

Strategies to Prevent Food Allergies in Children

Jacob Kattan, MD

Assistant Professor

Director of the Food Allergy Treatment and Research Center

Jaffe Food Allergy Institute

Mount Sinai Kravis Children's Hospital | Icahn School of Medicine

Valley Medical Group



**Mount
Sinai**

Kravis Children's Hospital

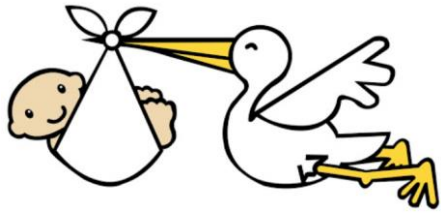
Faculty Disclosure

- ▶ There are no commercial products or services being discussed
- ▶ No financial disclosures
- ▶ No unlabeled use of a product is being discussed

Objectives

1. To understand key studies investigating early food introduction
2. To review current guidelines related to early food introduction
3. To discuss additional interventions for the prevention of food allergy

How can we *prevent* food allergy?



Mode of birth/delivery



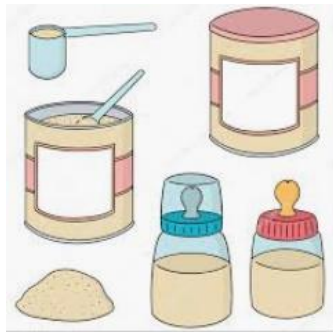
Breastfeeding + duration



Timing of infant food introduction



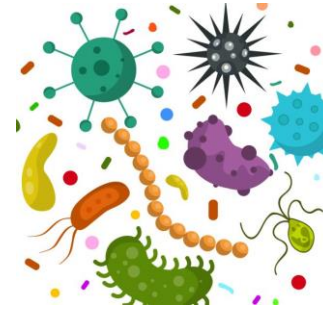
Maternal diet



Formula selection



Probiotics



Microbiome



Eczema and skin care

Learning Early About Peanut Allergy Trial

The **NEW ENGLAND**
JOURNAL of MEDICINE

ESTABLISHED IN 1812

FEBRUARY 26, 2015

VOL. 372 NO. 9

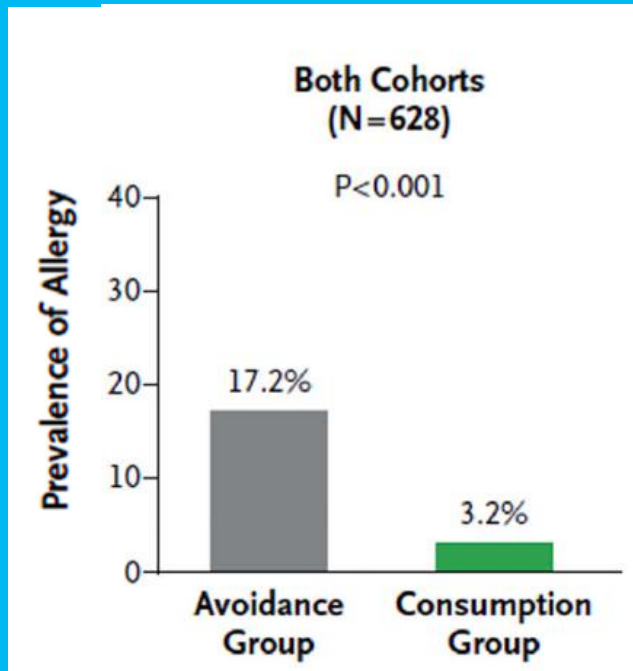
**Randomized Trial of Peanut Consumption
in Infants at Risk for Peanut Allergy**

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*

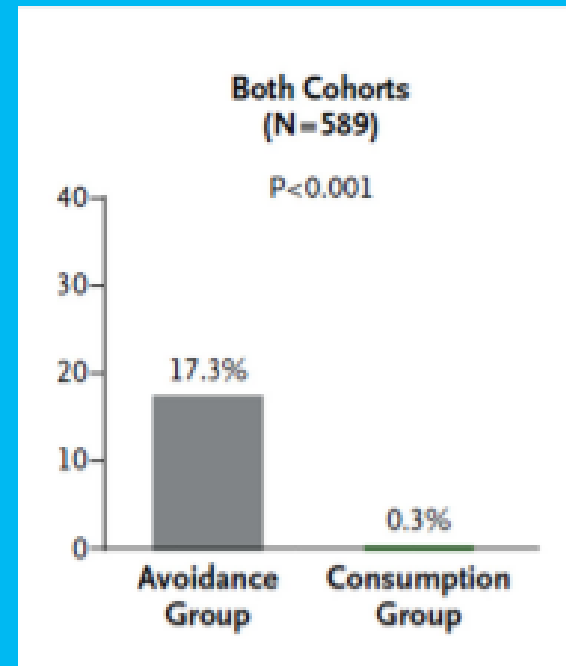
- ▶ **Purpose:** Determine whether early introduction of peanut will prevent development of allergy in non-allergic “high risk” infants. **This was not a treatment study.**
- ▶ “High risk” defined as young infants with:
 - **Egg allergy:**
 - Skin test bigger than 6 mm to egg
 - Skin test bigger than 3 mm to egg & history of reaction to egg
 - **Severe eczema:**
 - Frequent use of topical steroids
 - Graded as severe by physician based on % body covered

Results from LEAP

Intention to Treat



Per-Protocol Analysis



Conclusion:

In infants at high risk of allergy (but were not allergic), peanut introduction between 4 and 11 months of life resulted in a significant reduction in peanut allergy prevalence at 5 years of age

NIAID Expert Panel 2017

Infant Criteria	Recommendations	Earliest Age of Peanut Intro
<p><u>Guideline #1:</u></p> <ul style="list-style-type: none">• Severe eczema, egg allergy or both	<p>Strongly consider evaluation by blood or skin test, and if necessary, an OFC. Based on testing, introduce peanut containing foods.</p>	<p>4-6 months</p>
<p><u>Guideline #2:</u></p> <ul style="list-style-type: none">• Mild to moderate eczema	<p>Introduce peanut containing foods</p>	<p>Around 6 months</p>
<p><u>Guideline #3:</u></p> <ul style="list-style-type: none">• No eczema or any food allergy	<p>Introduce peanut containing foods</p>	<p>Age appropriate and in accordance with family preferences and culture</p>

Concerns Regarding Recommendations

- ▶ Classification of “severe eczema” is subjective, and may lead to over-referrals
- ▶ In Pediatric studies from the US, UK, and Australia, about 10% of children show sensitization to peanut, while only 1-2% of the pediatric population has a peanut allergy
- ▶ In Australia, it was estimated that:
 - 29% screened with serum IgE testing would require follow up for positive skin tests
 - 23% of allergy cases would be missed if screening restricted to “high risk”

Turner et al. JAMA 2017 Mar 21;317(11):1111–1112

Greenhawt et al. J Allergy Clin Immunol Pract. 2016 Mar–Apr;4(2):221–225

Sicherer et al. J Allergy Clin Immunol Pract. 2013 Jan;1(1):1-13

Koplin et al. J Allergy Clin Immunol. 2016 Oct;138(4):1131–41

Turner et al. J Allergy Clin Immunol Pract. 2018 Mar - Apr;6(2):367–375

Stukus et al. J Allergy Clin Immunol Pract. 2018 Sep - Oct;6(5):1784–1786

Implementation: Potential Barriers

Nationwide surveys of pediatricians and allergists conducted in late 2018

Article	Population	Aware of Guidelines	Full Implement.	Partial Implement.	Barriers
Gupta et al. JAMA 2020	Pediatricians	93%	29%	64%	<ol style="list-style-type: none"> 1. Concern for reaction – parent (37%) 2. Uncertainty in understanding and applying the guidelines (33%) 3. Conducting in-office supervised feedings (32%)
Johnson et al. JACI 2020	Allergists	97%	65%	34%	<ol style="list-style-type: none"> 1. Concern for reactions (parent 48%, self 22%) 2. Lack of referrals (34%) 3. Uninterested (28%) 4. Lack of clinic time (21%)

Implementation: Concern for Reactions

Editorial

Increasing Awareness of the Low Risk of Severe Reaction at Infant Peanut Introduction: Implications During COVID-19 and Beyond



Elissa M. Abrams, MD, MPH^a, Marie-Noel Primeau, MD^b, Harold Kim, MD^{c,d}, Jennifer Gerdts, MD^e, and Edmond S. Chan, MD, FRCPC^f *Winnipeg, MB, Canada; Montreal, QC, Canada; London, Hamilton, and Toronto, ON, Canada; and Vancouver, BC, Canada*

- ▶ **Outcomes of reactions are better in infants than older children:**
 - Allergic reactions are less severe, respiratory symptoms less frequent
 - Biphasic reactions and hospitalizations are uncommon
 - Mortality upon first ingestion during infant food introduction has not been described

Implementation: Concern for Reactions

Differences in oral food challenge reaction severity based on increasing age in a pediatric population

Katie Kennedy, MD^{*}; Maria Katerina C. Alfaro, MS^{*}; Zachary C. Spergel[†]; Stacy L. Dorris, MD[‡]; Jonathan M. Spergel, MD, PhD^{*}; Peter Capucilli, MD[§]

^{*} Division of Allergy and Clinical Immunology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

[†] University of Rochester, Rochester, New York

[‡] Division of Allergy and Clinical Immunology, Vanderbilt University Medical Center, Nashville, Tennessee

[§] Division of Allergy and Clinical Immunology, Rochester Regional Health, Rochester, New York

- ▶ **Outcomes of reactions are better in infants than older children:**
 - Infants and toddlers had fewer reactions involving cardiovascular, neurologic, lower respiratory, or laryngeal symptoms
 - Epinephrine was required less frequently during reactions in infants and toddlers

Newer, real-world data on milder severity of reactions in infants can be used to reassure families/clinicians and instill more confidence

Enquiring about Tolerance (EAT) Trial

1162 exclusively breastfed infants at 3 months from the general population

Early Feeding (n=567)

Between 3-6 months

- Cow's milk (1st)
- Peanut
- Cooked (boiled) egg
- Sesame
- Whitefish
- Wheat (last)

2g of protein twice/week

Standard (n=595)

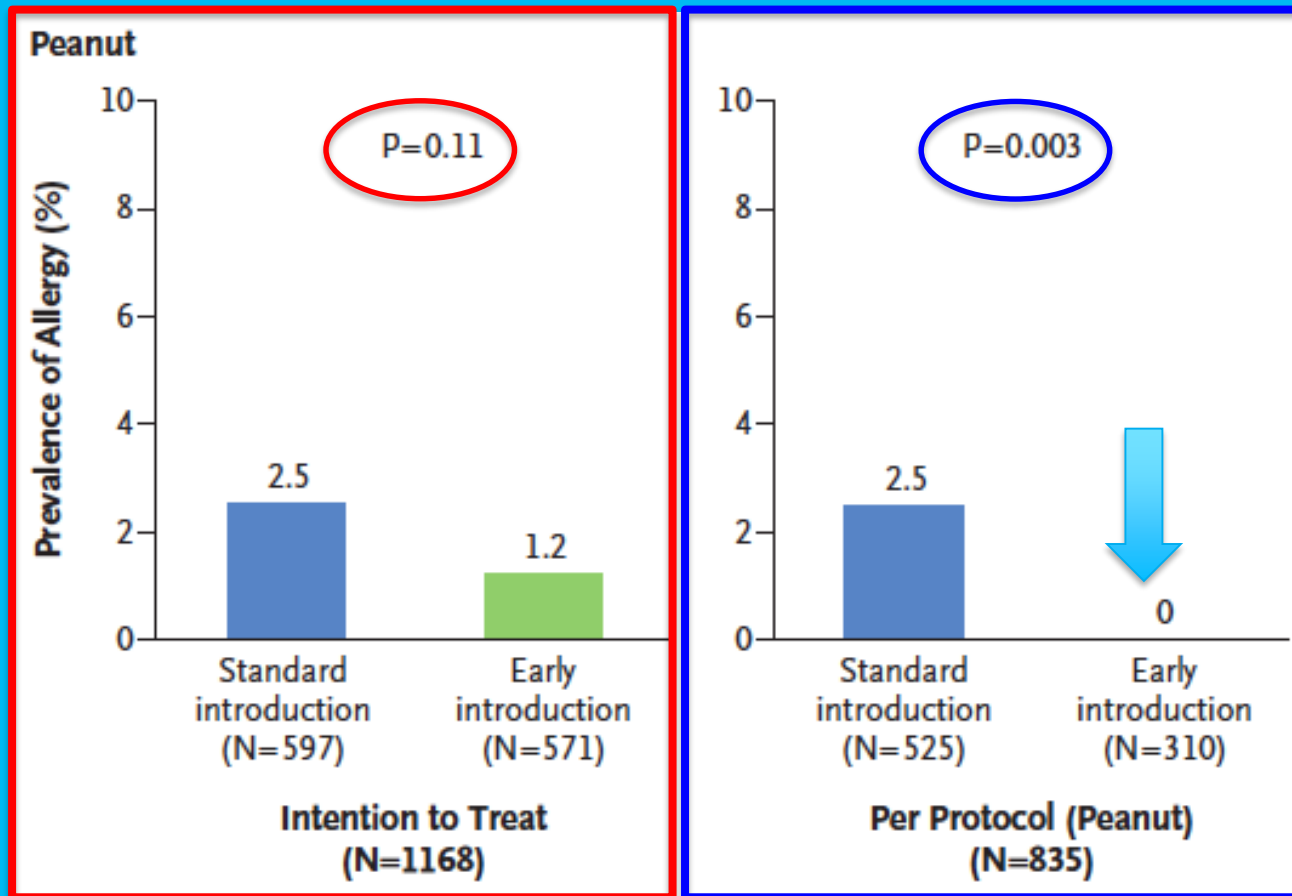
Exclusively breastfed until 6 months

BOTH GROUPS:

After 6 months of age, consumption of allergenic foods as per parent's discretion

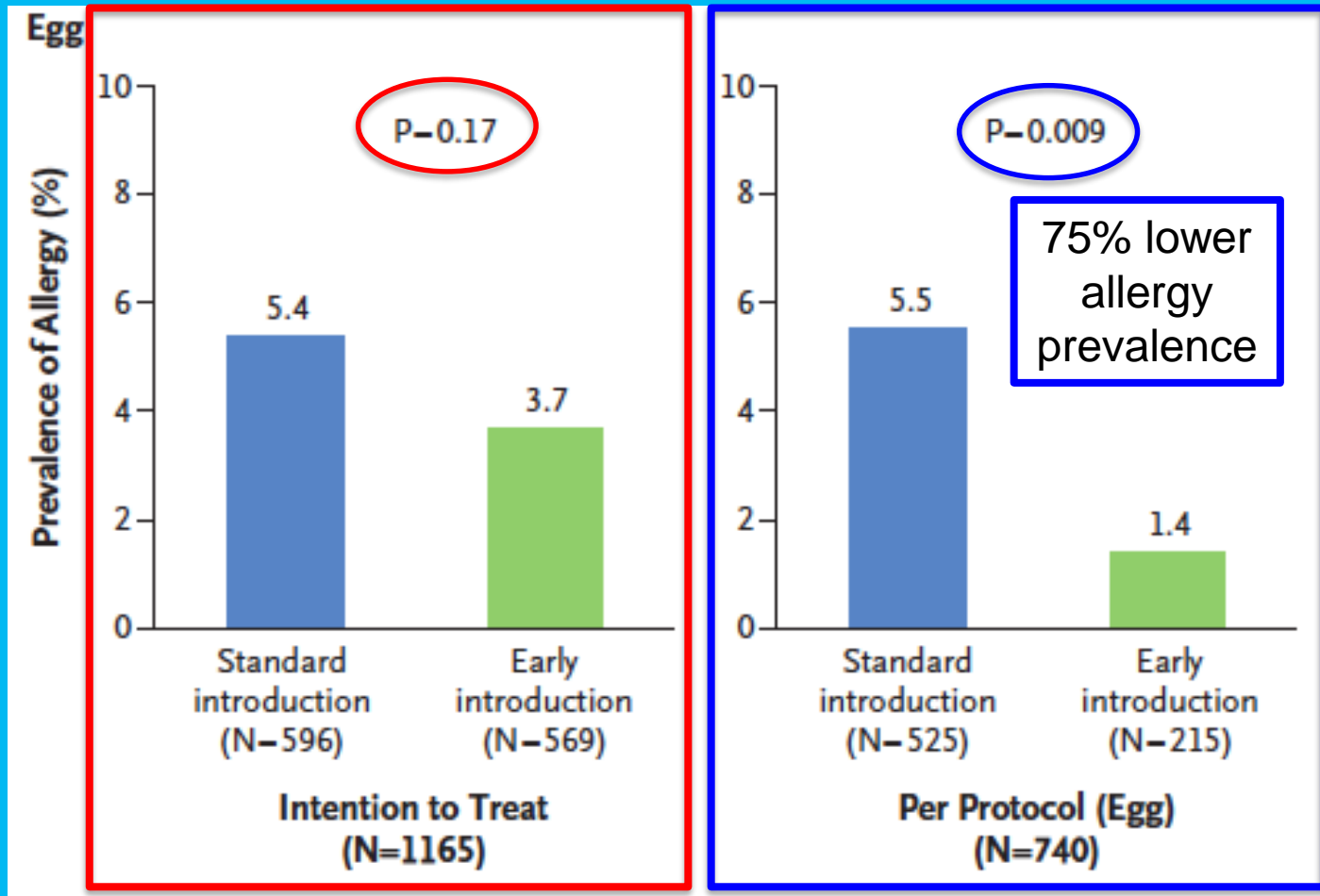
**Primary Outcome:
Food Allergy to 1 of the 6 foods
between 1 yo and 3 yo**

EAT Trial- Peanut



Conclusion: Children who were introduced peanut from 3 months of age PER PROTOCOL were significantly less likely to have peanut allergy

EAT Trial- Egg



Adherence defined as eating at least 75% of the recommended amount of the food for at least 5 weeks

Conclusion: Early introduction of cooked egg was a safe approach and was associated with a significantly lower prevalence of egg allergy

EAT Trial- Other Allergens

- ▶ **There were no significant effects with respect to:**
 - Milk
 - Sesame
 - Fish
 - Wheat
- ▶ **Partial adherence not associated with an increase in prevalence of allergy**
- ▶ **Early food introduction did not affect growth or duration of breastfeeding**

Standard: 98% still BF at 6 mo
Early: 97% still BF at 6 mo
UK: 81% still BF at 6 mo
($P < 0.001$)

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

A Systematic Review and Meta-analysis

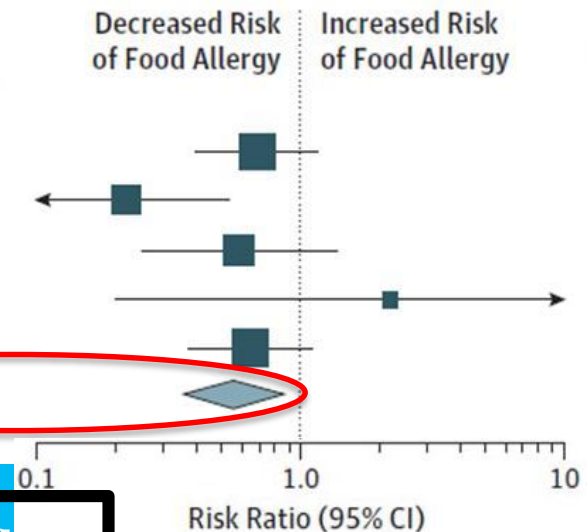
Despo Ierodiakonou, MD, PhD; Vanessa Garcia-Larsen, PhD; Andrew Logan, PhD; Annabel Groome, BSc; Sergio Cunha, MD; Jennifer Chivinge, BSc; Zoe Robinson, BSc; Natalie Geoghegan, BSc; Katharine Jarrold, BSc; Tim Reeves, BSc; Nara Tagiyeva-Milne, PhD; Ulugbek Nurmatov, MD, PhD; Marialena Trivella, DPhil; Jo Leonardi-Bee, PhD; Robert J. Boyle, MD, PhD

A Risk of food allergy



Dietary Introduction of Allergenic Food

Outcome	Early		Late		Risk Ratio (95% CI)
	No. of Events	Total No.	No. of Events	Total No.	
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		943		972	0.56 (0.36-0.87)
Heterogeneity: $I^2 = 35.8\%$; $P = .18$					



Moderate-certainty evidence from 5 trials (n=1915) that early egg introduction at 4 to 6 months was associated with reduced egg allergy

Dietary Intervention Clinical Trials with Milk



Clinical Trial	Conclusion
SPADE: Sakihara et al. JACI 2020	Consuming small amounts of CMF between 1 and 2 months of age prevented development of OFC confirmed CMA in infants from the general population. (Modified ITT, CMA in ingestion group 0.8% vs avoidance 6.8%, $P < 0.001$)
ABC: Urashima et al. JAMA 2019	Avoidance of cow's milk during the first 3 days of life had a protective effect against the development of milk sensitization by 2 years. (Relative risk 0.52, 95%CI 0.34-0.81)
EAT: Perkin et al. NEJM 2016	No significant effects of early milk introduction. (per protocol, $P = 0.63$)
MACS: Lowe et al. JACI 2011	No significant difference between early introduction group (CMF) and avoidance group (soy formula). (OR 1.26, 95%CI 0.84-1.88)

Additional Studies on Early Milk Introduction are Needed

The Strategy for Prevention of Milk Allergy by Daily Ingestion of Infant Formula in Early Infancy (SPADE): Sakihara et al. *JACI* Sept 2020
 The Atopy Induced by Breastfeeding or Cow's Milk Formula (ABC): Urashima et al. *JAMA* 2019
 Enquiring About Tolerance (EAT): Perkin et al. *NEJM* 2016
 The Melbourne Atopy Cohort Study (MACS) Lowe et al. *JACI* 2011

Dietary Intervention Clinical Trials with Tree Nuts



▶ TREE NUTS: No completed RCTs

- Ongoing RCTs called **TreEAT** (NCT04801823, home vs OFC intro of mixed tree nuts (almond, cashew, walnut, hazelnut) in high-risk infants)
- **The Cashew Study** (ACTRN12618000228280, dose response RCT investigating cashew ingestion in 6-12 month old infants)

Dietary Intervention Clinical Trials

► MULTI-FOOD:



TEFFA: Tolerance Induction through Early Feeding to prevent Food Allergy (DRKS00016770)

- 150 infants with eczema starting at 4-8 months
- Effect of early intro of **egg, cow's milk, peanut, hazelnut** via “rusk-like feeding powder” ingested daily for 6-8 months
- **Outcome:** IgE-mediated food allergy assessed at 1 yo. Sensitized infants will undergo OFC.

SEED: Start Eating Early Diet

- 900 infants in the US over 3 years (FARE/Northwestern)
- Effect of multiple foods, **milk, egg, peanut, cashew, walnut, sesame, soy, almond**, eaten in the first year on FA outcomes assessed at 12mo, 24mo, 36mo

A Consensus Approach to the Primary Prevention of Food Allergy Through Nutrition: Guidance from the American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma, and Immunology; and the Canadian Society for Allergy and Clinical Immunology

David M. Fleischer, MD • Edmond S. Chan, MD • Carina Venter, PhD, RD • ... Marion Groetch, RD • Marcus Shaker, MD, MS • Matthew Greenhawt, MD, MBA, MSc   • [Show all authors](#)

Published: November 26, 2020 • DOI: <https://doi.org/10.1016/j.jaip.2020.11.002>

- ▶ **There is strong evidence that early introduction of peanut and egg within the first year of life can prevent the development of food allergy to these respective foods**
 - Around 6 months but not before 4 months
 - Use only cooked forms of egg (about 1/3 of a cooked egg)
- ▶ **Screening infants for evidence of sensitization to peanut and/or egg before initial introduction is not required, though this may be a preference-sensitive care choice for some families.**
 - Encourage home introduction

A Consensus Approach to the Primary Prevention of Food Allergy Through Nutrition: Guidance from the American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma, and Immunology; and the Canadian Society for Allergy and Clinical Immunology

David M. Fleischer, MD • Edmond S. Chan, MD • Carina Venter, PhD, RD • ... Marion Groetch, RD •

Marcus Shaker, MD, MS • Matthew Greenhawt, MD, MBA, MSc   • [Show all authors](#)

Published: November 26, 2020 • DOI: <https://doi.org/10.1016/j.jaip.2020.11.002>

- ▶ If screening is performed, the clinician should consider offering sensitized infants an OFC to determine an objective outcome of allergy or tolerance
- ▶ With respect to **other potentially allergenic foods** (cow's milk, soy, wheat, tree nut, sesame, fish, shellfish):
 - While no RCT suggests benefit from early introduction of these items, there are no data suggesting that early introduction at around 6 months of life is harmful.
 - There are observational data suggesting harm from intentional delayed introduction

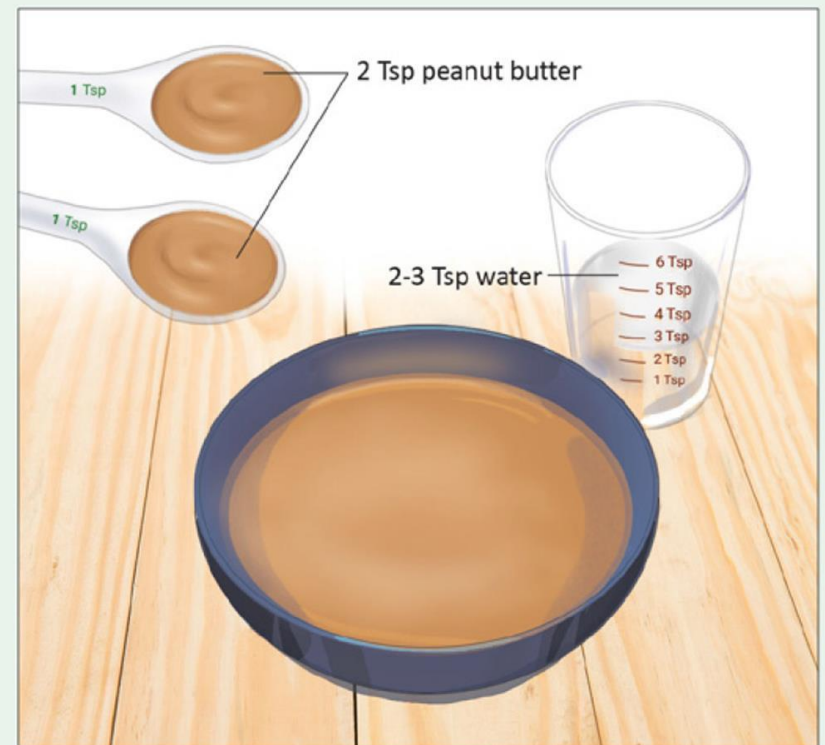
How Much do Infants Need to Eat?

- ▶ Peanut: About 1-2 teaspoons peanut butter/powder per serving, served 2-3 times per week as tolerated
- ▶ Egg: About 1/3 of a well-cooked egg, 2-3 times per week
- ▶ New consensus guidelines say that there is insufficient evidence to support a precise dose and frequency necessary to support tolerance. Panel recommended “parents focus on feeding amounts and types of peanut-or egg-containing foods that their child likes and tolerates with some frequency...such as 1-2 teaspoons of peanut butter or egg at least once weekly, should be encouraged, and larger amounts if the child enjoys the food.”

APPENDIX D. INSTRUCTIONS FOR HOME FEEDING OF PEANUT PROTEIN FOR INFANTS AT LOW RISK OF AN ALLERGIC REACTION TO PEANUT



Option 1: Bamba (Osem, Israel), 21 pieces (approximately 2 g of peanut protein)



Option 2: Thinned smooth peanut butter, 2 teaspoons (9-10 g of peanut butter; approximately 2 g of peanut protein)

Implementation: Commercial Products

► Commercial vs Conventional Products for Early Introduction

TABLE IV. Commercial products for early introduction of food allergens compared with conventional foods*

Features	Commercial	Conventional
Cost	More expensive	Less expensive
Convenience	More convenient for families spending little time preparing foods	Can be convenient to families, cooking and preparing most of their meals
Additional ingredients	These foods can act as food allergens too	Ability to use a pure source of the food allergen only
Nutritional composition	Generally low in calories and lacking a wider nutritional profile	Rich sources of other nutrients: see Table E1 in this article's Online Repository at www.jaci-inpractice.org
Dose of food allergen	Some products contain far less food allergen compared with doses used in research and those recommended by international guidelines	A desired dose can be chosen from allergen-containing foods
Degree of heating	Degree of heating/cooking of the allergen may be not similar to those used in research and those recommended by international guidelines	A desired degree of cooking/heating can be chosen from allergen-containing foods

Clinical Communications

J Allergy Clin Immunol Pract 2021 Sep;9(9):3517-3520.e1.

Allergic reactions in infants using commercial early allergen introduction products

Amanda L. Cox, MD, Ami Shah, MD,
Marion Groetch, MS, RDN, and Scott H. Sicherer, MD



Schroer, Groetch, Mack, Venter. JACI in Practice. Oct 2020

Diet Diversity

- ▶ **Infants should be fed a diverse diet as this may help foster prevention of food allergy.**
 - **AAAAI/ACAAI/CSACI Consensus Document 2020**
 - Increased Diet Diversity within 1st year of life associated with decrease food allergy over first 10 years of life (Roduit et al).

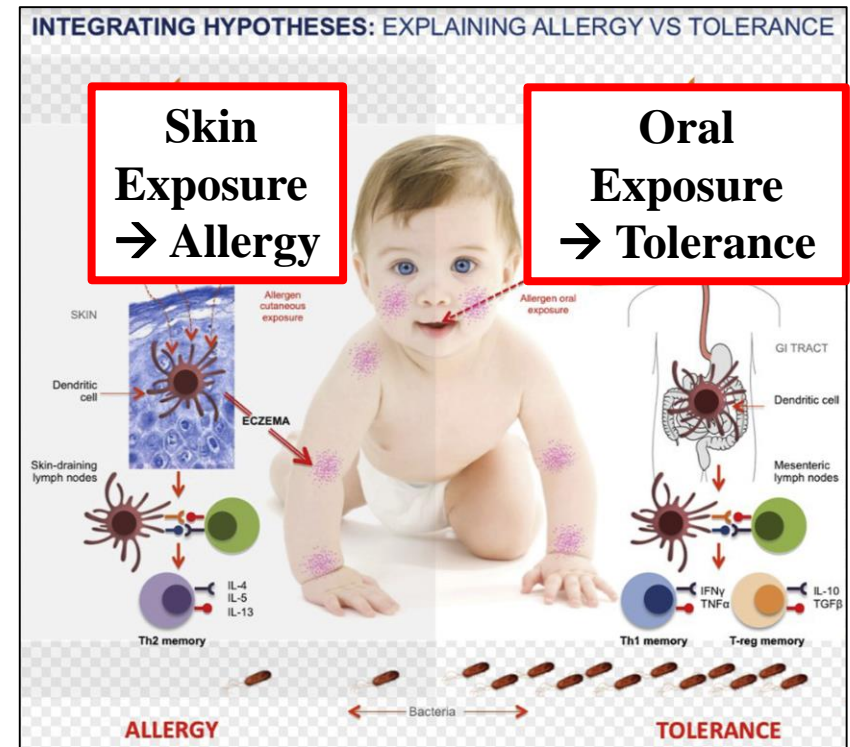
- ▶ **Maternal diet diversity in pregnancy**
 - A maternal diet rich in **vegetables and yogurt** and with **reduced intake of red meat, cold cereal, fried potatoes, rice and grains, and 100% fruit juice** was associated with reduced odds of many allergic outcomes (AR, AD, asthma, wheezing) **but not food allergy**

Grimshaw KE, et al. J Allergy Clin Immunol 2014; 133:511-9.
Grimshaw KE, et al. Pediatrics 2013;132:e1529-38.
Roduit C, et al. J Allergy Clin Immunol 2014;133:1056-64.
Venter et al. Allergy. 2022; 77(1):162-172.

Skin Barrier

Enhancement of Skin Barrier to Prevent Atopic Dermatitis and Food Allergy

- ▶ **Meta-analysis of 10 studies:**
 - Did not find that use of daily emollients in early infancy was protective against eczema or food allergy
 - Some benefit if high-risk population and emollient used continuously
- ▶ **RCTs planned/underway to assess affect on food allergy development**
 - PEBBLES (NCT03667651)
 - SEAL (NCT03742414)
 - PACI (UMIN000028043)



Du Toit et al. J Allergy Clin Immunol. 2018 Jan;141(1):30-40
Zhong Y, et al. Allergy. 2022 Jun;77(6):1685-1699.
Lowe A, et al. BMJ Open. 2019 Mar 13;9(3):e024594.
Yamamoto-Hanada K, et al. Clin Transl Allergy. 2018 Nov 23;8:47.

Breastfeeding and Formula Selection

- ▶ **Exclusive breast feeding – insufficient evidence on food allergy prevention**
 - di Mauro et al. *World Allergy Organ J.* 2016 Aug 18;9:28
 - Lodge et al. *Acta Paediatr.* 2015 Dec;104(467):38-53
 - AAAAI/ACAAI/CSACI Consensus Document 2020

Maternal Diet: Pregnancy and Breastfeeding



- ▶ **No evidence that a maternal exclusion diet (including cow's milk, egg, peanuts) during pregnancy or during lactation affects the development of atopic disease in infants.**
 - Kramer et al. Cochrane Database Syst Rev 2012; 9:CD000133.
 - AAAAI/ACAAI/CSACI Consensus Document 2020
- ▶ **Maternal peanut intake during the first trimester was associated with a 47% reduction in the odds of childhood peanut allergic reaction**
 - Bunyavanich et al. JACI 2014;133:1373-82

Maternal Diet: Pregnancy and Breastfeeding

- ▶ **Ongoing RCT, PrEggNut** (ACTRN12618000937213)
 - Pregnant women to eat 6 eggs and 60 peanuts per week from 22 wks of pregnancy to 4 months of age while BF (compared to 3 eggs and 30 peanuts)
 - Outcome: Egg and/or Peanut Allergy (SPT and OFC) at 12 months

Supplements

- ▶ Prenatal or perinatal maternal or infant use of supplements has no clear benefit for the prevention of food allergy.

- AAAAI/ACAAI/CSACI Consensus Document 2020

- ▶ Vitamin D – no proven benefit

- Allen et al JACI. 2013;131:1109-16: Vitamin D insufficiency associated with food allergy in infants
- di Mauro et al. World Allergy Organ J. 2016 Aug 18;9:28
- RCT underway: VITALITY (NCT02112734)
 - Effect of Vit D supplementation from 2 months to 1 year on food allergy (SPT and OFC) at 12 months



© MaaHoo Studio / Stocksy United

- ▶ Probiotics – possible benefit for prevention of eczema; currently inconclusive for food allergy

- Huang et al. J Allergy Clin Immunol. 2017 Apr; 139(4): 1099–1110.
- Fiocchi et al. World Allergy Organ J. 2015 Jan 27;8(1):4.



activate



Immune
Tolerance
Network

A study about the infant microbiome and allergy development

Exposure to Vaginal Microbiome in C-section Infants at High-risk for Allergies – A Pilot Study (NCT03567707)

Intervention: Vaginal Seeding at Birth

Outcome: Food Allergen Sensitization at 12 months

Study sites: Mount Sinai Hospital and Mount Sinai West

ACTIVATE@mssm.edu
(212) 241-8449

activatestudy.org

If you are pregnant and you or a family member has a history of allergies or asthma, you may be eligible to participate.

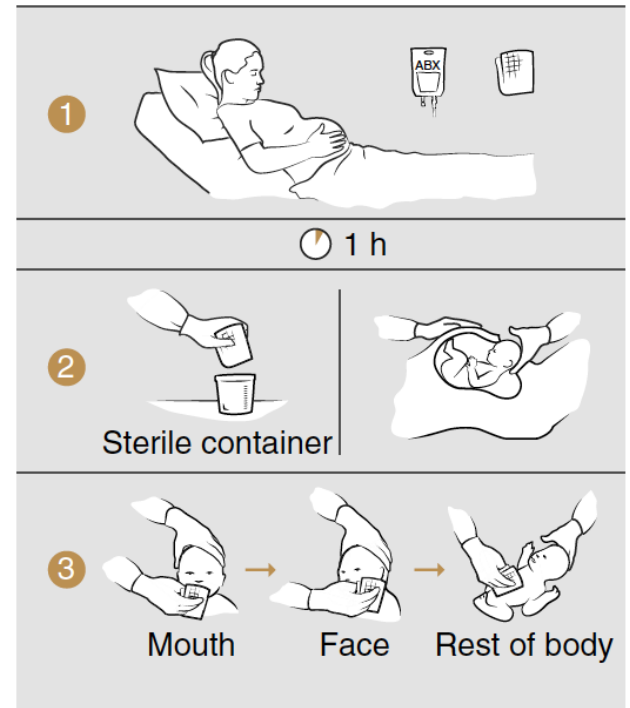


Image: M.J. Schoen

- ❖ Daily administration of a **living bio-therapeutic (STMC-103)** containing three beneficial gut microorganisms for 1 year:
 - *Lactobacillus crispatus*
 - *Akkermansia muciniphila*
 - *Faecalibacterium prausnitzii*
- ❖ **Objective:** To assess the **safety, tolerability, and preliminary efficacy** of STMC-103H in infants at risk for allergic disease.
- ❖ Enrolling Newborns **14 days or younger** who will be followed for approximately 2 years
- ❖ **CONTACT: FOODALLERGYRESEARCH@MSSM.EDU**



SUNBEAM

Systems Biology of Early Atopy



- ▶ Nationwide, multi-center study evaluating for determinants of allergic diseases, in particular **food allergy and eczema**
 - clinical, environmental, biological, genetic, early-life factors
- ▶ Recruiting from the general population and must be **delivering at Mount Sinai Hospital**
- ▶ Enrolling during pregnancy, and infants followed until 3 years of age

Contact: Sunbeam@mssm.edu



Take Home Points

- ▶ Testing results in many false positives. Allergy panels are not harmless!
- ▶ Early introduction (starting at 4-6 months of age) of egg and peanut have shown to reduce the development of these food allergies, and are be encouraged
- ▶ Prevention of other food allergies may occur with earlier introduction, but additional studies are needed
- ▶ While concern for reaction was cited as the top barrier to early introduction, early introduction of food allergens appears safe

Take Home Points

- ▶ Early food introduction does not negatively affect rates of breastfeeding
- ▶ Guidelines are constantly being updated based on new studies
- ▶ There is currently insufficient evidence that skin emollients, vitamin supplements/probiotics, or maternal elimination diets are protective, but further studies are underway

Thank you!

For More Information:

Phone number:

Mount Sinai: 212-241-5548

Valley Medical Group: 201-614-6124

Social media and research newsletter:

www.facebook.com/MountSinaiJaffeFoodAllergyInstitute

[@MountSinaiJaffeFoodAllergyInstitute](https://twitter.com/MountSinaiJaffeFoodAllergyInstitute)

foodallergyresearch@mssm.edu