



Bambino Gesù  
OSPEDALE PEDIATRICO

# L'hai sentita l'ultima sullo svezzamento?

Alessandro Fiocchi  
OPBG  
Roma

Caserta, 5 maggio 2016

**1. In principio era il verbo**

Le raccomandazioni cambiano verso

3. Lo studio LEAP

4. La Consensus Communication on Early Peanut Introduction

5. Possibili conseguenze: NIH guidelines

6. Gli studi del 2016

7. Conclusioni

In the beginning was the Word,  
and the Word was with God.

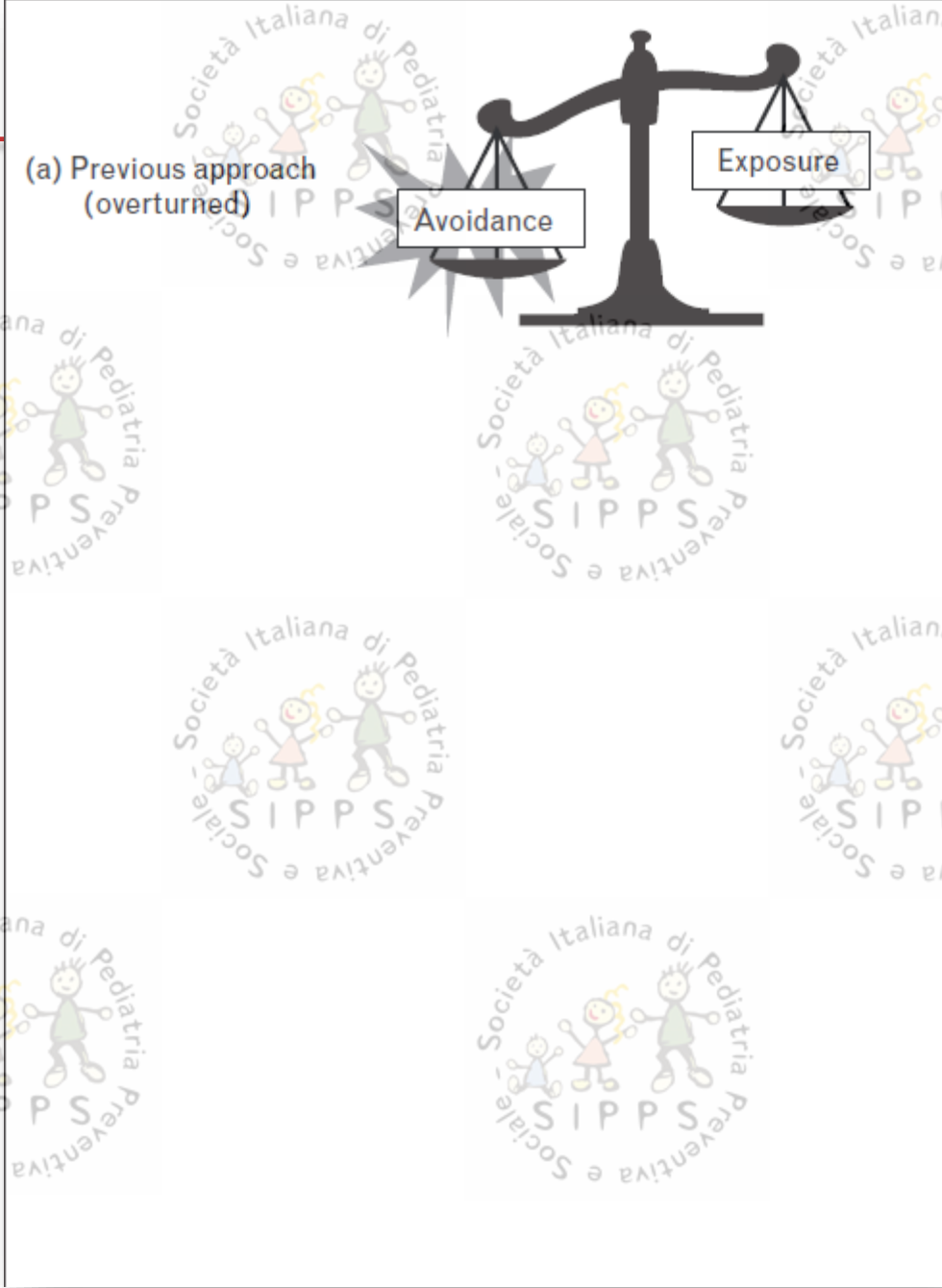
In the

Beginning

## Weaning & food allergy prevention

1. Breastfeeding is indicated during the first 6 months
2. Complementary feeding from the sixth month of life
3. Delay exposure to solid foods for prevention of food allergies
4. Introduce foods individually and gradually
5. Mixed foods containing various food allergens should not be given as starting foods
6. Cooked, homogenised foods preferred to their fresh counterparts when processing reduces allergenicity





Pregcotti S, Fiocchi A. Avoidance or exposure to foods in prevention and treatment of food allergy? *Corr Opin Allergy Clin Immunol* 2010,10:258-66

## Current recommendations:

- breastfeed as long as possible
  - feed a child:
    - when they are hungry and developmentally ready;
    - around 4-6 months.
- no specific recommendations re. allergenic foods

Year (author)

2007 - P

2008

2008 - Agos

2010

NIH

Primary



# EAACI food allergy guidelines

Recommendation	Evidence level	Grade
Exclusive breastfeeding is recommended for all infants for the first 4-6 months	II-III	C
No dietary restrictions for all pregnant or the lactating mother for allergy preventive purposes	I-II	B
If breastfeeding is insufficient or not possible:		
<ul style="list-style-type: none"> <li>- high-risk infants → hypoallergenic formula with documented preventive effect</li> <li>- other infants → standard formula</li> </ul>	I	A-B
<b>Complementary foods after the age of 4 months → normal standard weaning practices</b>	I	A-B
No withholding or encouraging exposure to “highly allergenic” foods such as cow’s milk, hens egg and peanuts irrespective of atopic heredity, once weaning has commenced	II-III	C



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

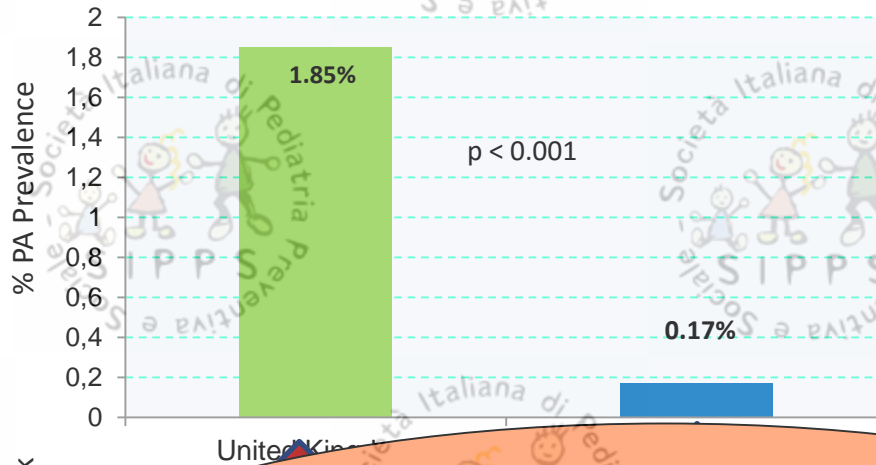


- 5171 Jewish school children in UK and 5615 Jewish school children in Israel were compared for food allergies and atopy.
- Questionnaire based assessment of peanut allergy validated by challenges.
- Infant weaning for peanut and other foods was determined in infants using a validated FFQ.

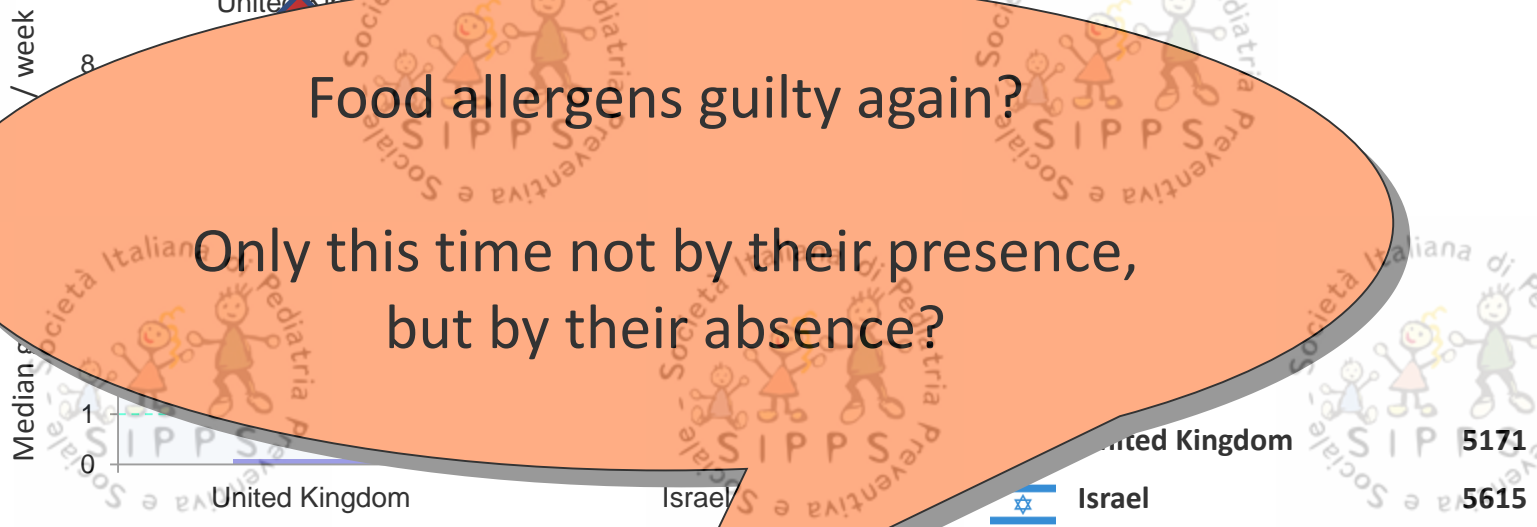
Du Toit G. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. J Allergy Clin Immunol. 2008;122:984-91

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

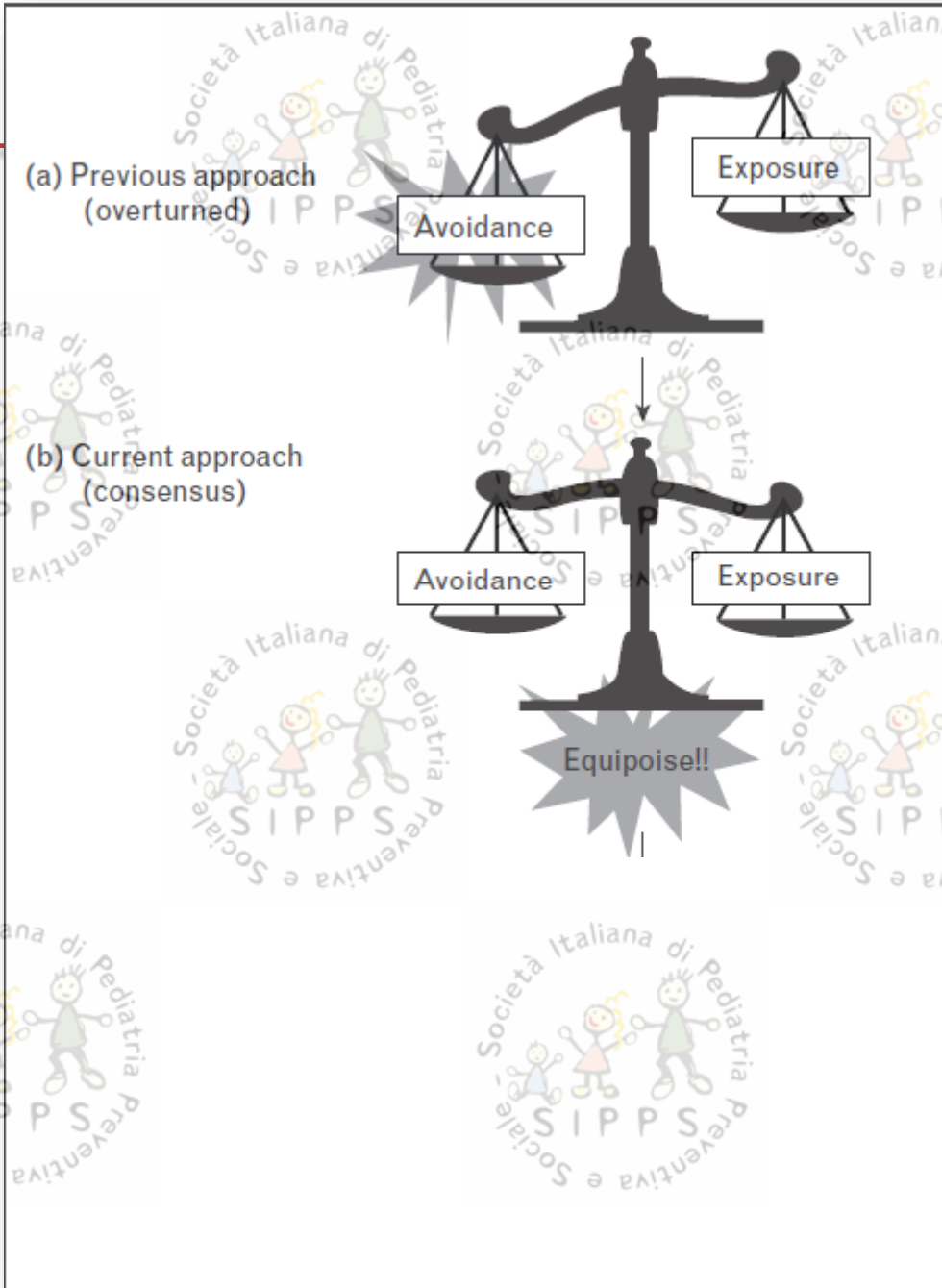
Du Toit G. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. J Allergy Clin Immunol. 2008;122:984-91



Prevalence of Peanut Allergy in Children 4 - 18yrs



Food allergens guilty again?  
 Only this time not by their presence,  
 but by their absence?



Pregcotti S. Avoidance or exposure to foods in prevention and treatment of food allergy? *Corr Opin Allergy Clin Immunol* 2010;10:258-66



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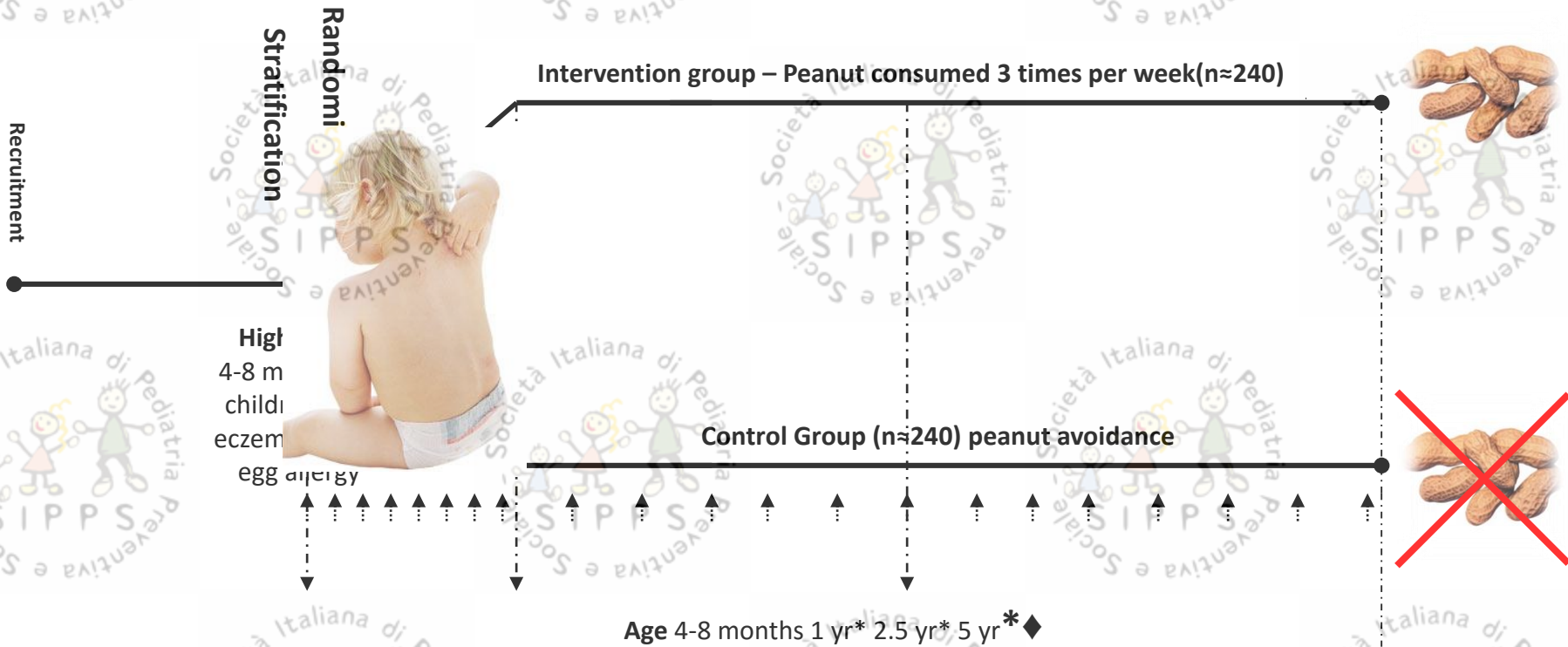






Società Italiana di Pediatria Preventiva e Sociale  
SIPPS

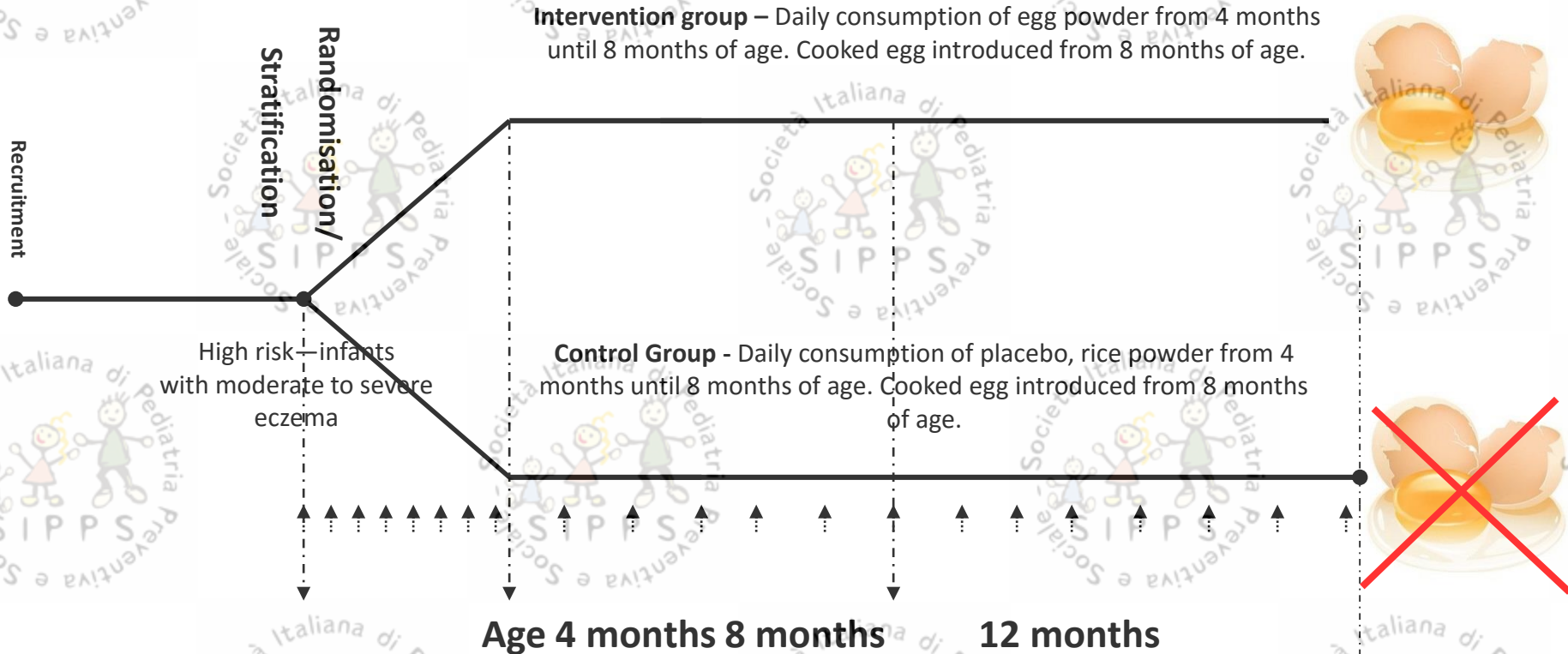
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**Outcome: Prevalence of clinically-defined peanut allergy at 5 years of age.**

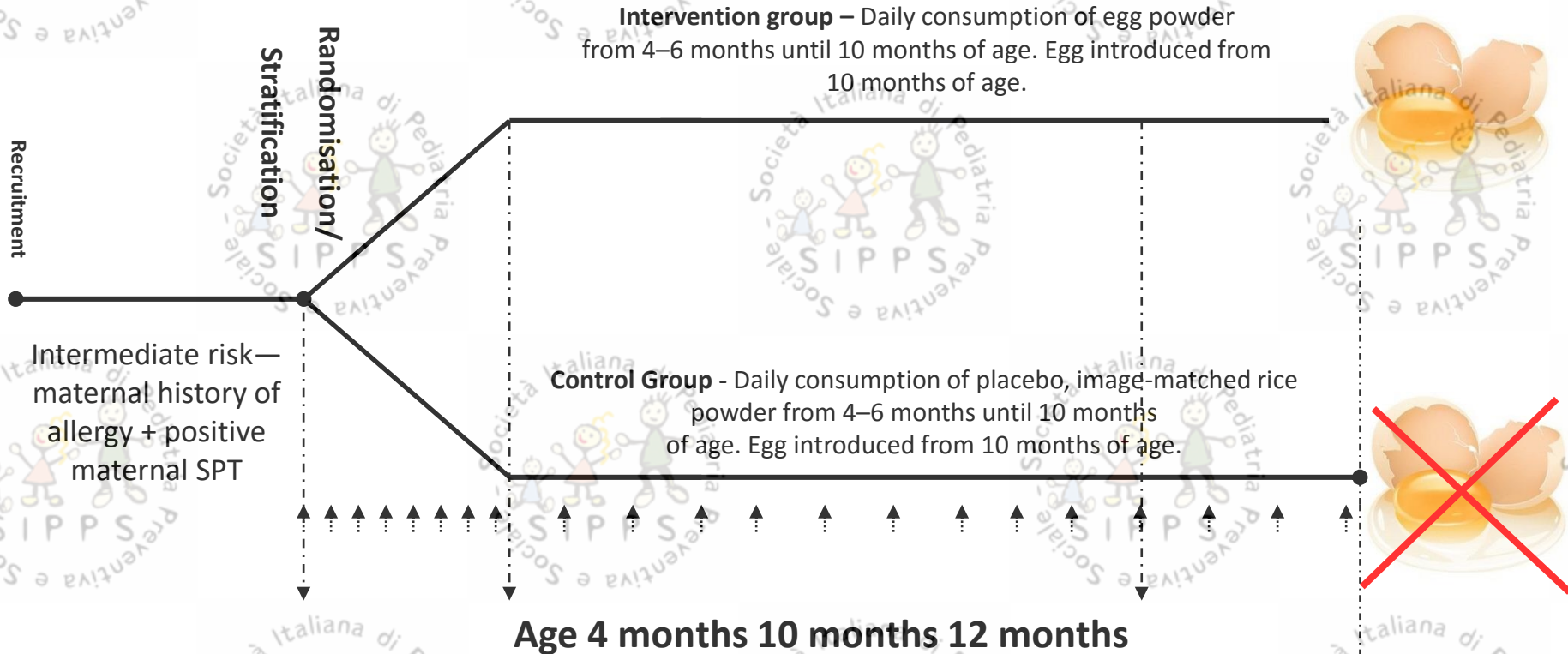


# STAR study (Adelaide & Perth, Australia)



**Outcome: IgE mediated egg allergy at 12 months of age based on positive SPT and egg challenge**

# STEP study (Adelaide & Perth, Australia)

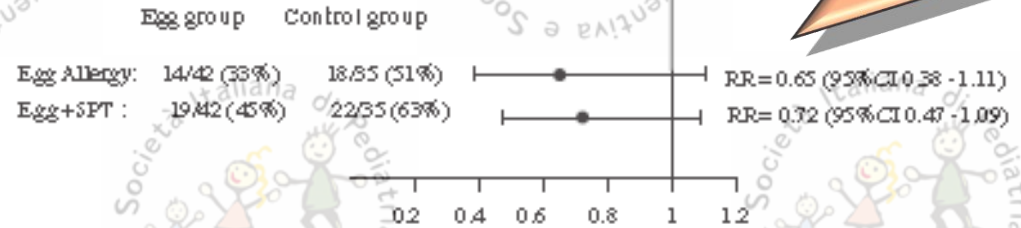
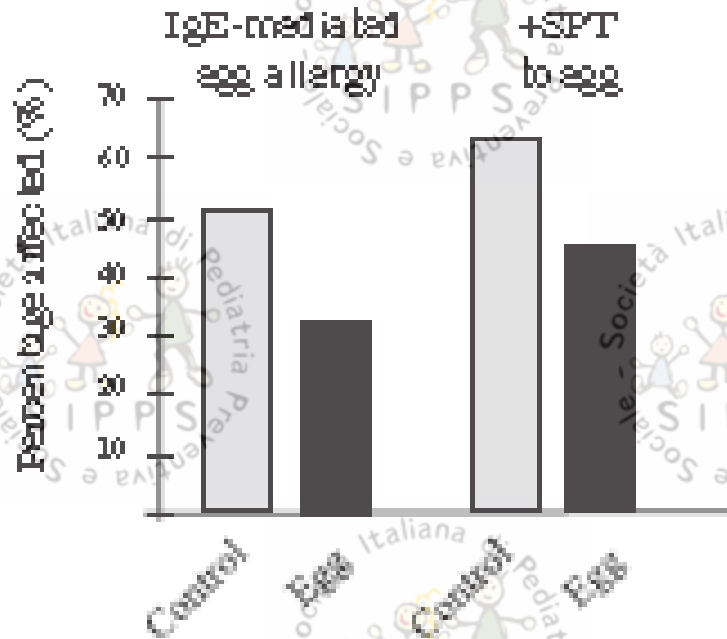


**Outcome: IgE mediated egg allergy at 12 months of age based on positive SPT and egg challenge**

# Egg allergy at 12 months

Egg group: 33%

Rice group: 51%



RR 0.65, p = 0.11



Società Italiana di Pediatria Preventiva e Sociale - SIPPSS

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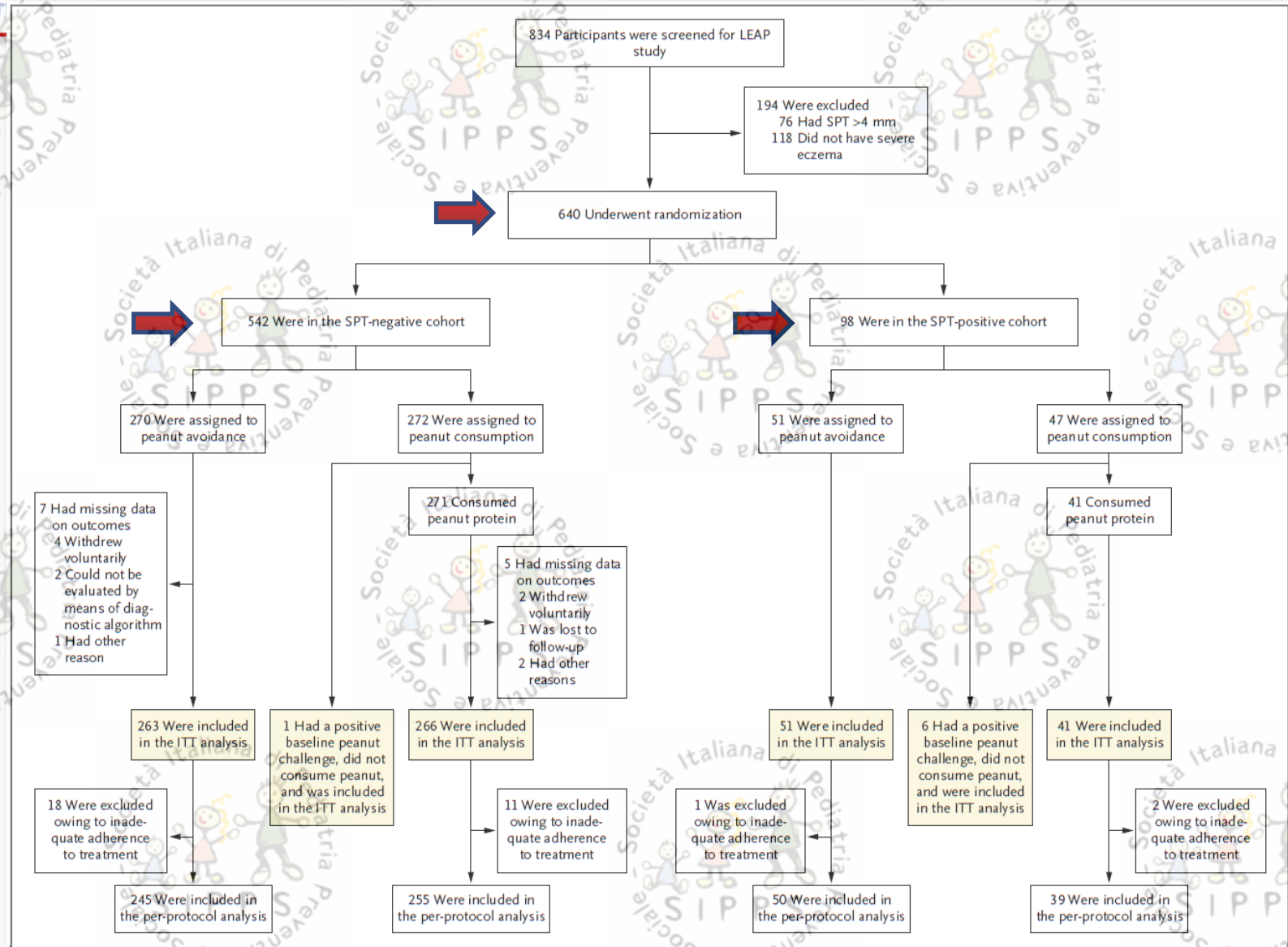
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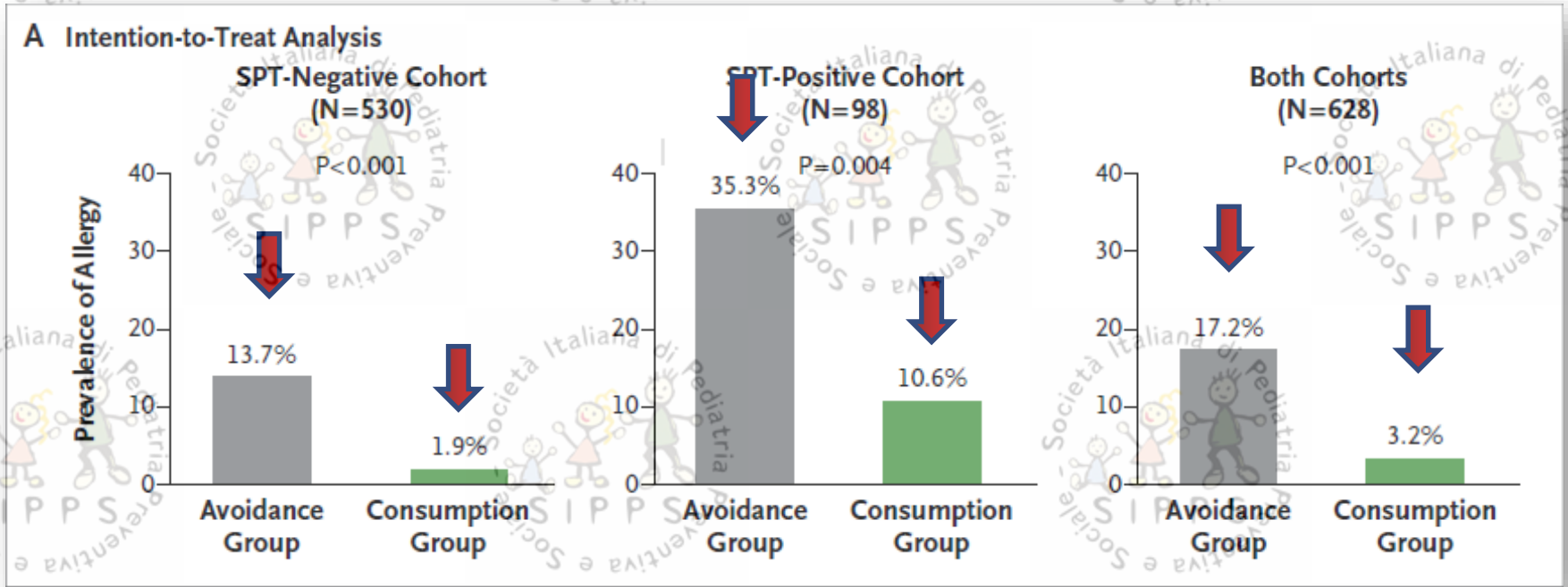
Società Italiana di Pediatria Preventiva e Sociale - SIPPSS

RESERVED

# LEAP study: enrollment & randomization

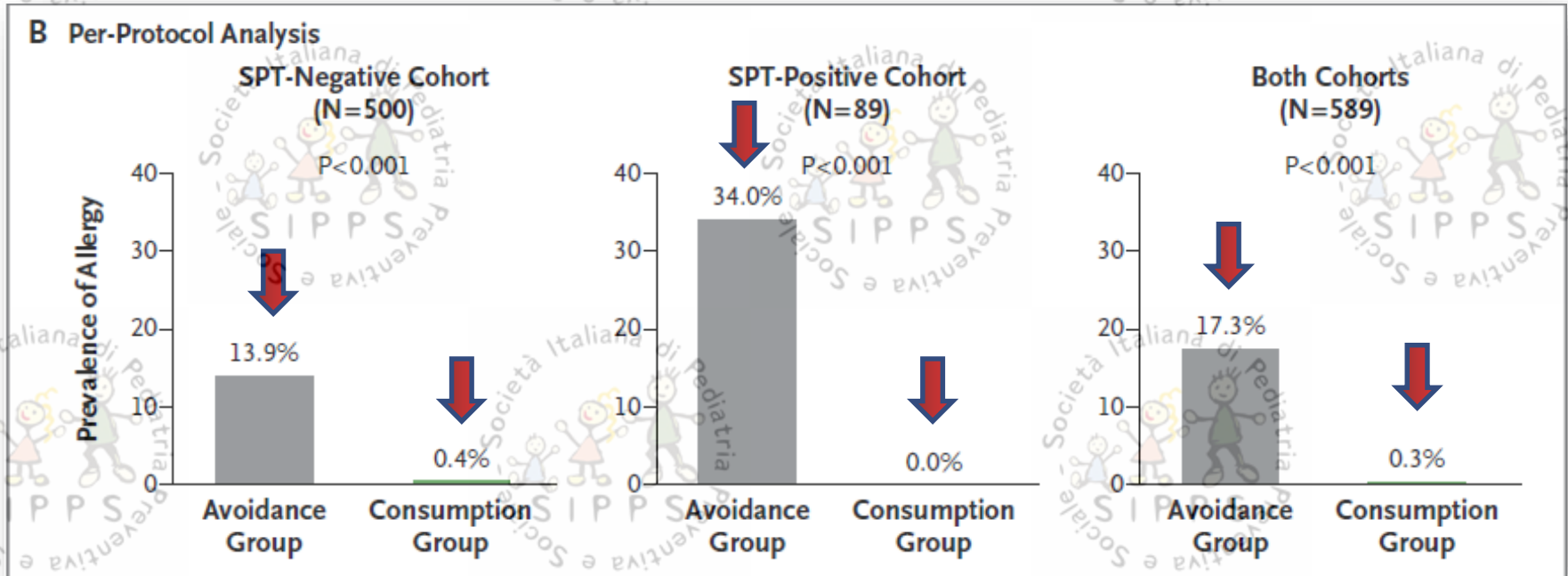


# LEAP study: primary outcome

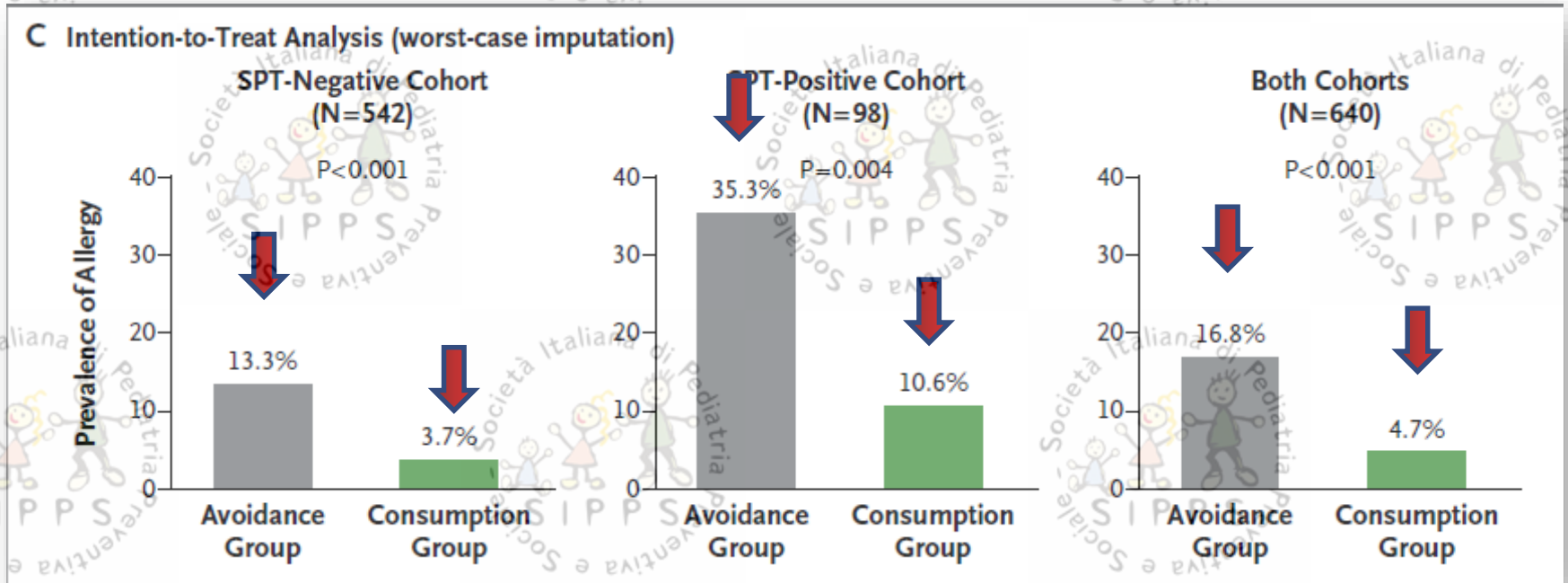


Du Toit G; LEAP Study Team. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015;372:803-13

# LEAP study: primary outcome



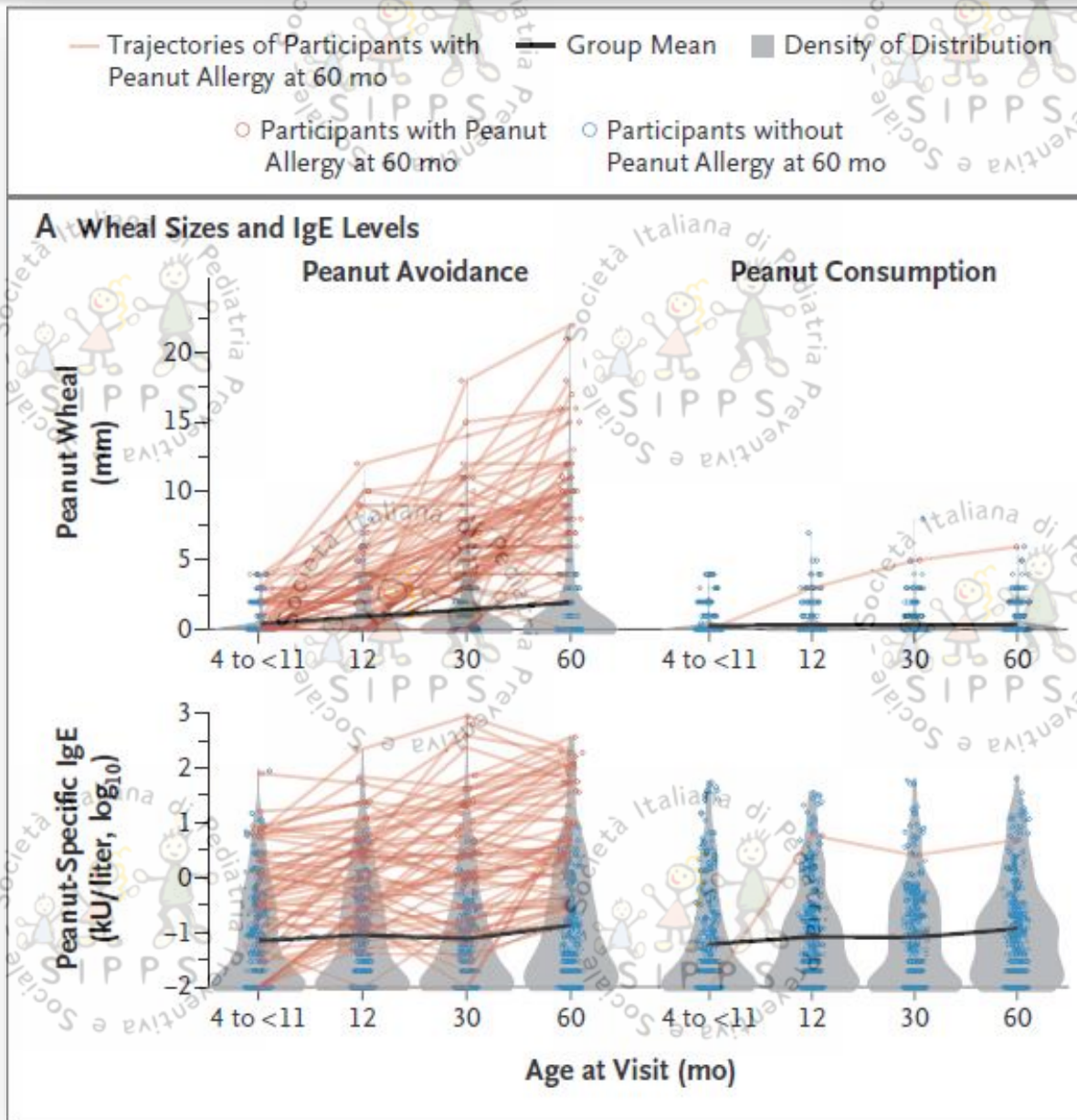
# LEAP study: primary outcome



Du Toit G; LEAP Study Team. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015;372:803-13

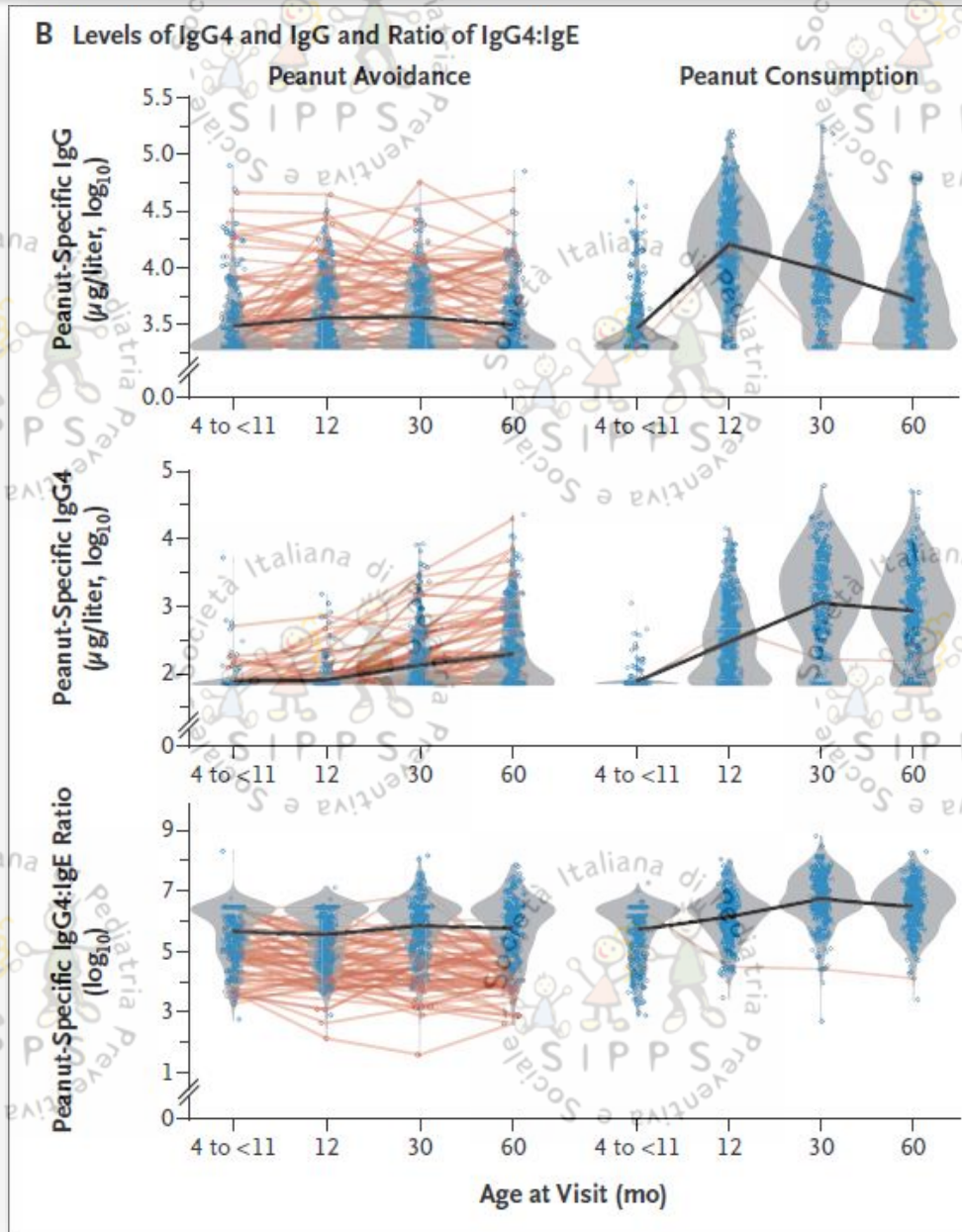


# LEAP study: peanut SPT wheal sizes & peanut-specific IgE



Du Toit G; LEAP Study Team. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015;372:803-13

# LEAP study: peanut-specific IgG, IgG4 & IgE

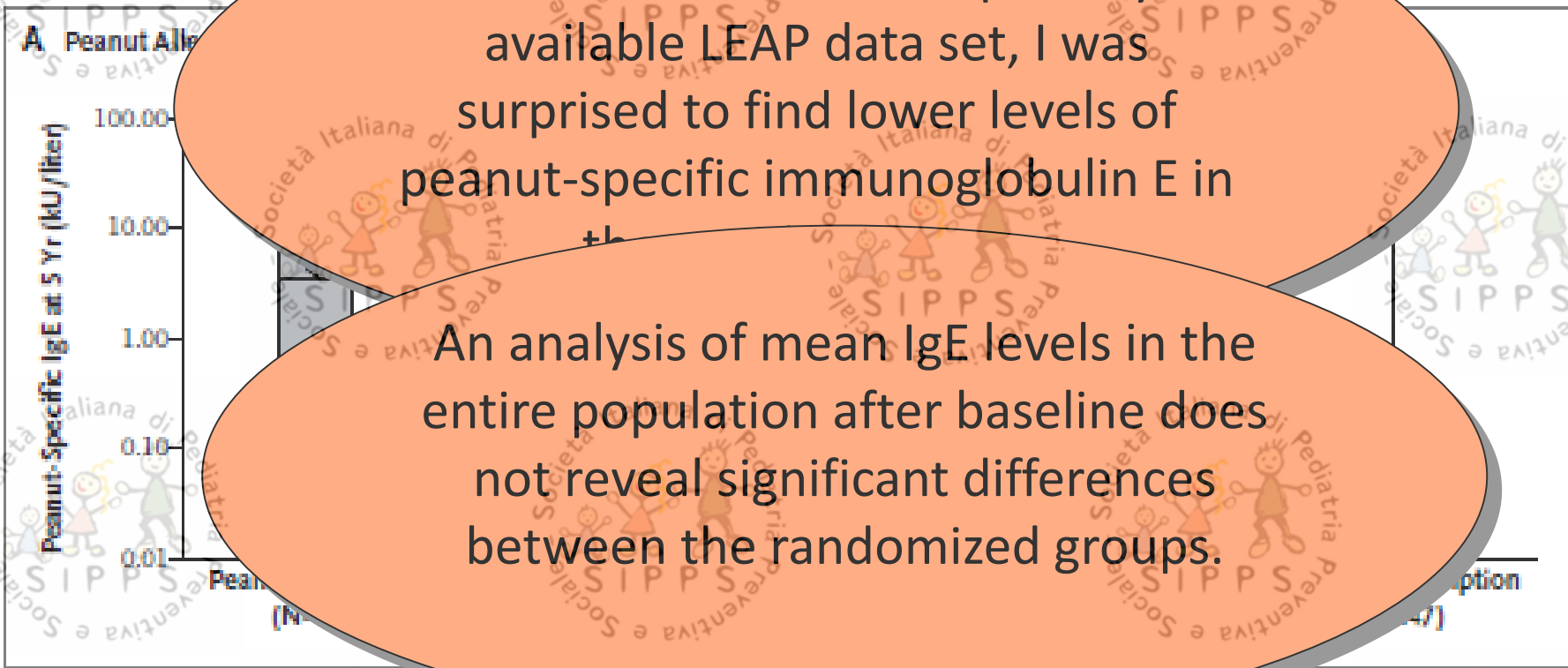


Du Toit G; LEAP Study Team. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015;372:803-13

## Grabenheinrich: peanut-specific IgE

When I examined the publicly available LEAP data set, I was surprised to find lower levels of peanut-specific immunoglobulin E in

An analysis of mean IgE levels in the entire population after baseline does not reveal significant differences between the randomized groups.



# Mito o realtà

## EBM PREVENTION AND MANAGEMENT OF PEDIATRIC ALLERGY



H. SAMPSON



# LEAP study: open questions

1. Should the guidelines be changed?
2. Should we recommend introducing peanuts to all infants before they reach 11 months of age?
3. Do infants need to ingest 2 g of peanut protein (approximately eight peanuts) three times a week on a regular basis for 5 years, or will it suffice to consume lesser amounts on a more intermittent basis for a shorter period of time?
4. If regular peanut consumption is discontinued for a prolonged period, will tolerance persist?
5. Can the findings of the LEAP study be applied to other foods, such as milk, eggs, and tree nuts?

## LEAP study: what now.

1. any infant between 4 months and 8 months of age at risk for peanut allergy should undergo skin-prick testing for peanut.
2. if the test results are negative, the child should be started on a diet that includes 2 g of peanut protein three times a week for at least 3 years,
3. if the results are positive - mild sensitivity (wheal 4 mm or less), the child should undergo a food challenge; children who are nonreactive should then be started on the peanut-containing diet.

We can do something now  
to reverse the increasing prevalence  
of peanut allergy.

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# Consensus communication

A landmark collaborative action, 10 medical professional organizations:

1. American Academy of Allergy, Asthma & Immunology (AAAAI)
2. American Academy of Pediatrics (AAP)
3. American College of Allergy, Asthma & Immunology (ACAAI)
4. Australasian Society of Clinical Immunology and Allergy (ASCIA)
5. Canadian Society of Allergy and Clinical Immunology (CSACI)
6. European Academy of Allergy and Clinical Immunology (EAACI)
7. Israel Association of Allergy and Clinical Immunology (IAACI)
8. Japanese Society for Allergology (JSA)
9. Society for Pediatric Dermatology (SPD)
10. World Allergy Organization (WAO)

→ a “Consensus communication” suggesting that the approaches taken in the LEAP trial should be actualized for clinical care “in more diverse settings throughout the world.”

Sicherer SH, Bock SA, Zeiger RS. Implications of the "Consensus Communication on Early Peanut Introduction in the Prevention of Peanut Allergy in High-Risk Infants" for Allergists, Primary Care Physicians, Patients, and Society. *J Allergy Clin Immunol Pract.* 2015;3:649-51



**WAO**  *journal*  
WORLD ALLERGY ORGANIZATION

# World Allergy Organization Journal

The official publication of the World Allergy Organization

- A new online-only journal featuring an accelerated publication process
- Instant access to monthly postings of scientific articles from across the globe
- Indispensable reading for all physicians concerned with the practice of allergy and clinical immunology

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*Journal*

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WORLD ALLERGY ORGANIZATION



Wolters Kluwer  
Health

Lippincott  
Williams & Wilkins

# Consensus communication

- Pediatricians and allergists should recommend introducing peanut-containing products into the diets of “high-risk” infants early in life (between 4 and 11 months of age) **in countries where peanut allergy is prevalent**
- Infants with early-onset atopic disease might benefit from evaluation by **an allergist or trained physician** to diagnose any food allergy and assist in implementing these suggestions

# Consensus communication

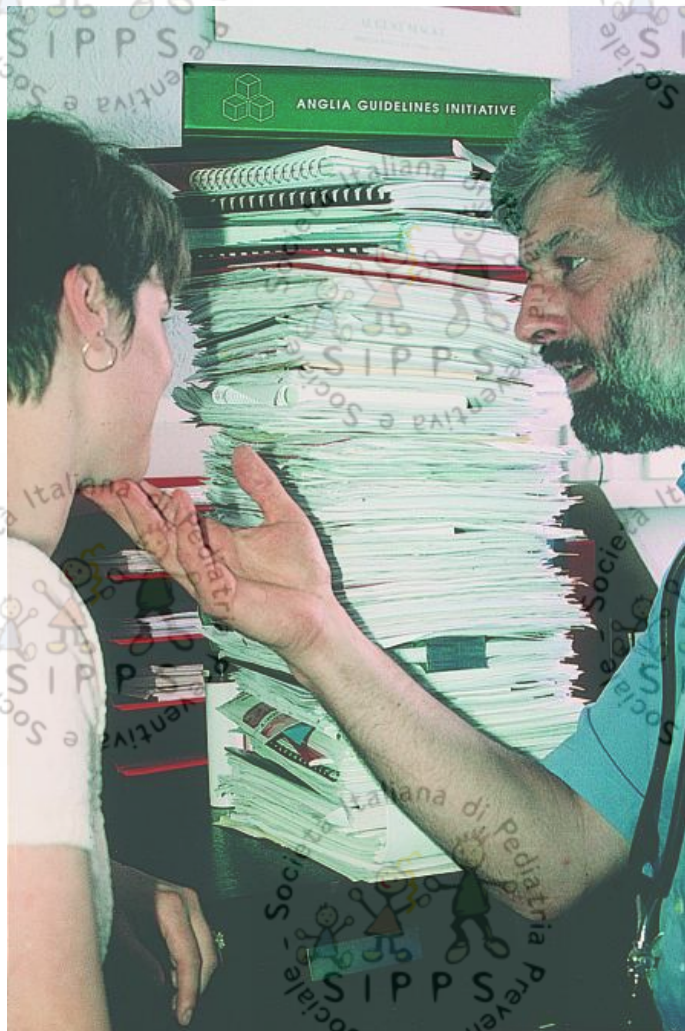
- Evaluation of such patients might consist of performing peanut **skin testing**, in-office **observed peanut ingestion**, or both, as deemed appropriate after discussion with the family
  - The clinician can perform an observed peanut challenge for those with evidence of a positive peanut skin test response to determine whether they are clinically reactive before initiating at-home peanut introduction
- If the child is not allergic to peanuts, they should be consumed at least three times a week, for the amount of at least 6 gms, up to 6 years.**

# Limitations and constraints

- no data about alternative dosing regimens
- no data about minimal length of time needed for “treatment”
- it has focused on “high risk” infants and peanut allergy and has not attempted to generalize the results to other foods or lower risk populations.
- feeding peanut early to high-risk infants will require engagement of the medical community to change the culture of early feeding practices.
- “a National Institute of Allergy and Infectious Diseases Working Group and European Academy of Allergy, Asthma and Clinical Immunology Guidelines Group are addressing a best-practices approach with more extensive guidelines”.

Fleischer DM. Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants. World Allergy Organ J. 2015 Aug 3;8(1):27

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855 different guidelines

A pile 68 cm high, weighing 28 kg

- 243 single page
- 195 two page guidelines
- 160 guidelines more than 10 pages long
- 25 presented as booklets or large folders

60% of the guidelines produced locally

30% had been produced by local trusts

- 30% by general practitioners

40% were produced nationally

4% by the pharmaceutical

4% by the local health authority

REVIEW ARTICLE

## World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines

Alessandro Fiocchi, (Chair), Jan Brozek, Holger Schönemann, (Chair), Sami L. Bahna, Andrea von Berg, Kirsten Beyer, Martin Bozzola, Julia Bradsher, Enrico Compalati, Motohiro Ebisawa, Maria Antonietta Guzman, Haiqi Li, Ralf G. Heine, Paul Keith, Gideon Lack, Massimo Landi, Alberto Martelli, Fabienne Rancé, Hugh Sampson, Airton Stein, Luigi Terracciano, and Stefan Vieths

Keywords: Cow milk allergy; oral food challenge; epidemiology; DBPCFC; amino acid formula; hydrolyzed milk formula; hydrolyzed rice formula; hydrolyzed soy formula; skin prick test; specific IgE; OIT; SOTI; GRADE

Authorship

## Guidelines for the Diagnosis and Management of Food Allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report

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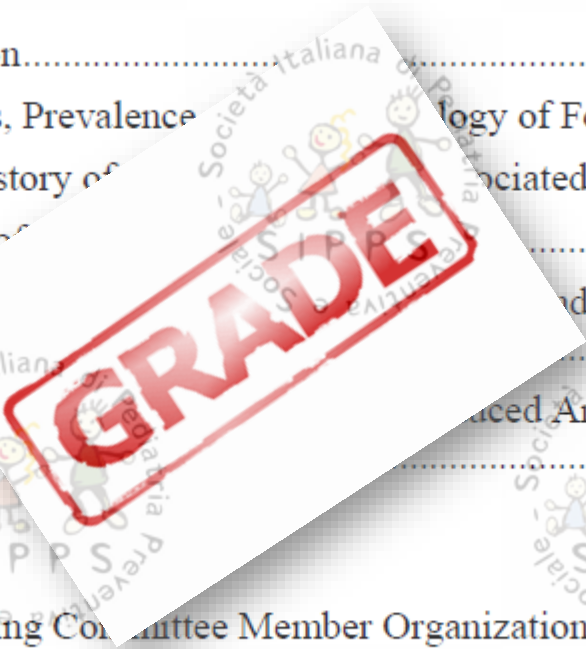
**NIAID-Sponsored Expert Panel Authors:** S. Hasan Arshad, MBBS, MRCP, DM, FRCP,<sup>k,j,m</sup> Sami L. Bahna, MD, DrPH,<sup>n</sup> Lisa A. Beck, MD,<sup>o</sup> Carol Byrd-Bredbenner, PhD, RD, FADA,<sup>p</sup> Carlos A. Camargo, Jr, MD, DrPH,<sup>b</sup> Lawrence Eichenfeld, MD,<sup>q,r</sup> Glenn T. Furuta, MD,<sup>s,t,u</sup> Jon M. Hanifin, MD,<sup>v</sup> Carol Jones, RN, AE-C,<sup>w</sup> Monica Kraft, MD,<sup>f</sup> Bruce D. Levy, MD,<sup>x</sup> Phil Lieberman, MD,<sup>y</sup> Stefano Lucciolli, MD,<sup>z</sup> Kathleen M. McCall, BSN, RN,<sup>z</sup> Lynda C. Schneider, MD,<sup>aa</sup> Ronald A. Schoen, MD,<sup>bb</sup> F. Estelle R. Simons, MD,<sup>cc</sup> Stephen J. Teach, MD, MPH,<sup>dd</sup> and Barbara P. Yawn, MD, MPH, MSc,<sup>ee,ff</sup>

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Boston, Mass, Cincinnati, Ohio, Durham, NC, Little Rock, Ark, New York and Rochester, NY, Baltimore, Bethesda, and College Park, South Hampton and Newport, Isle of Wight, United Kingdom, Shreveport, La, New Brunswick, NJ, San Diego and Orange, Calif, Aurora, Denver, Colo, Portland, Ore, McLean, Va, Memphis, Tenn, Winnipeg, Manitoba, Canada, Washington, DC, and Rochester and Minneapolis

# NIH guidelines for the diagnosis and management of food allergy

5	<b>TABLE OF CONTENTS</b>	
6	<b>Section 1</b>	Introduction..... 1
7	<b>Section 2</b>	Definitions, Prevalence and Pathology of Food Allergy..... 7
8	<b>Section 3</b>	Natural History of Food Allergy and Associated Disorders..... 21
9	<b>Section 4</b>	Diagnosis of Food Allergy..... 38
10	<b>Section 5</b>	Management of Food Allergy..... 61
11	Prevention of Food Allergy..... 61	
12	<b>Section 6</b>	Diagnosis of Food-Induced Anaphylaxis and
13	Other Acute allergic Reactions..... 91	
14	<b>Appendices</b>	
15	<b>Appendix A:</b>	Coordinating Committee Member Organizations..... 111
16	<b>Appendix B:</b>	Expert Panel Members..... 112
17	<b>Appendix C:</b>	Sample Of An Anaphylaxis Emergency Action Plan..... 116





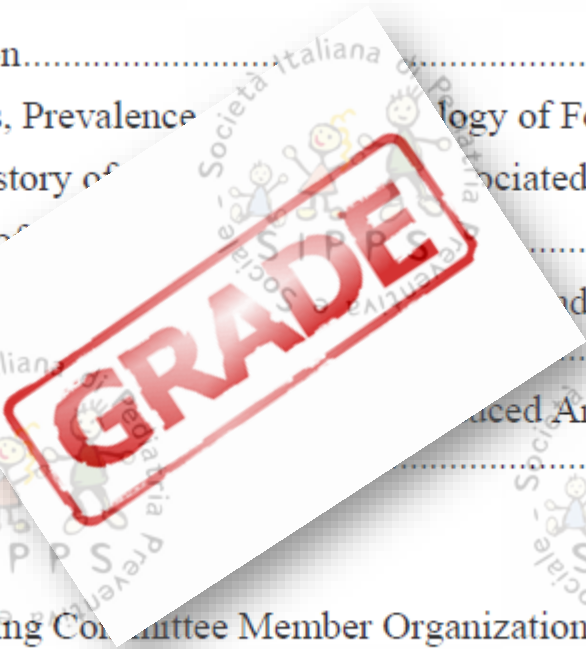


# NIH guidelines for the prevention of food allergy

Guideline 32: [...] Patients at risk for developing FA are defined as those with a biological parent or sibling with existing, or history of, allergic rhinitis, asthma, AD, or FA. This definition of “at risk” is used throughout sections 5.2 and 5.3.

# NIH guidelines for the diagnosis and management of food allergy

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13		Other Acute allergic Reactions..... 91
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15	<b>Appendix A:</b>	Coordinating Committee Member Organizations..... 111
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# NIH guidelines for the prevention of food allergy

**Guideline 37:** [...] all infants be exclusively breast-fed until 4 to 6 months of age, unless breastfeeding is contraindicated for medical reasons.

**Guideline 40:** [...] the introduction of solid foods should not be delayed beyond 4 to 6 months of age. Potentially allergenic foods may be introduced at this time as well.

# The NIAID guidelines modification

NIH was asked to urgently include the evidence from LEAP study in their food allergy guidelines.

An urgent meeting in June – an expert panel named by NIH

Not able to bring the matter to a consensus →

→ another meeting scheduled for November, addendum produced.

→ **The new recommendations are intended to supplement Guidelines 36-40 in 90 Section 5.3.4 of the 2010 Guidelines: “Prevention of Food Allergy.”**

Matters that are very contentious are the following:

- 1) Use the LEAP data as published, i.e. skin test all infants with eczema and introduce peanuts at 4 months of age? If so, discussion re. size of the skin tests.
- 2) Who would do the skin tests and where will the peanuts be introduced, home or office. If office, whose office? Peds or allergist?
- 3) Extrapolate the data to all children without eczema and tell all of America that they should introduce peanuts in the diet at 4 months of age or not?

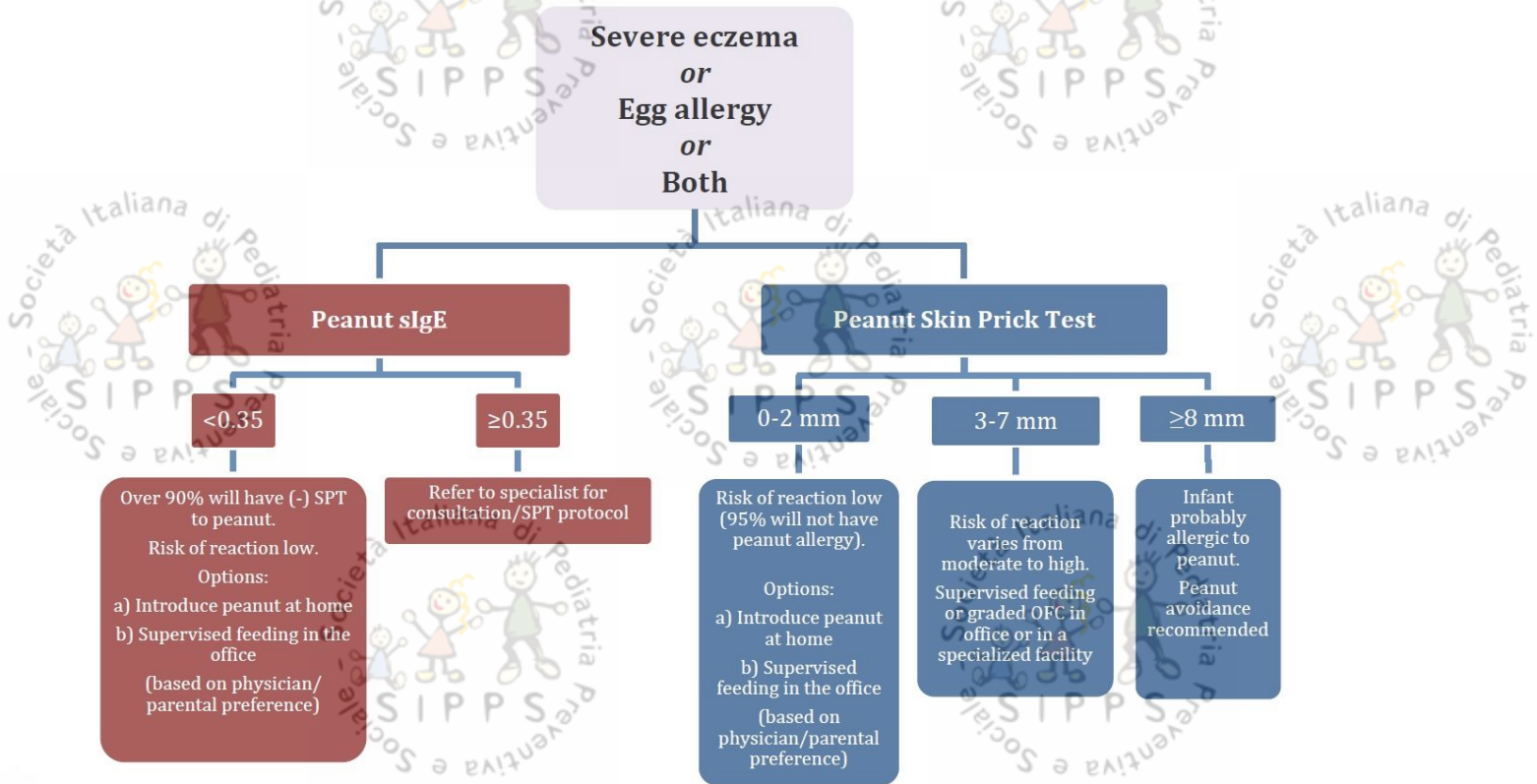
# NIH guidelines for the prevention of peanut allergy

**Addendum Guideline 1:** The EP recommends that infants with **severe eczema**, egg allergy or both have introduction of age-appropriate peanut-containing food as early as 4-6 months of age to reduce the risk of peanut allergy.

Peanut should not be the initial solid food introduced into an infant's diet. Other solid food should be tried first to show the infant is developmentally ready.

The EP recommends that evaluation with peanut-specific IgE or skin prick testing be strongly considered before introduction of peanut to determine if peanut should be introduced and, if so, the preferred method of introduction

# NIH guidelines for the prevention of peanut allergy



NIAID-Sponsored Expert Panel. Guidelines for the diagnosis and management of food allergy in the United States. Currently unavailable



# NIH guidelines for the prevention of peanut allergy

**Addendum Guideline 2:** The EP suggests that infants with **mild to moderate eczema** should have introduction of age-appropriate peanut-containing food as early as 4-6 months of age, in accordance with family preferences and cultural practices, to reduce the risk of peanut allergy. Peanut should not be the initial solid food introduced into an infant's diet. Other solid food should be tried first to show the infant is developmentally ready. Infants in this category may have dietary peanut introduced at home without an in-office evaluation. However, the EP recognizes that some caregivers and health care providers may desire an in-office evaluation, in which case the decision points shown in Figure 1 should apply.

# NIH guidelines for the prevention of peanut allergy

**Addendum Guideline 3:** The EP recommends that infants **without eczema** or any food allergy have age-appropriate peanut-containing foods freely introduced in the diet, together with other solid foods, and in accordance with family preferences and cultural practices.

NIAID-Sponsored Expert Panel. Guidelines for the diagnosis and management of food allergy in the United States. Currently unavailable



# Consensus communication – open questions

Can the medical system handle performing skin tests and feeding tests on a potentially large number of high-risk children?

Could attempts at applying detailed protocol-like feeding instructions to routine care result in unintended consequences, such as increased reactions if peanut is discontinued for various lengths of time?

Would this approach potentially increase risks in situations when peanut is not a typical component of the diet?

**Look before you LEAP: Risk of anaphylaxis in high-risk infants with early introduction of peanut**

## Timing of gluten introduction & CD: 2006

- observational study
- first degree relatives of patients with Diabetes type 1
  - or HLA-DR3/4 positive infants

→ introduce gluten containing food between 4 and 6 months

→ Avoid earlier and later introduction.

Norris JM. Risk of celiac disease autoimmunity and timing of gluten introduction in the diet of infants at increased risk of disease. JAMA. 2005;239:2343–51

- a review and meta-analysis considered
- six observational case–control studies

- an association between duration of breastfeeding and reduced risk of developing CD

Akobeng AK. Effect of breast feeding on risk of celiac disease: a systematic review and meta-analysis of observational studies. Arch Dis Child. 2006;91:39–43,

# Timing of gluten introduction & CD: 2008

Recent observational studies suggest that the introduction of small amounts of gluten while the infant is still breast-fed may reduce the risk of CD

More recently, both early (<3 months) and late (>7 months) introduction of gluten-containing cereals were associated with an increased risk of CD.

- On the basis of current data, the Committee considers it prudent to avoid both early (<4 months) and late (>7 months) introduction of gluten
- to introduce small amounts of gluten gradually while the infant is still breast-fed.

## Timing of gluten introduction & CD: after 2008

### “Prevent CD”:

- dietary-intervention trial
- 944 children HLA-DQ2 or -DQ8 positive, with at least one first-degree relative with CD.
- placebo or 100 mg of gluten from 16 to 24 weeks of age
- No differences among gluten group and placebo group (5,9 % and 4,5 % respectively).
- Breastfeeding did not influence CD development.

➤ The introduction of small amounts of gluten during breastfeeding in the window between 16 and 24 weeks of age do not protect genetically predisposed infants from CD.

Vriezinga SL. Randomized feeding intervention in infants at high risk for celiac disease. N Engl J Med. 2014;371:1304–15

### The Risk of CD and Age at Gluten Introduction (CELIPREV):

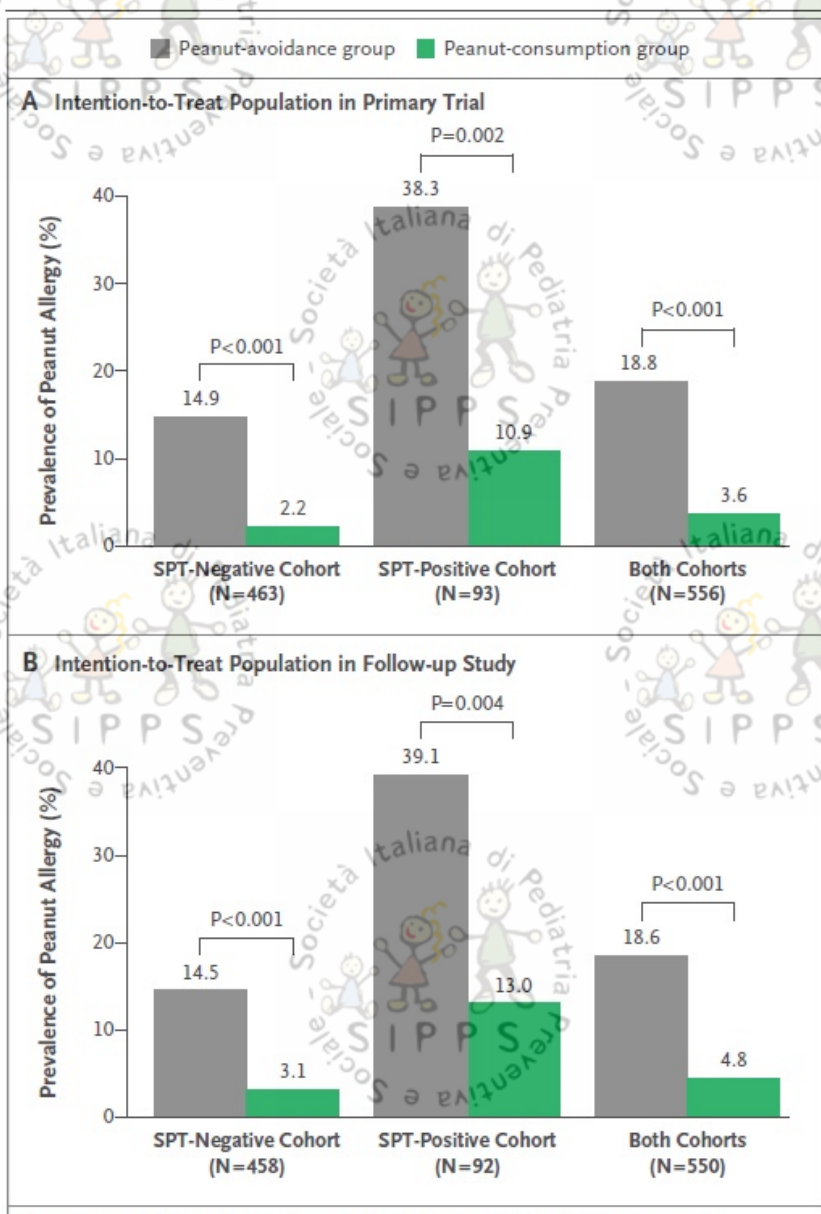
- Interventional trial
- 832 newborns with a first-degree relative with CD
- gluten introduction at 6 months (group A) or 12 months (group B)
- CD higher in group A at 2 years – no differences at 5 years

➤ The timing of gluten introduction do not significantly impact the risk of CD.

Lionetti E. Introduction of gluten, HLA status, and the risk of celiac disease in children. N Engl J Med. 2014;371:1295–303

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# Is the LEAP effect persistent? The LEAP-on trial

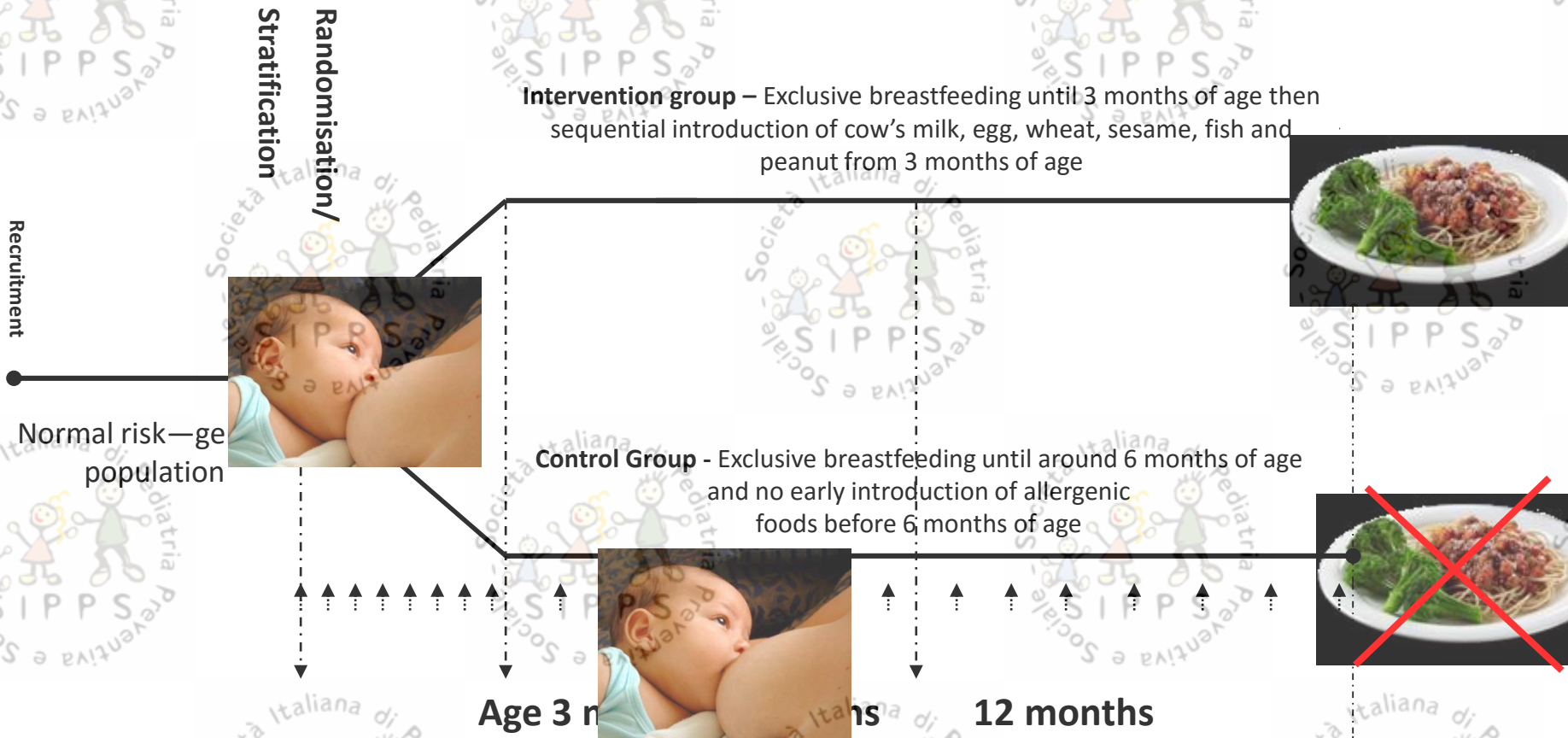


At the end of the primary LEAP trial, we instructed all the participants to avoid peanuts for 12 months. The primary outcome was the percentage of participants with peanut allergy at the end of the 12-month period, when the participants were 72 months of age

Among children at high risk for allergy in whom peanuts had been introduced in the first year of life and continued until 5 years of age, a 12-month period of peanut avoidance was not associated with an increase in the prevalence of peanut allergy

Du Toit G. Effect of Avoidance on Peanut Allergy after Early Peanut Consumption.

# Does early intro prevent all food allergies? The EAT study

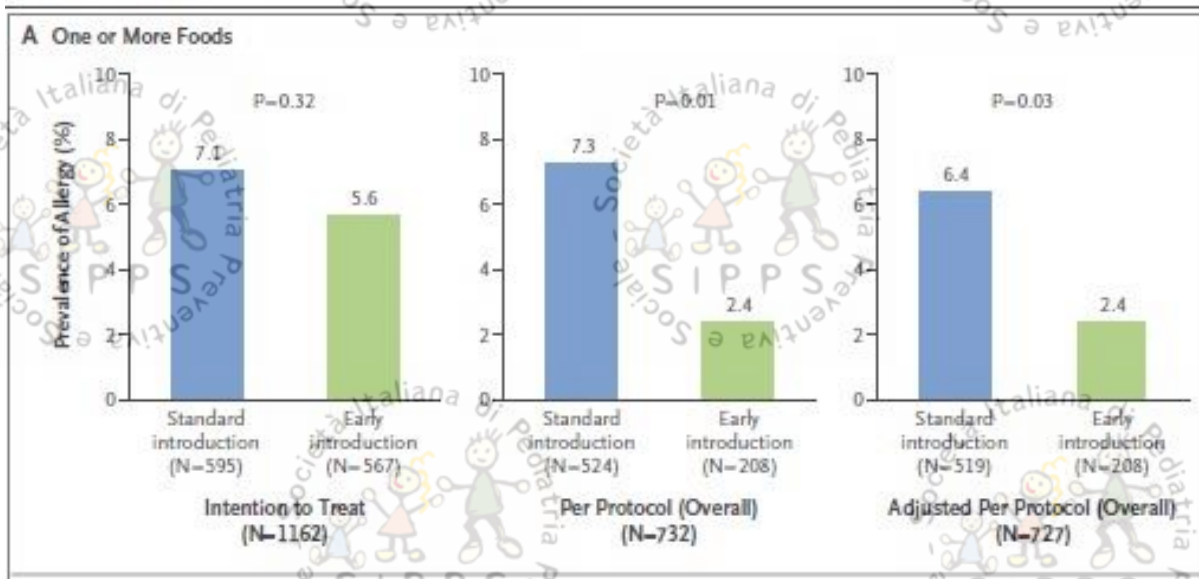


**Outcome: Prevalence of IgE mediated food allergy to any of the 6 foods at 1 - 3 years of age, as defined by OFC.**

# Does early intro prevent all food allergies?

1303 exclusively breast-fed infants from the general population - 3 months of age - randomly assigned to the early introduction of six allergenic foods (peanut, cooked egg, cow's milk, sesame, whitefish, and wheat) or to exclusive breast-feeding to approximately 6 months of age (standard introduction group).

Allergy to one or more of the six foods **7.1% (42/595) vs. 5.6% (32/567)** ( $P = 0.32$ ; ITT)  
**2.4% (38/524) vs. 7.3% (5/208)** ( $P = 0.01$ ; *pp*)

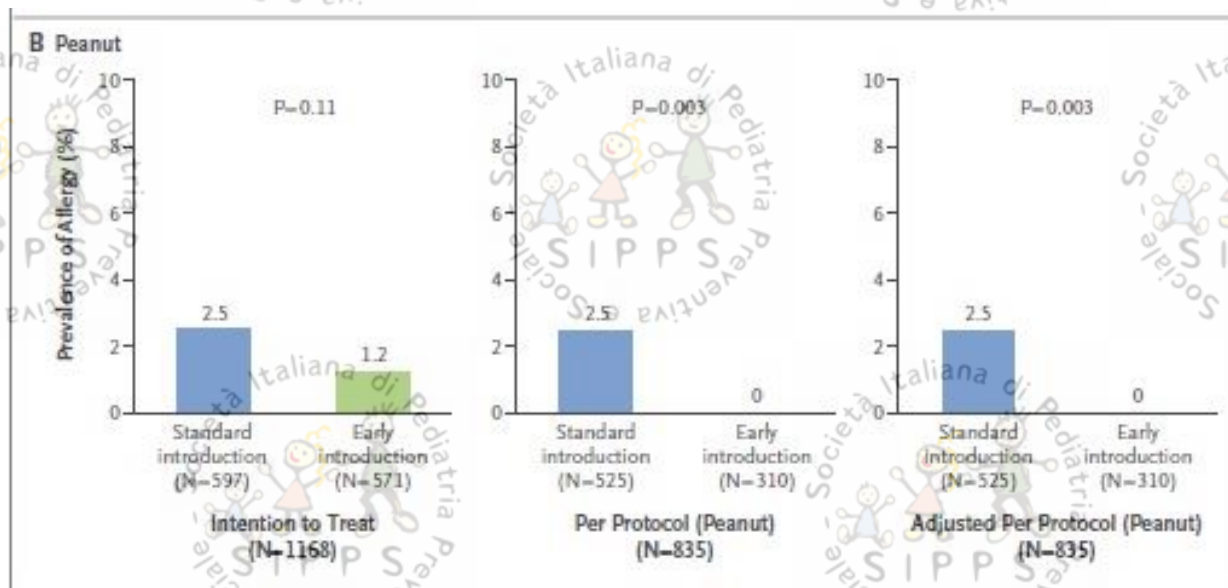




# Does early intro prevent peanut allergy?

1303 exclusively breast-fed infants from the general population - 3 months of age - randomly assigned to the early introduction of six allergenic foods (peanut, cooked egg, cow's milk, sesame, whitefish, and wheat) or to exclusive breast-feeding to approximately 6 months of age (standard introduction group).

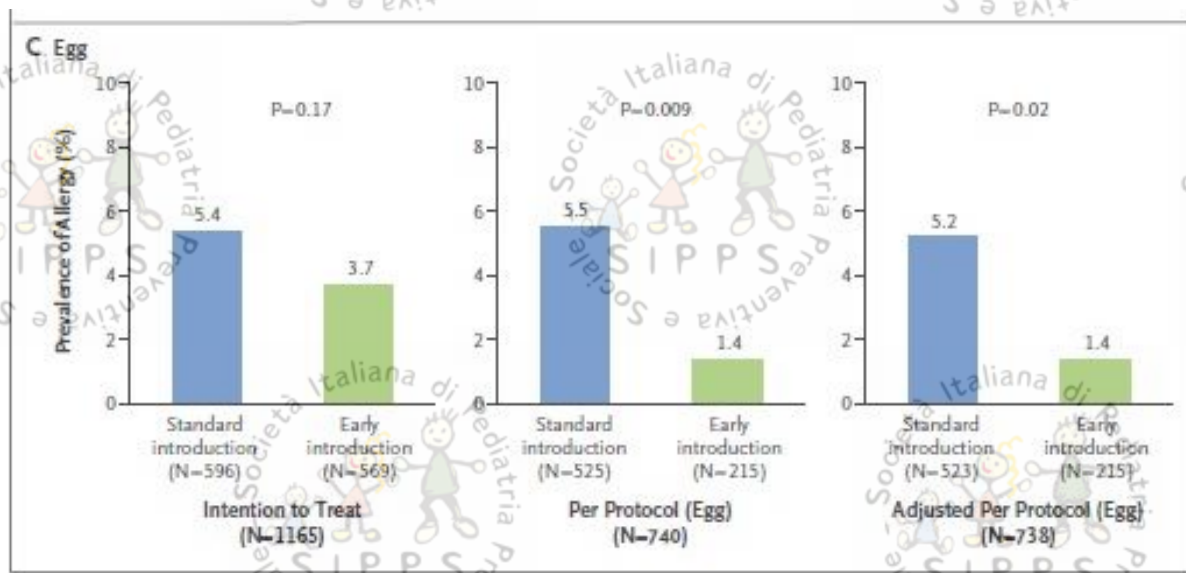
Allergy to peanut **1.2% (42/595) vs. 2.5% (32/567)** ( $P = 0.11$ ; ITT)  
**0% (0/310) vs. 2.5% (13/525)** ( $P = 0.003$ ; *pp*)



# Does early intro prevent egg allergy?

1303 exclusively breast-fed infants from the general population - 3 months of age - randomly assigned to the early introduction of six allergenic foods (peanut, cooked egg, cow's milk, sesame, whitefish, and wheat) or to exclusive breast-feeding to approximately 6 months of age (standard introduction group).

Allergy to peanut **3.7% (42/596) vs. 5.3% (32/569)** ( $P = 0.17$ ; ITT)  
**1.4% (7/525) vs. 5.5% (16/215)** ( $P = 0.009$ ; *pp*)





Feed your children and hope  
that they will EAT!

Wong GW. Preventing Food Allergy in Infancy - Early Consumption or Avoidance? N Engl J Med. 2016 May 5;374:1783-1784

1. In principio era il verbo
2. Le raccomandazioni cambiano verso
3. Lo studio LEAP
4. La Consensus Communication on Early Peanut Introduction
5. Possibili conseguenze: NIH guidelines
6. Gli studi del 2016
7. Conclusioni

# Conclusions

The results of the LEAP trial are impressive

They can have a revolutionary impact in clinical practice

They are not exportable to other food allergies

They are not exportable to other risk categories

They may not have interest in countries at low peanut-allergy risk

In countries at high allergy risk, their implementation may pose practical difficulties

Inserting them in a GRADE guideline without a full GRADE evaluation is not warranted

Systematic reviews on interventional studies on the introduction of food allergens are not feasible



# Simple observations

## argue against benefits of early exposure

- Cows milk protein is typically the earliest “food” apart from breast milk.
- If early exposure promotes tolerance: why is milk allergy one of the most common food allergies?

Food allergens among children in different countries\*

Australia	France	Israel	Italy**	Japan	Singapore**	Spain
Egg	Egg	Egg	Fish	Egg	Bird's nest	Egg
<b>Milk</b>	Peanut	<b>Milk</b>	<b>Milk</b>	<b>Milk</b>	Seafood	Fish
Peanut	<b>Milk</b>	Sesame	Nuts	Seafood	Egg	<b>Milk</b>
Nuts	Mustard	Peanut	Egg	Wheat	<b>Milk</b>	Peach
Sesame	Cod	Soy	Fruit	Snacks	Chinese herbs	Nuts
Wheat	Hazelnut	Nuts	Cereals	Beans		Lentil
Soy	Kiwi	Strawberry	Vegetables	Chicken		Peanut
Fish	Wheat	Beef	Goat milk	Vegetables, Nuts		Chick pea



# World Allergy Symposium

Rome, April 28 – 29°, 2017

