1-3 years)
Treatment related systemic allergic reactions	14.2%	2%
Severe allergic reactions	4.3%	0%

- Real-world Canadian preschool peanut OIT data (average 23 months of age):
 - 0.4% had a severe allergic reaction

Epicutaneous desensitisation

- Patch impregnated with allergen onto *intact* skin
 - Peanut
 - Cow's milk
 - Egg
- Patch well tolerated in peanut allergic adults and children:
 - Mild cutaneous symptoms
 - No systemic allergic reactions
 - No worsening asthma control



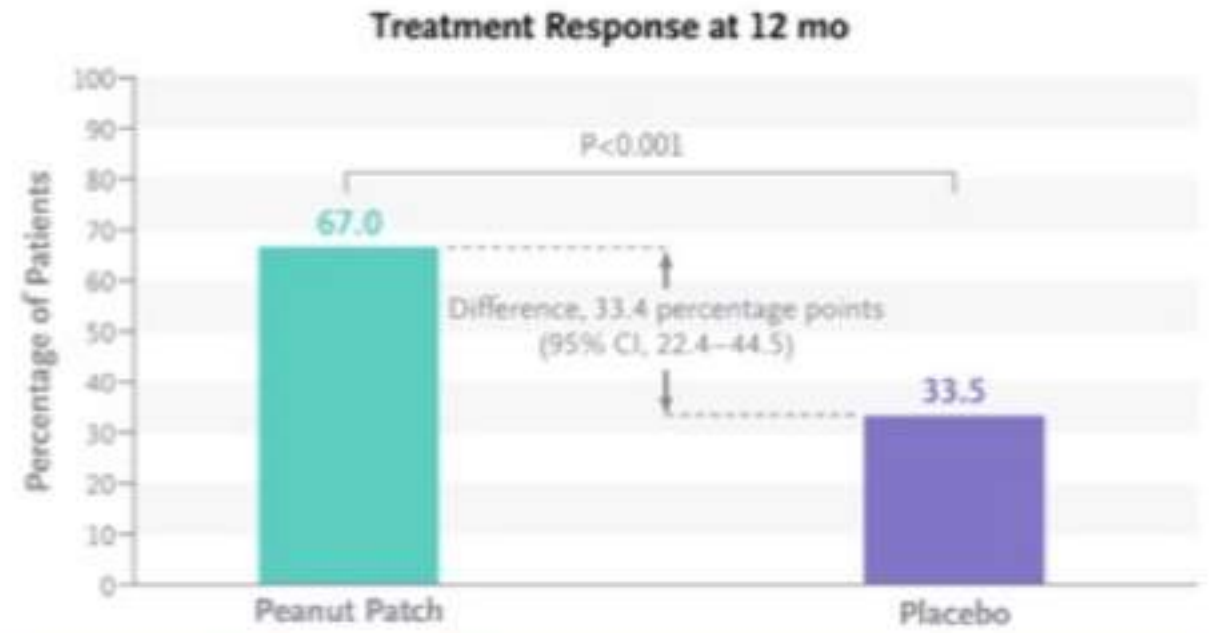
PEPITES RCT

- 356 children, age 4-11y
- Active – 12m peanut patch therapy (daily dose of 250mcg peanut protein)
- Key finding:
 - Responder rate: 35.3% vs 13.6% (active vs placebo)



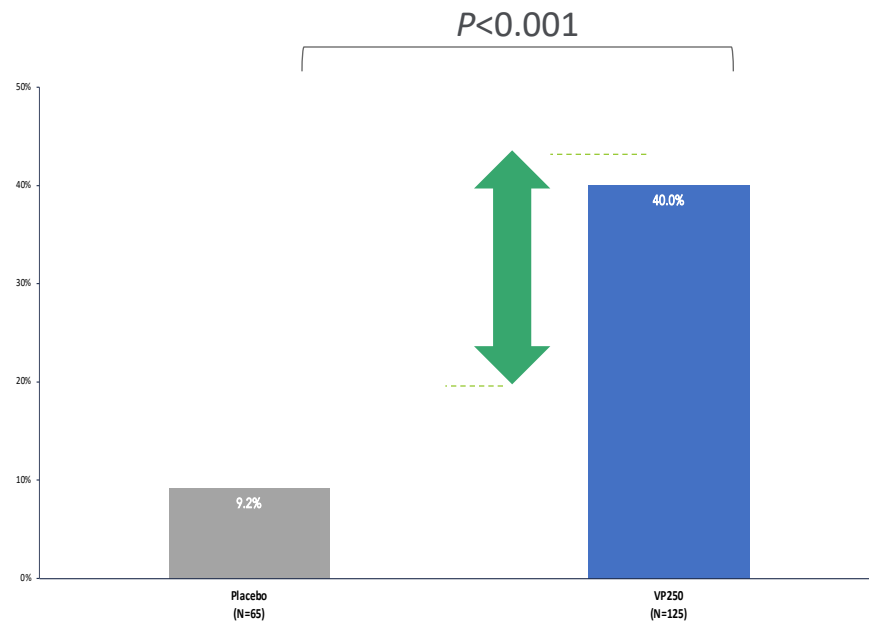
EPITOPE RCT

- 362 patients, age 1-3y
- Active – 12m peanut patch therapy (250mcg peanut protein)

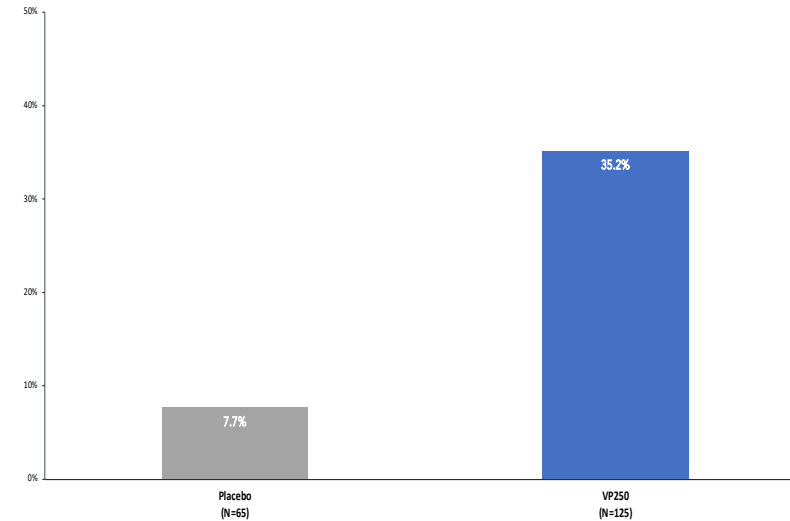


Post-Hoc Analysis of PEPITES Data Supports Concept That Greater Gains in Desensitization May be Achieved in Younger vs Older Children¹

Treatment Responders
Children Ages 4-7 Years



ED \geq 1,000 mg at Month 12
Children Ages 4-7 Years



- Greater treatment effect evident in **subjects aged 4–7 years ($\Delta = 30.8\%$) versus subjects aged 8–11 years ($\Delta = 11.2\%$; 95% CI: -3.4–23.4)** who received Viaskin Peanut 250 μ g (VP250) versus placebo
- The safety profile in the subgroup of children aged 4–7 years was consistent with that observed in the overall 4 to 11-year-old PEPITES population

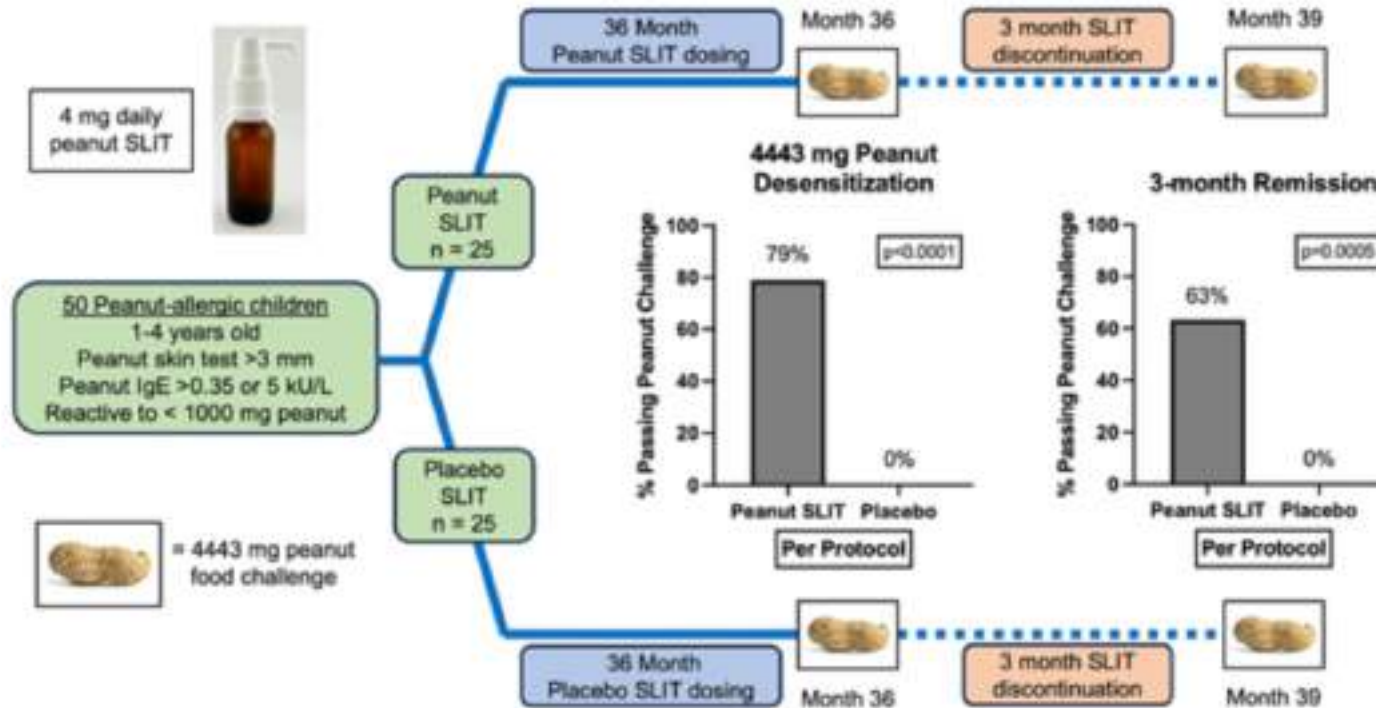
CI=Confidence interval.

1. Efficacy of Epicutaneous Immunotherapy with Viaskin™ Peanut for 4–7-Year-Old Peanut-Allergic Children in a Phase 3 Clinical Trial (PEPITES). David Fleischer, MD Presented at Canadian Society for Allergy and Clinical Immunology Annual Meeting, September 2022.

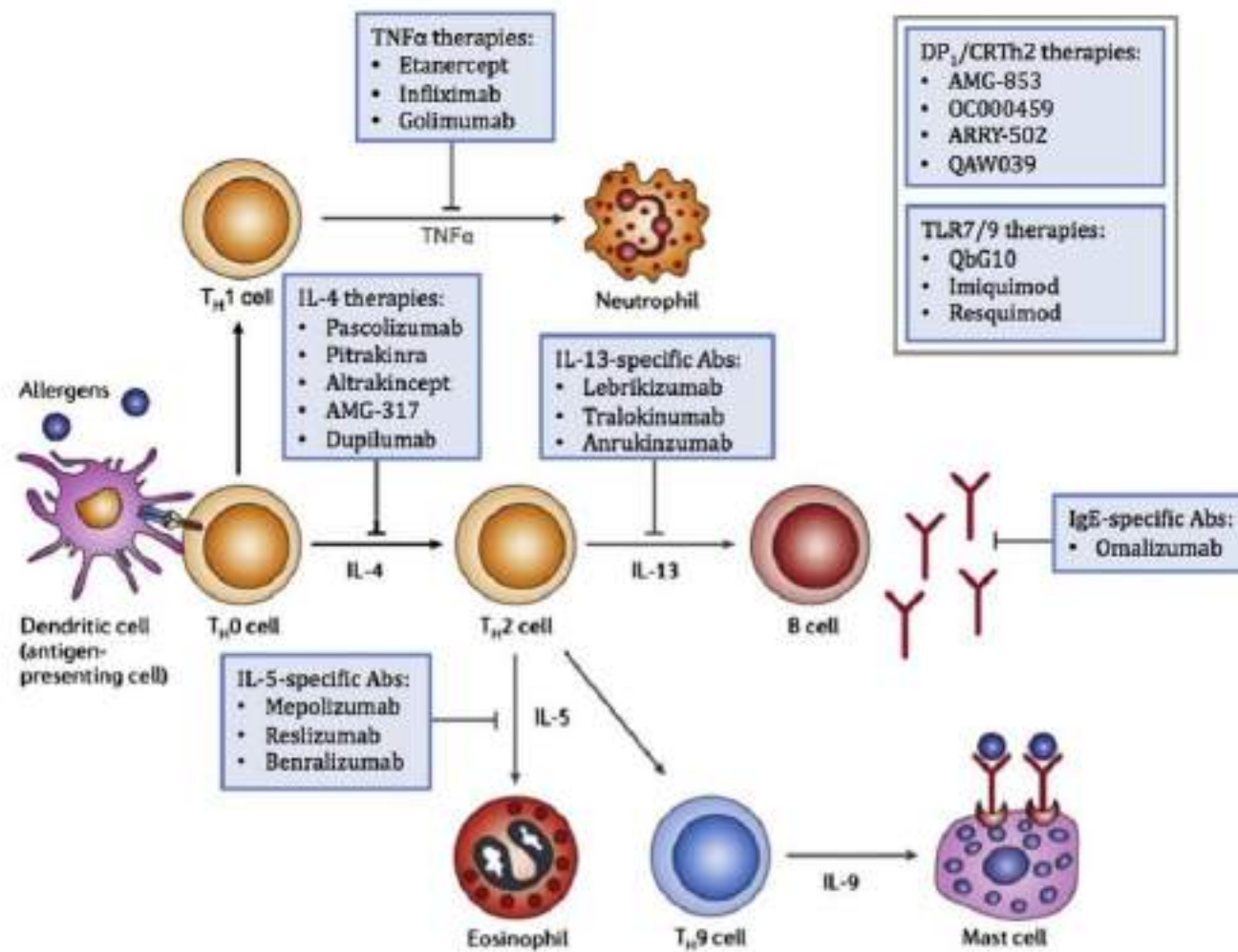
Sublingual peanut immunotherapy





Desensitization and Remission after Peanut Sublingual Immunotherapy in 1-4 year-old Peanut Allergic Children: a Randomized, Placebo-Controlled Trial



Biologic treatments



Omalizumab for the Treatment of Multiple Food Allergies

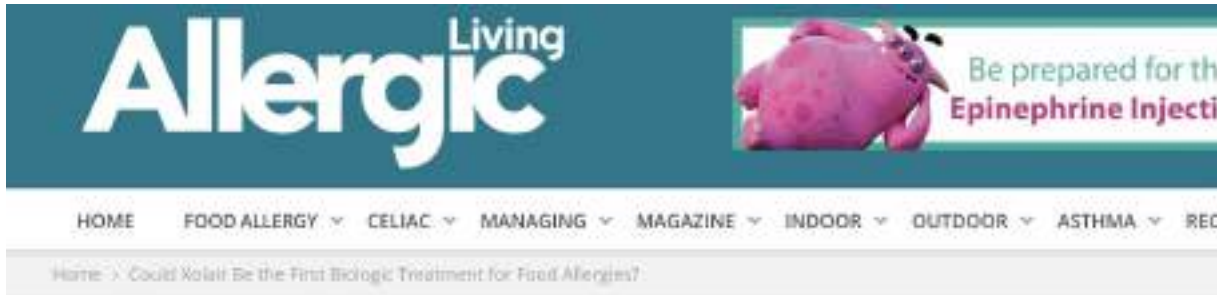
Authors: Robert A. Wood, M.D., Alkis Togias, M.D., Scott H. Sicherer, M.D., Wayne G. Shreffler, M.D., Ph.D. , Edwin H. Kim, M.D., Stacie M. Jones, M.D., Donald Y.M. Leung, M.D., Ph.D., , and R. Sharon Chinthrajah, M.D. [Author Info & Affiliations](#)

Published February 25, 2024 | N Engl J Med 2024;390:889-899 | DOI: 10.1056/NEJMoa2312382

VOL. 390 NO. 10

67% participants on Omalizumab were able to tolerate ≥ 600 mg of peanut protein (about 2.5 peanuts) compared to 7% on placebo ($p < 0.001$)

Are Biologics the future?



Could Xolair Be the First Biologic Treatment for Food Allergies?

By: Jennifer Goodwin in Food Allergy, Food Allergy News
Published: October 14, 2022



Biologic medications that neutralize IgE antibodies have long been considered a promising food allergy treatment. Now, one such medication – omalizumab (or Xolair) – looks likely to become the first “anti-IgE” biologic drug contender to treat multiple food allergies.

Researchers from the [Consortium of Food Allergy Research](#) are studying omalizumab in two ways for child and adult patients. The first is as a standalone treatment to protect against reacting to accidental exposures in those with allergies to peanut plus two or more other foods: milk, egg, wheat, cashew, hazelnut or walnut.

The second method is as an add-on treatment for oral immunotherapy (OIT) to reduce adverse reactions and improve safety.

1. OIT + TLR (Phase I GLA)
2. Omalizumab +/- OIT (faster, safer, variable response, efficacy the same)
3. Dupilimab (IL4/13) +/- OIT (under trial)
4. Etokimab, ANB020, inhibits IL-33

Summary

- Food allergy prevalence is on the rise;
- Eczema is a significant risk factor for food allergies;
- Early intervention is an effective strategy but must be done in earlier stages of life (i.e. <12 months of age);
- Oral/epicutaneous/sublingual immunotherapy treatments are useful but greater success in younger children;
- Timing is of the essence!



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