Update on Prevention of Allergic Disease

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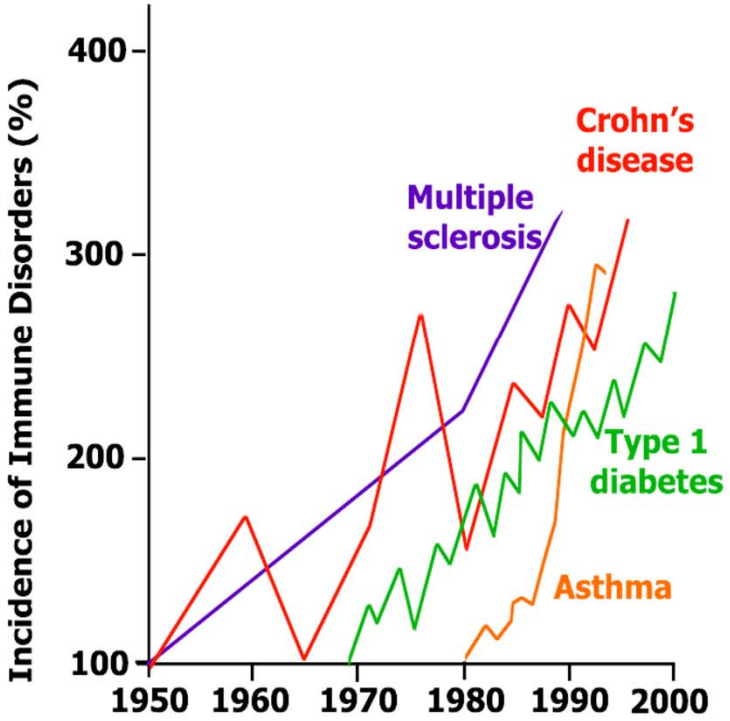
Conflict of Interest Declaration

- Employment
  - Royal Children's Hospital, Melbourne, Vic
  - Murdoch Childrens Research Institute, Melbourne, Vic
  - Dorevitch Pathology, Heidelberg, Vic
  - Prota Therapeutics, Melbourne, Vic
- Advisory boards
  - Nestle Nutrition Institute, Medical Advisory Board Oceania
- Consultancy
  - Bayer
- Grant funding
  - NHMRC
- Other
  - Share interest in Prota Therapeutics

Presentation Outline

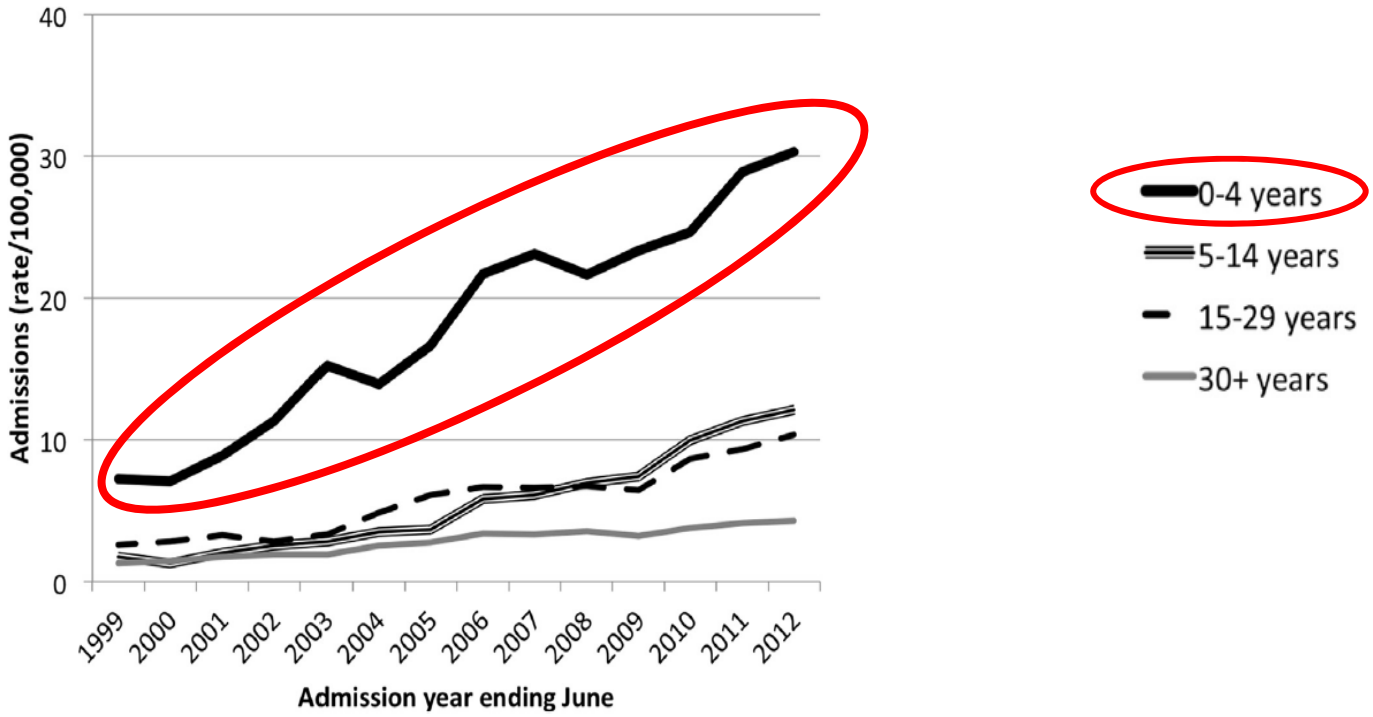
- ASCIA Infant Feeding and Allergy Prevention Guidelines - Updated in May 2016
  - Several important changes from 2008 advice….
- New research informing the updated guidelines ….
  - Role of hydrolysed formulas
  - Timing of introduction of solids: LEAP and other trials

Rising Rates of Immune Disorders



Bach, NEJM 2002;347: 911-920

Food Anaphylaxis Admissions in Australia 1998-2012



Mullins R, Dear K, Tang MLK. J Allergy Clin Immunol 2015

Environmental Influences

- Microbial exposures in early life
  - Hygiene hypothesis
  - Intestinal microbiota
- Diet
  - Breastfeeding
  - Long term diet
  - Immunomodulatory factors
  - Timing of exposure to food allergens
- Vitamin D / UV exposure
- Pollutants

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Guidelines

Infant feeding and allergy prevention

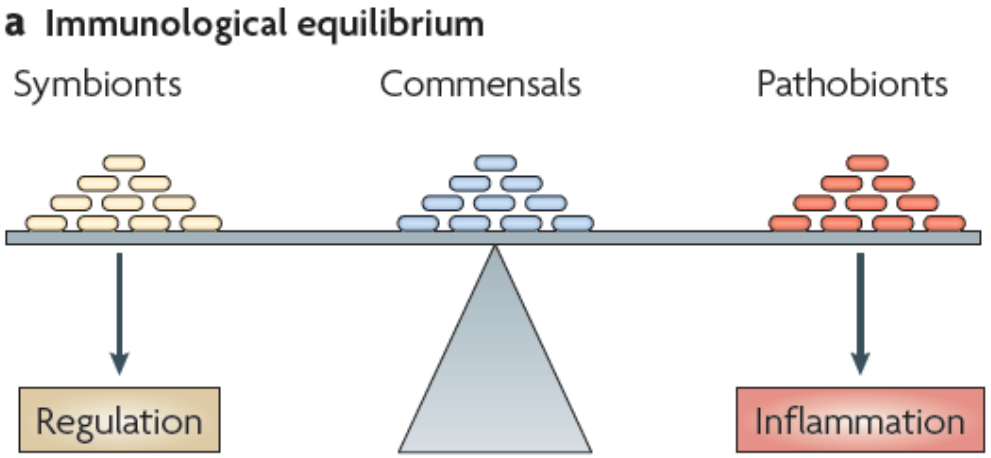
Pregnancy and Breastfeeding

Probiotics and Prebiotics

- *Probiotics* are live microbial organisms which beneficially affect the host by improving its intestinal microbial balance
    - Lactobacilli and Bifidobacteria most common
    - Live bacteria that adhere to gut epithelium
    - Promote growth of other beneficial bacteria
    - Have direct and indirect immune effects

- A *prebiotic* selectively stimulates the growth and/or activity of one or more microbial species in the gut microbiota (leading to changes in the composition or activity of the microbiota) that confers health benefits to the host
    - Must not be digested in upper GI
    - Selective substrate for beneficial bacteria
    - Most interest in oligosaccharides
    - Have direct and indirect immune effects

Intestinal Microbiota and Immune Homeostasis



Round and Mazmanian. Nature Rev Immunol 2009

Fiocchi et al. World Allergy Organization Journal (2015) 8:4
DOI 10.1186/s40413-015-0055-2

WAO journal
WORLD ALLERGY ORGANIZATION

POSITION ARTICLE AND GUIDELINES Open Access

World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Probiotics

Alessandro Fiocchi[1†], Ruby Pawankar[2†], Carlos Cuello-Garcia[3,4], Kangmo Ahn[5], Suleiman Al-Hammadi[6], Arnav Agarwal[3,7], Kirsten Beyer[8], Wesley Burks[9], Giorgio W Canonica[10], Motohiro Ebisawa[11], Shreyas Gandhi[3,7], Rose Kamenwa[12], Bee Wah Lee[13], Haiqi Li[14], Susan Prescott[15], John J Riva[16], Lanny Rosenwasser[17], Hugh Sampson[18], Michael Spigler[19], Luigi Terracciano[20], Andrea Vereda-Ortiz[22], Susan Waserman[21], Juan José Yepes-Nuñez[3], Jan L Brożek[3,21*] and Holger J Schünemann[3,21]

The WAO guideline panel suggests: a) using probiotics in pregnant women at high risk for having an allergic child; b) using probiotics in women who breastfeed infants at high risk of developing allergy; and c) using probiotics in infants at high risk of developing allergy. All recommendations are conditional and supported by very low quality evidence.

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Guidelines

Infant feeding and allergy prevention

Breastfeeding and Infant Formula

Breastfeeding and infant formula

- Breastfeeding is recommended for at least 6 months and for as long as mother and infant wish to continue. There is no consistent evidence that breastfeeding is effective for the prevention of allergic disease. However, breastfeeding is recommended for the many benefits it provides to mother and infant.

- Breastfeeding during the period that solid foods are first introduced to infants from around 6 months may help reduce the risk of the infant developing allergies, although evidence for this is low.

- If breastfeeding is not possible, a standard cow's milk based formula can be given. There is no evidence that soy or goat's milk formula reduce the risk of allergic disease when used in preference to standard cow's milk based formula.

- Based on a recently published review of studies, there is no consistent convincing evidence to support a protective role for partially hydrolysed formulas (usually labelled 'HA' or Hypoallergenic) or extensively hydrolysed formulas for the **prevention** of eczema, food allergy, asthma or allergic rhinitis in infants or children.

Hydrolysed formula and risk of allergic or autoimmune disease: systematic review and meta-analysis

Robert J Boyle,[1] Despo Ierodiakonou,[1,2] Tasnia Khan,[1] Jennifer Chivinge,[1] Zoe Robinson,[1] Natalie Geoghegan,[1] Katharine Jarrold,[1] Thalia Afxentiou,[1] Tim Reeves,[2] Sergio Cunha,[3] Marialena Trivella,[4] Vanessa Garcia-Larsen,[2] Jo Leonardi-Bee[5]

WHAT IS ALREADY KNOWN ON THIS TOPIC

Breastfeeding is the optimum mode of nutrition for infants

Substitution with infant formula has been associated with allergic and autoimmune disease

International guidelines recommend use of a hydrolysed formula in place of standard infant formula for infants at risk of allergic disease to prevent eczema and allergy to cows' milk

WHAT THIS STUDY ADDS

There is no consistent evidence to support the use of hydrolysed formula for the prevention of allergic or autoimmune disease

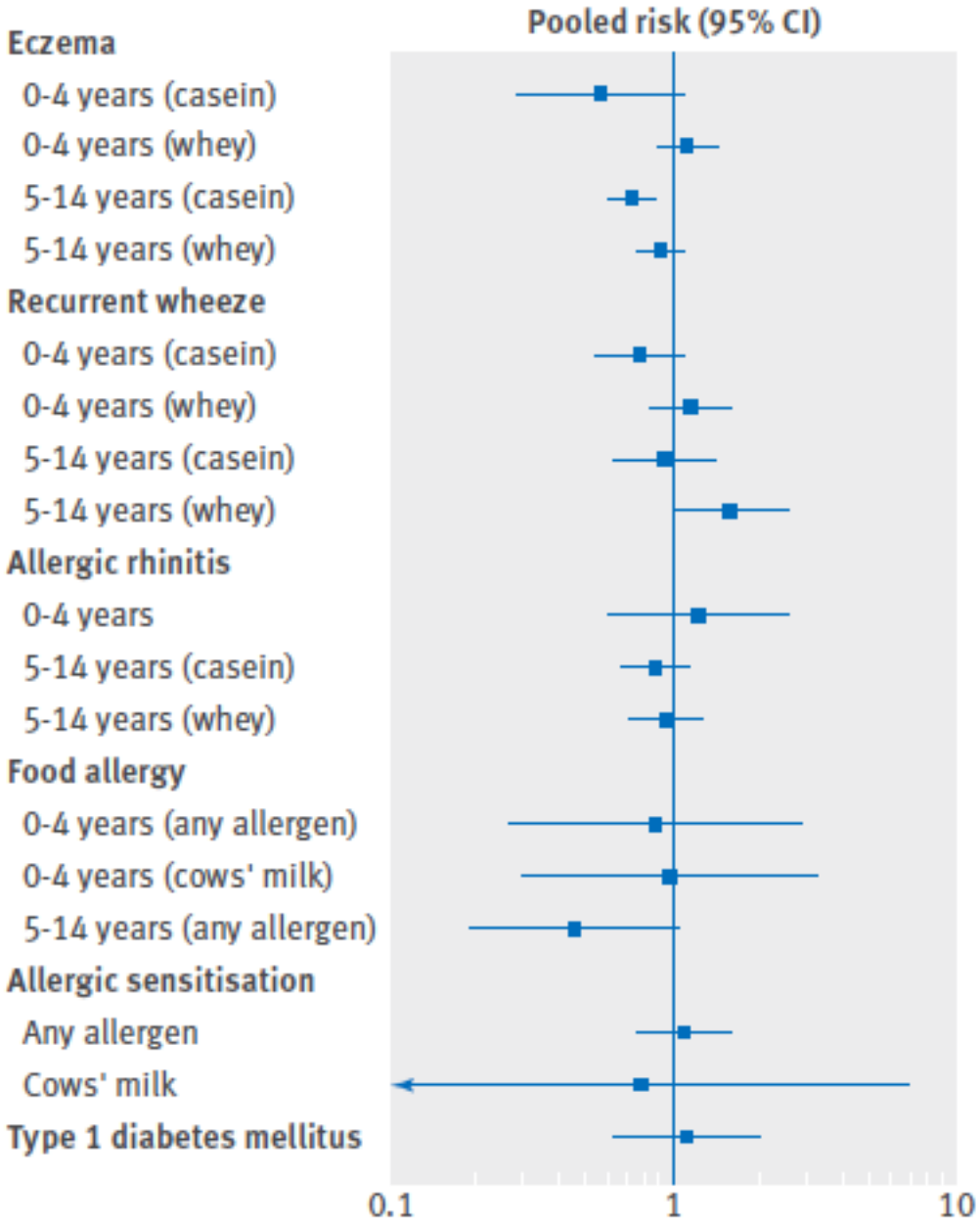

Fig 3 | Summary of treatment effects of hydrolysed formula on different outcome measures.

Data shown are mean risk ratios (for allergic rhinitis at age 0-4; food allergy; allergic sensitisation; diabetes) or odds ratios (all other outcomes) with 95% confidence intervals for extensively hydrolysed formula compared with standard cows' milk formula

Boyle et al. BMJ 2016

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Guidelines

Infant feeding and allergy prevention

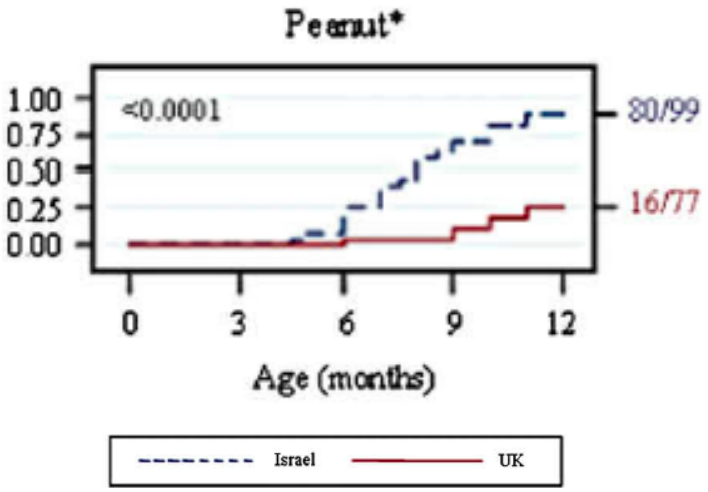
Introduce solid foods from around 6 months, but not before 4 months, when your infant is developmentally ready whilst continuing to breastfeed

- Infants differ in the age that they are developmentally ready for solid foods.
- Signs that your infant may be developmentally ready to start solids include: being able to sit relatively unaided, loss of the tongue-thrust reflex that pushes food back out, and trying to reach out and grab food.

- When your infant is ready, introduce foods according to what the family usually eats, regardless of whether the food is considered to be a common food allergen. There is some evidence that the introduction of common allergenic foods (including cooked eggs as raw egg is not recommended, peanuts, nuts, wheat, fish) should not be delayed. However further evidence is required to clarify optimal timing for each food.

A Window of Opportunity for Tolerance Induction

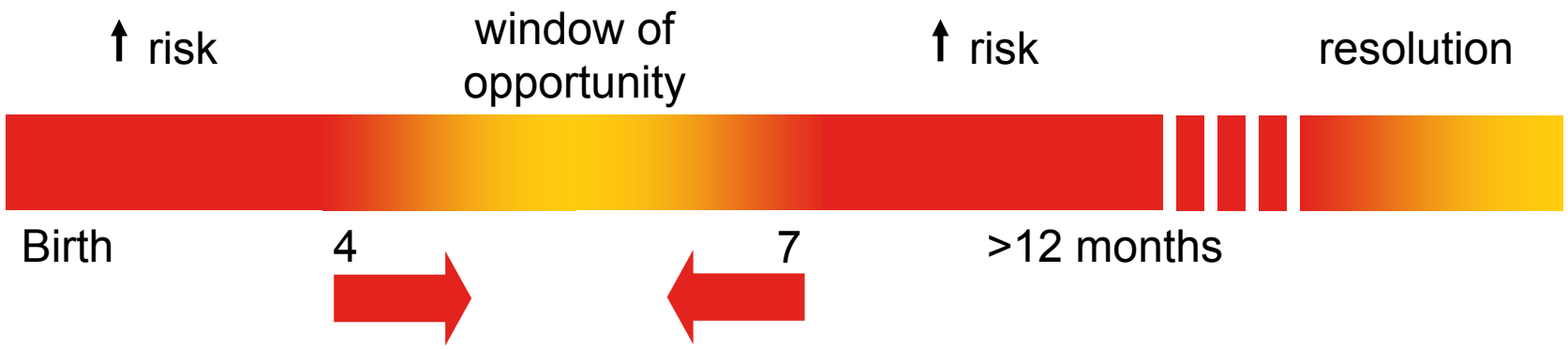
Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy



	Peanut	
	RR (95% CI)	*P* value
All individuals		
Unadjusted	10.8 (5.2-22.3)	<.001
Adjusted for age group* and sex§	10.4 (4.8-22.2)	<.001
Adjusted for age group,* sex,§ food allergy,‡ and atopy†	5.8 (2.8-11.8)	<.001

Du Toit et al. J Allergy Clin Immunol 2008

A Window of Opportunity for Tolerance Induction



Prescott et al. Pediatr Allergy Immunol 2008

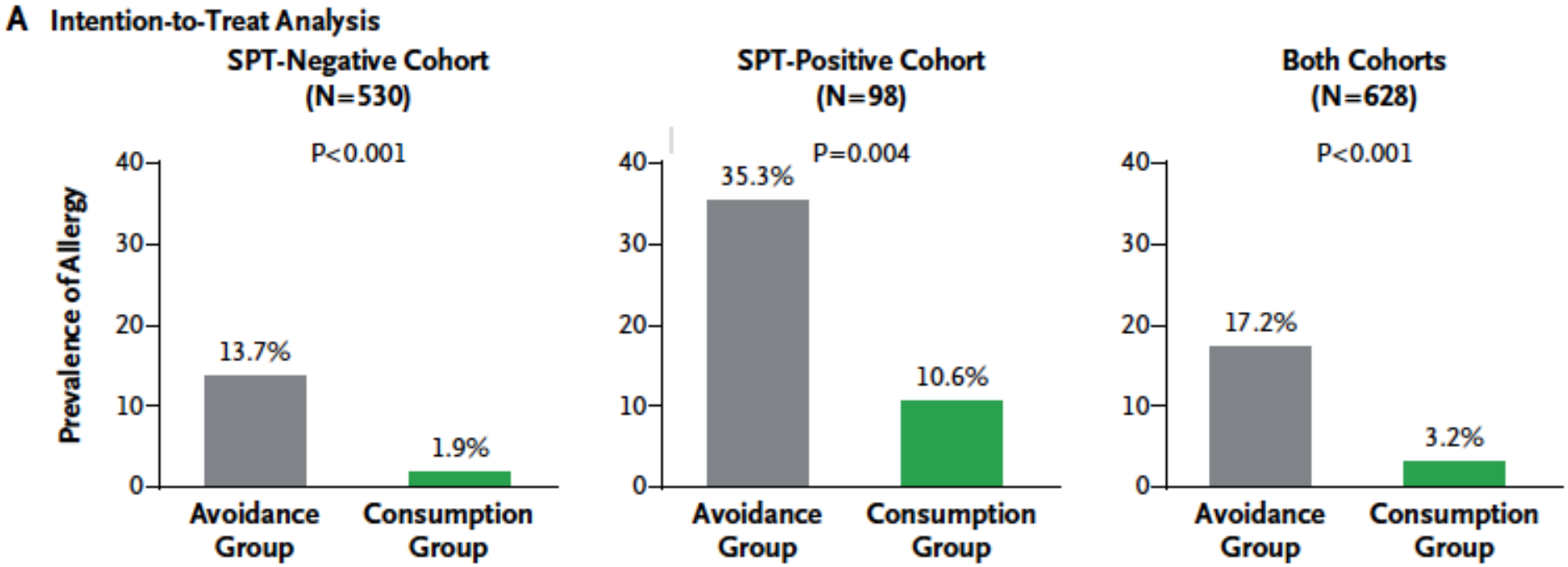
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 26, 2015 VOL. 372 NO. 9

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

George Du Toit, M.B., B.Ch., Graham Roberts, D.M., Peter H. Sayre, M.D., Ph.D., Henry T. Bahnson, M.P.H., Suzana Radulovic, M.D., Alexandra F. Santos, M.D., Helen A. Brough, M.B., B.S., Deborah Phippard, Ph.D., Monica Basting, M.A., Mary Feeney, M.Sc., R.D., Victor Turcanu, M.D., Ph.D., Michelle L. Sever, M.S.P.H., Ph.D., Margarita Gomez Lorenzo, M.D., Marshall Plaut, M.D., and Gideon Lack, M.B., B.Ch., for the LEAP Study Team*

LEAP Study



Du Toit et al. NEJM 2015;372:803

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants

Michael R. Perkin, Ph.D., Kirsty Logan, Ph.D., Anna Tseng, R.D., Bunmi Raji, R.D., Salma Ayis, Ph.D., Janet Peacock, Ph.D., Helen Brough, Ph.D., Tom Marrs, B.M., B.S., Suzana Radulovic, M.D., Joanna Craven, M.P.H., Carsten Flohr, Ph.D., and Gideon Lack, M.B., B.Ch., for the EAT Study Team*

Perkin et al. *NEJM* 2016

EAT Study

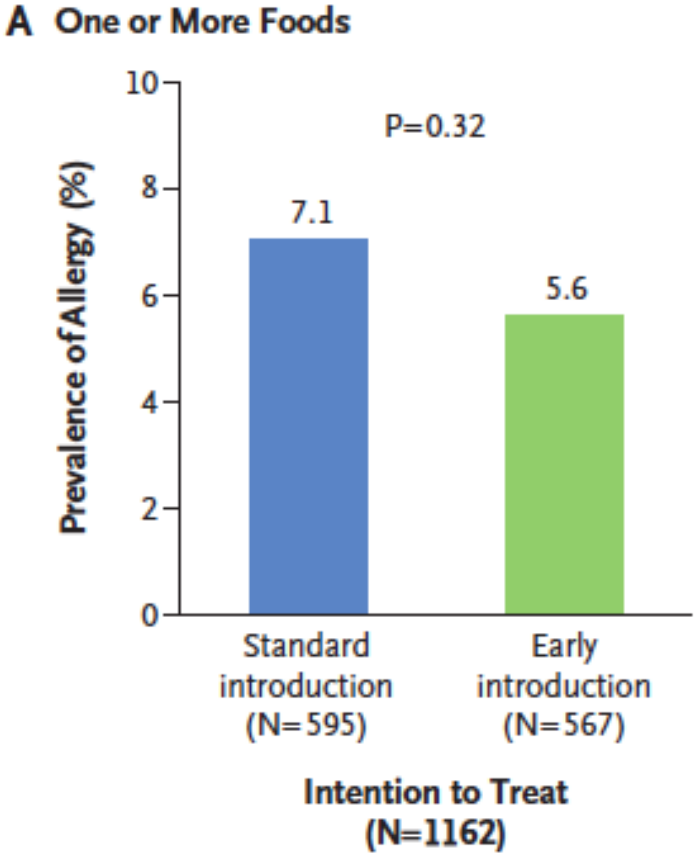
- Introduction of six allergenic foods (egg, milk, peanut, sesame, fish, wheat) into the diet of infants from 3 months of age vs 6 months, alongside continued breastfeeding → prevalence of food allergy by 3 years of age

- Randomized controlled trial – general population
  - Group 1: followed current UK government weaning advice i.e. aim for exclusive breastfeeding until six months
  - Group 2: six allergenic foods from 3 months of age alongside continued breastfeeding, screened for pre-existing food allergy

- Early introduction of all 6 foods was only achieved in ~37%
  - Cow's milk 85%, wheat 100% (introduced last)
  - Peanut 61.9%, fish 60%
  - Sesame 50.7%, egg 43.1%,

Perkin et al. *NEJM* 2016

EAT Study



Perkin et al. *NEJM* 2016

Randomized controlled trial of early regular egg intake to prevent egg allergy

Debra J. Palmer, PhD,[a,b] Thomas R. Sullivan, BMa&CompSc(Hons),[c] Michael S. Gold, MD,[d] Susan L. Prescott, MD, PhD,[a,e] and Maria Makrides, PhD[b,d,f] *Perth and Adelaide, Australia*

Randomized placebo-controlled trial of hen's egg consumption for primary prevention in infants

Johanna Bellach,[a] Veronika Schwarz, MD,[a] Birgit Ahrens, MD,[a] Valérie Trendelenburg, MSc,[a] Özlem Aksünger,[a] Birgit Kalb, MD,[a] Bodo Niggemann, MD,[a] Thomas Keil, MD, MPH,[b] and Kirsten Beyer, MD[a,c] *Berlin, Germany, and New York, NY*

A randomized trial of egg introduction from 4 months of age in infants at risk for egg allergy

John Wei-Liang Tan, MD, FRACP, Carolina Valerio, BN, Elizabeth H. Barnes, BAppSc, MStat, Paul J. Turner, MD, PhD, Peter A. Van Asperen, MD, FRACP, PhD, Alyson M. Kakakios, MD, FRACP, Dianne E. Campbell, MD, PhD, Elizabeth H. Barnes, Dianne E. Campbell, Namita Doa, Lara Ford, Maria Gacis, Peter Hsu, Preeti Joshi, Alyson M. Kakakios, Sam Mehr, Reta Nambiar, Claire Nicholls, John Wei-Liang Tan, Paul J. Turner, Carolina Valerio, Peter A. Van Asperen, Karla Villafana Soto, Andrew Williams, Melanie Wong

Timing of Allergenic Food Introduction to the Infant Diet and Risk of Allergic or Autoimmune Disease

A Systematic Review and Meta-analysis

- Moderate-certainty evidence from 5 trials (1915 participants)
  - *Early egg introduction at 4 to 6 months associated with reduced egg allergy* (RR 0.56; 95%CI, 0.36-0.87; I2 = 36%; P = .009).
  - Absolute risk reduction for a population with 5.4% incidence of egg allergy was 24 cases (95%CI, 7-35 cases) per 1000 population.

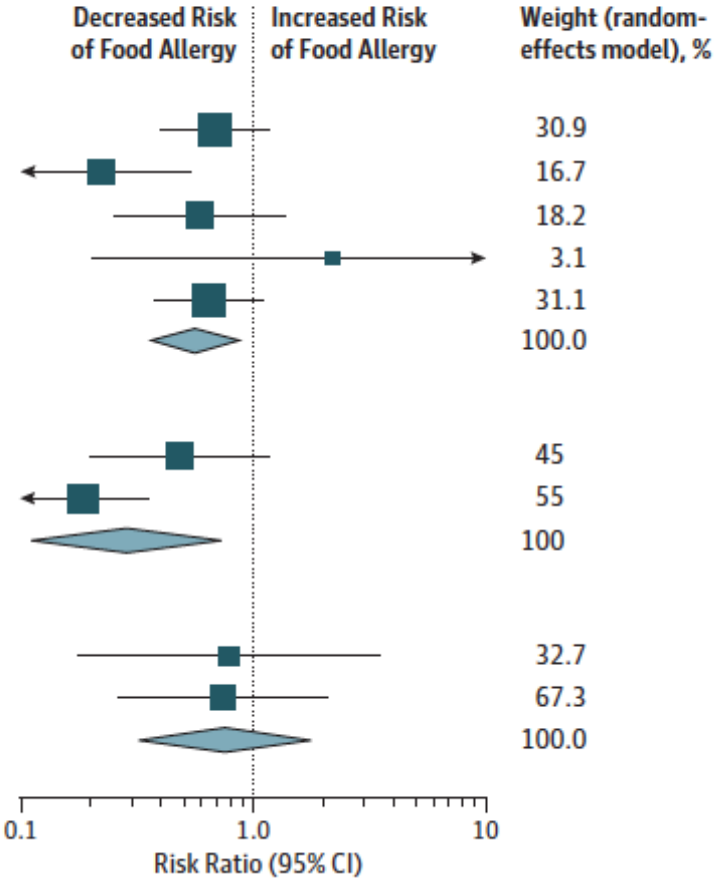
- Moderate-certainty evidence from 2 trials (1550 participants) that
  - *Early peanut introduction at 4 to 11 months associated with reduced peanut allergy* (RR 0.29; 95%CI 0.11-0.74; I2 = 66%; P = .009).
  - Absolute risk reduction for a population with 2.5% incidence of peanut allergy was 18 cases (95%CI, 6-22 cases) per 1000 population.

Ierodiakonou et al. JAMA. 2016;316(11):1181-1192

Figure 1. Early Allergenic Food Introduction and Risk of Food Allergy or Food Sensitization

A Risk of food allergy

Outcome	Dietary Introduction of Allergenic Food: Early — No. of Events	Early — Total No.	Late — No. of Events	Late — Total No.	Risk Ratio (95% CI)
Egg allergy					
Perkin et al,[6] 2016	21	569	32	596	0.69 (0.40-1.18)
Natsume et al,[17] 2016	5	60	23	61	0.22 (0.09-0.54)
Tan et al,[18] 2016	8	130	13	124	0.59 (0.25-1.37)
Bellach et al,[16] 2015	2	142	1	156	2.20 (0.20-23.97)
Palmer et al,[15] 2013	14	42	18	35	0.65 (0.38-1.11)
Random-effects model Heterogeneity: $I^2 = 35.8\%$; $P = .18$		943		972	0.56 (0.36-0.87)
Peanut allergy					
Perkin et al,[6] 2016	7	571	15	597	0.49 (0.20-1.19)
Du Toit et al,[4] 2015	10	312	54	313	0.19 (0.10-0.36)
Random-effects model Heterogeneity: $I^2 = 66.1\%$; $P = .09$		883		910	0.29 (0.11-0.74)
Milk allergy					
Perkin et al,[6] 2016	3	569	4	597	0.79 (0.18-3.50)
Lowe et al,[19] 2011	6	193	8	191	0.74 (0.26-2.10)
Random-effects model Heterogeneity: $I^2 = 0\%$; $P = .95$		762		788	0.76 (0.32-1.78)



Ierodiakonou et al. JAMA. 2016;316(11):1181-1192

International Consensus Recommendations on Prevention of Peanut Allergy

- ***Infants with severe eczema or egg allergy by 4-6 months of age may benefit from specialist evaluation and advice*** regarding introduction of peanut, which *might include SPT +/- observed peanut ingestion / challenge*

- This guidance is limited to the select group of high risk infants studied in LEAP…. The guidance aims to apply the LEAP findings to "other similar children at high risk in more diverse settings around the world"

Fleischer et al. J Allergy Clin Immunol 2015;136:258-61

Updated Recommendations on Prevention of Peanut Allergy in the USA

Addendum guidelines for the prevention of peanut allergy in the United States (NIAID expert panel) – January 2017

- In *infants with severe eczema, egg allergy or both* introduce peanut-containing food as early as 4-6 months of age to reduce the risk of peanut allergy.

- In these infants, *peanut-specific IgE or SPT should be strongly considered* before introduction of peanut to determine if peanut should be introduced, and if so, the preferred method of introduction.

Togias et al. J Allergy Clin Immunol 2017;139:29-44

Updated Recommendations on Prevention of Peanut Allergy in the USA

Addendum guidelines for the prevention of peanut allergy in the United States (NIAID expert panel) – January 2017

- Infants with *mild to moderate eczema* should receive age-appropriate peanut-containing food as early as 4-6 months of age

- These infants may have dietary peanut introduced at home *without an in-office evaluation.*

Togias et al. J Allergy Clin Immunol 2017;139:29-44

Updated Recommendations on Prevention of Peanut Allergy in the USA

Addendum guidelines for the prevention of peanut allergy in the United States (NIAID expert panel) – January 2017

- Infants *without eczema or any food allergy* have age-appropriate peanut-containing foods freely introduced in the diet, together with other solid foods

- These infants may have dietary peanut introduced at home *without an in-office evaluation.*

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Guidelines

Infant feeding and allergy prevention

Introduce solid foods from around 6 months, but not before 4 months, when your infant is developmentally ready whilst continuing to breastfeed

- When your infant is ready, introduce foods according to what the family usually eats, regardless of whether the food is considered to be a common food allergen. There is some evidence that the introduction of common allergenic foods (including cooked eggs as raw egg is not recommended, peanuts, nuts, wheat, fish) should not be delayed. However further evidence is required to clarify optimal timing for each food.

- There is moderate evidence that introducing cooked egg (raw egg is not recommended) into an infant's diet before 8 months of age, where there is a family history of allergy, can reduce the risk of developing egg allergy.

- There is good evidence that for infants with severe eczema and/or egg allergy, that regular peanut intake before 12 months of age can reduce the risk of developing peanut allergy. If your child already has an egg allergy or other food allergies or severe eczema, you should discuss how to do this with your doctor.

What advice should health practitioners give?

Should SPT or sIgE testing be performed in 'high risk' infants prior to introducing allergenic foods?

- Previous international guidelines recommended *introducing solid foods (including the allergenic foods) from 4-6 months* without specific recommendation to seek medical advice or perform prior allergy testing….

- International Consensus Recommendations (2015) and NIAID Updated Recommendations (2017)
  - ***For infants with severe eczema or egg allergy by 4-6 months of age → strongly recommended to perform SPT or sIgE followed by observed peanut ingestion / challenge if positive***

1. What proportion of infants are 'high risk'?

In the HealthNuts cohort….

- **11% of 6 month old infants and 16% of 12 month old infants** had egg allergy or severe eczema → consensus recommendations apply

- **~89% of 6 month old infants are not high risk** → follow current allergy prevention guidelines and introduce ***without*** any testing

- ***What number of infants does 11% of infants per year equate to?***
  - In Australia, with a birth rate of 300,000 annually, this equates to 33,000 new referrals to allergists every year and an additional 4,488 challenges (for infants with SPT 1-4mm)
  - Existing allergy services would struggle to see these infants in a timely manner

Koplin et al JACI 2016 In press

2. Are there potential risks associated with implementing the consensus recommendations?

Will infants with eczema / egg allergy (~11%) be placed at risk?

In the LEAP study…

- 75.7% of high risk infants had peanut SPT 0mm at study entry
  - Only 1 of 272 had a reaction to peanut at baseline (rash, itch)
  - *These infants could have taken peanut without delay*
- 13.7% had SPT 1-4mm → peanut challenge
  - 12.8% failed the peanut challenge
  - *87% passed and could have taken peanut without delay*
- ***The majority of high risk infants could safely introduce peanut without prior SPT***
  - In regions where there are long wait times to see an allergist, these infants will have unnecessarily delayed peanut introduction while waiting for specialist evaluation / testing

Can we avoid unnecessary delay in peanut Introduction for the majority of high-risk Infants?

One alternative approach to minimize unnecessary delay in peanut introduction, is for GPs or pediatricians to perform initial evaluation of high risk infants using ***peanut sIgE testing***

→ only refer infants with +ve peanut sIgE to an allergy specialist for further assessment and advice.

- In LEAP, *64% of high risk infants had negative peanut sIgE* (Table S3)
  → these infants could introduce peanut after minimal delay
- The remaining 36% of high risk infants with positive peanut sIgE could be referred to a specialist for further evaluation including SPT
- This would *reduce the number of infants requiring specialist evaluation to 4%*
  - avoid unnecessary delay of peanut introduction for the majority of high risk infants

Peanut sIgE Testing Prior to Introducing Peanut

Severe eczema
or
Egg allergy
or
Both

Can we avoid unnecessary delay in peanut Introduction for the majority of high-risk Infants?

Another alternative option in settings where allergy services are limited might be to introduce peanut in all infants at ~6 months

- Few infants are expected to react to peanut at 6-12 months
  - Prevalence of peanut allergy at 12 months was 3% in HealthNuts; early introduction would result in a lower rate
  - If early introduction of peanut is effective, the rate of peanut allergy at 12 months would be ~1-2%

- The majority of reactions on introduction of peanut in young infants are mild, irrespective of whether peanut is introduced at home or in the hospital, and irrespective of SPT wheal size or clinical risk factors

Koplin et al Manuscript under revision

3. Is it safe to introduce peanut without prior testing?

Most reactions to peanut in the first year of life are mild

- In the LEAP study, 2.2% (7 of 319) high risk infants randomized to peanut ingestion reacted to peanut during the study entry challenge
  - All reactions were mild; no infants required adrenaline, no hospitalisation
  - NB… No challenges in infants with SPT >4mm
- In HealthNuts, 3% of infants who commenced peanut before 12 months reported a possible reaction
  - No cases of anaphylaxis
- Introducing peanut cautiously would further reduce the likelihood of a severe reaction – eg graded daily doses starting with a smear to the inside lip on day 1, 1/8th of a tsp on day 2, ¼ of a tsp on day 3, etc

Koplin et al Manuscript under revision; Du Toit et al. NEJM 2015;372:803

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- There is moderate evidence that introducing cooked egg (raw egg is not recommended) into an infant's diet before 8 months of age, where there is a family history of allergy, can reduce the risk of developing egg allergy.

- There is good evidence that for infants with severe eczema and/or egg allergy, that regular peanut intake before 12 months of age can reduce the risk of developing peanut allergy. If your child already has an egg allergy or other food allergies or severe eczema, you should discuss how to do this with your doctor.

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Infant feeding and allergy prevention

- It is important to understand that the facial skin in babies is very sensitive and that many foods (including citrus, tomatoes, berries, other fruit and vegemite) can irritate the skin and cause redness on contact – this is not food allergy. Smearing food on the skin will not help to identify possible food allergies.

- **Some infants will develop food allergies. If there is any allergic reaction to any food, that food should be stopped and you should you should seek advice from a doctor with experience in food allergy.**

Summary

- 2016 ASCIA Allergy Prevention and Infant Feeding Guidelines
  - Apply to ALL infants, including those with family history of allergic disease
  - Breastfeed for at least 6 months (and while introducing solids)
  - *Introduce solid foods (including allergenic foods) from around 6 months but not before 4 months*
  - *No consistent evidence to support the use of hydrolysed formulas*
  - *Insufficient evidence to recommend use of probiotics*

- Guidance for introduction of peanut….
  - Infants with *severe eczema or egg allergy* → peanut sIgE testing first
    → if sIgE ≥0.35 kU/L, refer to specialist (SPT +/- challenge)
    → if sIgE <0.35 kU/L, introduce peanut at home
  - If *mild or moderate eczema* → introduce peanut *without testing*
  - If *no eczema or food allergy* → introduce peanut *without testing*