

FOOD ALLERGY –Recent Research- UPDATE

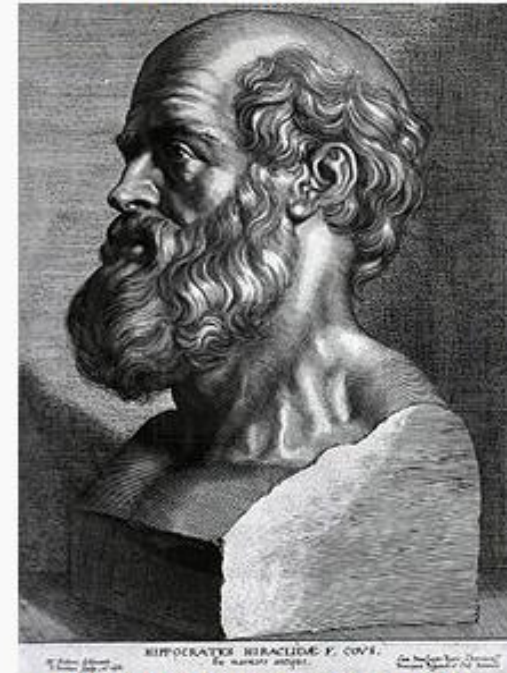
פרופ' יצחק כץ

הפקולטה לרפואת ילדים, בית הספר לרפואה ע"ש סאקלר אוניברסיטת תל-אביב.

Hippocrates

- There are in fact two things,
 - **science** and **opinion!**
- the former begets **knowledge**,
- the later **ignorance**.

Hippocrates of Kos



Engraving by Peter Paul Rubens, 1638, courtesy of the National Library of Medicine.^[1]

Born	ca. 460 BC Kos, Greece
Died	ca. 377 BC Larissa, Greece
Other names	Greek: Ἱπποκράτης
Occupation	Physician

In Fielding Hudson Garrison, *An Introduction to the History of Medicine* (1929)

Food Allergy

Prevalence ?

Trends

Risk factors

Preventive interventions

Diagnosing and Managing Common Food Allergies

1848 JAMA, May 12, 2010—Vol 303,

A Systematic Review

Data Synthesis A total of 12 378 citations were identified and 72 citations were included. **Food allergy affects more than 1% to 2% but less than 10% of the population.** It is unclear if the prevalence of food allergies is increasing. Summary receiver

Conclusion The evidence for the prevalence and management of food allergy is greatly limited by a lack of uniformity for criteria for making a diagnosis.

JAMA. 2010;303(18):1848-1856

www.jama.com

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JAMA. 2010;303(18):1848-1856

www.jama.com

Increase in the prevalence of food allergy - world

- ❑ Koplín JJ, Mills ENC, Allen KJ. Epidemiology of food allergy and food induced anaphylaxis : is there really a Western world epidemic – *Curr Opin Allergy Clin Immunol* 2015; 15:409-416
- ❑ THE RISE IN THE PREVALENCE OF ALLERGIC DISEASE HAS OCCURRED MORE RAPIDLY THAN CAN BE ACCOUNTED FOR BY POPULATION BASED CHANGES IN GENETIC SEQUENCE....
- ❑ Yu W, Freedland DMB, Nadeau KC. Food Allergy: Immune mechanisms, diagnosis and immunotherapy. *Nature Reviews Immunology*. 2016; on line Oct 31. doi.10.1038/nri.2016.111
- ❑ 1997-2007 – SELF REPORTED INCREASE BY 18% ~ 5% IN 2011, OTHER STUDY 8%,
- ❑ UK AND WALES: FOOD RELATED ANAPHYLAXIS 1998-2012 INCREASED 137%,
- ❑ AUSTRALIA 1997-2013 – FOOD ALLERGY FATALITIES INCREASE BY AN AVERAGE OF 9.7% PER YEAR.
- ❑ THE APPARENT INCREASE IN FOOD ALLERGY PREVALENCE OVER A SHORT PERIOD SUGGEST THAT ENVIRONMENTAL FACTORS HAVE A ROLE IN THIS ETIOLOGY.

INFANT FEEDING GUIDELINES – some historical points.

- ❑ First guidelines were written by **Samuel J Fomon** (See Infant feeding in the 20th century: formula and Beikost – J Nutrition 2001;131:409S)- “...in mid 1960s the Committee finally gained nutritional prominence through its assistance to the FDA in defining nutritional requirements for infant formulas... **Dr. Fomon was a nephrologist!**”
- ❑ The final rule, published in FDA 1985, specified minimum concentrations of 29 nutrients and maximum concentrations of 9 of these nutrients.
- ❑ Only around mid 1990 we started to instruct mother what to feed, and in which order...what to eat and what to avoid
- ❑ **“In the early 1970s, most infant in the US were fed beikost by 6 wk of age...”**

How many people die each year from peanut allergies?

BY HOWSTUFFWORKS.COM CONTRIBUTORS HEALTH | PEANUT ALLERGIES

[Ad Topics](#) [Kids Food Allergy](#) [Brittle Nails](#) [Dental Veneers](#) [Natural Healing](#) [Common Cold Treatment](#) [Diarrhea Remedies](#) [Home Remedies For Allergies](#)

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[Peanut allergies](#) are the body's overreaction to certain proteins found in peanuts. The immune system's response to these allergens is to trigger an antibody, which then triggers other chemicals. One of the scariest results of these chemicals is the chance for anaphylaxis, which is a potentially fatal condition in which sufferers have trouble breathing because of constricted airways, experience a sudden and drastic drop in blood pressure, have an increased pulse rate, and sometimes even pass out.

Estimates say that in the United States, thousands of people visit the emergency room annually because of allergic reactions to food. Somewhere around 150 to 200 people die in the U.S. each year because of food [allergies](#). It's estimated that around 50 percent to 62 percent of those fatal cases of anaphylaxis were caused by peanut allergies. Meanwhile, around 10 people in the United Kingdom die each year because of food allergies. However, these figures are not completely reliable, in part because allergic deaths aren't considered reportable events.

Nov 15th 2016

What are the reasons for the ambiguity and uncertainty about the prevalence and trends food allergy- Peanut allergy as an example

PEANUT ALLERGY

- 4.1 Peanuts were introduced into the UK at around the time of the Second World War, providing a history of consumption and exposure over the last 50 years. The
- 2.1 Recent publications in the scientific literature have suggested that the incidence of peanut allergy in the United Kingdom is increasing.¹⁻⁴ It has been proposed that this may be due to (i) a general increase in atopic diseases over the past 10 to 20 years, and/or (ii) an increased consumption of peanuts by pregnant and breast-feeding mothers resulting in sensitisation at an early age.⁴ In addition, there is a greater awareness of the possible

DELAY INTRODUCTION OF PEANUT – National recommendations

- 1. Committee on Toxicity of chemicals in Food. Consumer Products and the environment (COT). Adverse reactions to food and food ingredients. London (United Kingdom): Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment 1998; 11:91-7.**
- 2. American Academy of Pediatrics Committee on nutrition. Hypoallergenic infant formulas. Pediatrics 2000; 106:346-9.**
- 3. Greer FR, Sicherer SH, Burks AW. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. Pediatrics 2008; 121:183-91.**
- 4. Prescott SL, Tang ML. The Australian Society of Clinical Immunology and Allergy position statement: summary of allergy prevention in children. Med J Aust 2005;182:464-7.**



Committee on
TOXICITY

PEANUT ALLERGY

Committee on Toxicity of chemicals in Food, Consumer Products and the environment (COT). Adverse reactions to food and food ingredients. London (United Kingdom): Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment 1998; 11:91-7.

13. The dietary recommendations from the 1998 COT report on peanut allergy¹ were that:

- “ (i) *pregnant women who are atopic, or for whom the father or any sibling of the unborn child has an atopic disease, may wish to avoid eating peanuts and peanut products during pregnancy;*
- (ii) *breast-feeding mothers who are atopic, or those for whom the father or any sibling of the baby has an atopic disease, may wish to avoid eating peanuts and peanut products during lactation;*
- (iii) a) *in common with the advice given for all children, infants with a parent or sibling with an atopic disease should, if possible, be breast-fed exclusively for four to six months;*
- b) *during weaning of these infants, and until they are at least three years of age, peanuts and peanut products should be avoided;*
- (iv) *infants or children who are allergic to peanuts should not consume peanuts or peanut products. ”*

PEANUT ALLERGY

which may result in fatal anaphylaxis. Sampson¹ and Hourihane and colleagues⁴ suggested that, in order to halt this apparent increase in the prevalence of peanut allergy, infants identified as “at risk”, i.e. those from atopic families, should have peanuts and peanut products eliminated from their diets and, furthermore, breast-feeding mothers should eliminate peanuts and peanut products from their own diets. In the light of the publications mentioned above, a Working Group of the Department of Health’s Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment was established to review the available scientific literature and to advise on the consumption of peanuts and peanut products by pregnant or breast-feeding women,

Table 2: Consumption of peanut and peanut products by British Infants aged 6-12 months. 186 survey data from reference 18

Food	% of survey consuming peanuts or peanut products	Average consumption over whole population (ie including non-consumers) (g/person/day)	Average consumption of those eating peanuts or peanut products (g/person/day)	Consumption at 97.5 percentile of consumers (g/person/day)	Average of maximum amounts of peanuts or peanut products consumed on one occasion (g/person/day)	Highest amount recorded for consumption of peanuts or peanut products in one day (g/person/day)
Whole peanuts	NC	-	-	-	NC	NC
Peanuts in mixes	NC	-	-	-	NC	NC
Peanut butter and spreads	3.4	0.1	2.5	5.5	10.8	25.7
Coated peanuts	NC	-	-	-	NC	NC
Peanuts in chocolate or cereal bars	NC	-	-	-	NC	NC
Peanuts in dishes	NC	-	-	-	NC	NC
TOTAL *	3.4	0.1	2.5	5.5	10.8	25.7

NC = no consumers



- a) Breastfeeding mothers should continue breast-feeding for the first year of life or longer. During this time, for infants at risk, hypoallergenic formulas can be used to supplement breast-feeding. Mothers should eliminate peanuts and tree nuts (eg, almonds, walnuts, etc) and consider eliminating eggs, cow's milk, fish, and perhaps other foods from their diets while nursing. Solid foods should not be introduced into the diet of high-risk infants until 6 months of age, with dairy products delayed until 1 year, eggs until 2 years, and peanuts, nuts, and fish until 3 years of age.
- b) No maternal dietary restrictions during pregnancy are necessary with the possible exception of excluding peanuts;

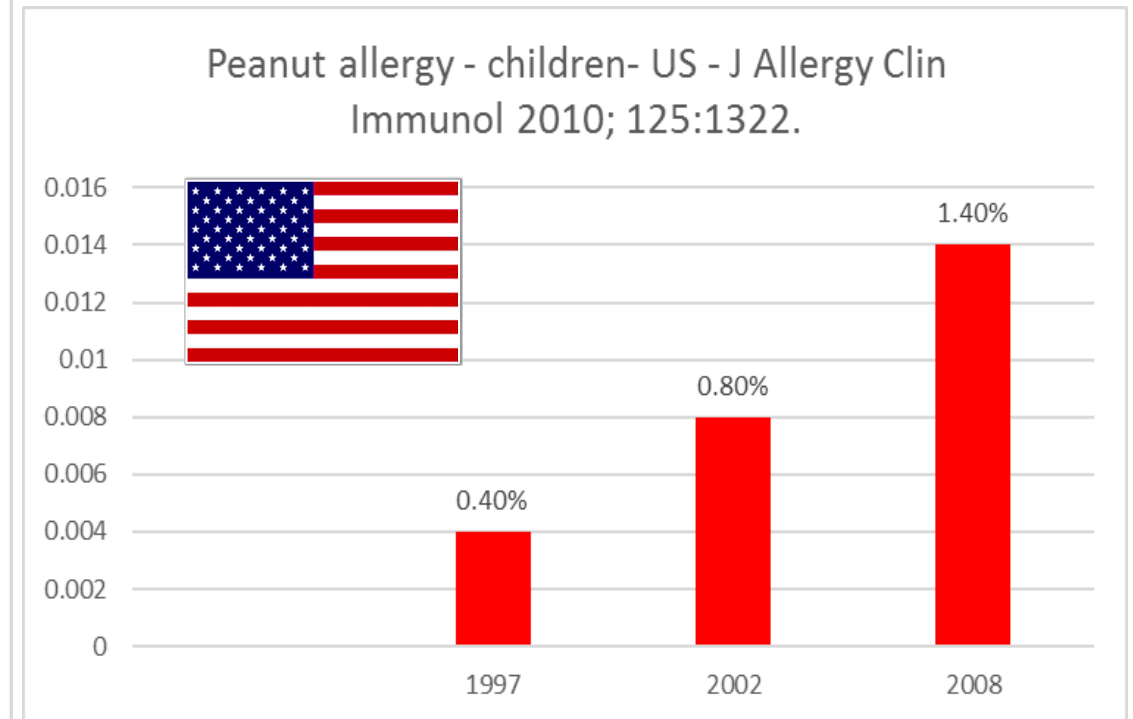
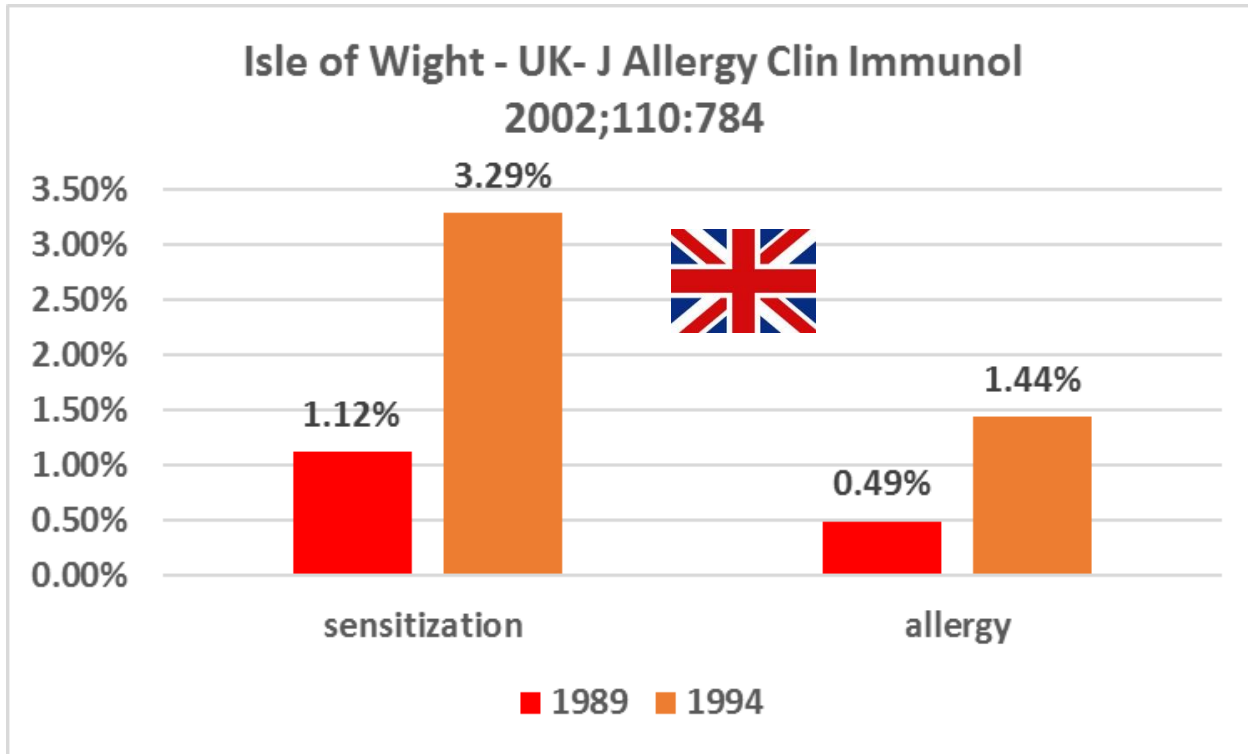
long-term benefits are not certain. In children with existing sensitisations or overt allergic disease (or those deemed to be at high risk for other reasons), it has been common clinical practice to recommend avoidance of potentially allergenic foods such as egg and milk until 12 months of age, and peanuts, nuts and shellfish until after 2–4 years of age. This practice is based on a theoretical benefit to protect

- Complementary foods (including normal cow's milk formulas) should be delayed until a child is aged at least 4–6 months, to protect an “immature immune system”.

Nevertheless, although the “benefit” is not known, the “costs” of doing nothing are perceived as high, and the “cost” of this intervention is relatively low. There is no evidence that avoiding peanuts, nuts and shellfish during early life is harmful for high-risk children.

the 4–6
Additional

What happened to peanut allergy ?



**SPT and history (1989),
SPT, OFC and history (1994)**

Self reported peanut allergy has doubled among children

More - Fading assumption

- ❖ Long time – Soy prevent milk allergy/eczema
- ❖ Recent
- ❖ Hydrolyzed Extensive or partially – reduce the risk for allergy or eczema.
- ❖ **Boyle RJ, et al. Hydrolyzed formula and risk of allergic or autoimmune disease: systematic review and meta-analysis. *BMJ* 2016;352:1974**

Lowe AJ, Hosking CS, Bennett CM et al. Effect of a partially hydrolyzed whey infant formula at weaning on risk of allergic disease in high-risk children. *J Allergy Clin Immunology* 2011;128:360-65, e4.

- **Partially hydrolyzed milk formula – reduce risk of allergy/eczema (GINI)**
- Von Berg A, Koletzko S, Grubl A et al. The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention (GINI) study, a randomized double-blind trial. *J Allergy Clin Immunology* 2003; 111:533-40.
- Von Berg A, Koletzko S, Filipiak-Pittroff B, et al. Certain hydrolyzed formula reduce the incidence of atopic dermatitis but not that of asthma: three year results of the German Infant Nutritional Intervention (GINI) study. *J Allergy Clin Immunology* 2007; 119:718-25.
- Von Berg A, Filipiak-Pittroff B, Kramer U, et al. Preventive effect of hydrolyzed infant formula persist until 6 years long-term results from the German Infant Nutritional Intervention (GINI) study. *J Allergy Clin Immunology* 2008; 121:1442-7
- Von Berg A, Filipiak-Pittroff B, Kramer et al. Allergies in high-risk schoolchildren after early intervention with cow's milk protein hydrolysates: 10-year results from the German Infant Nutritional Intervention (GINI) study. *J Allergy Clin Immunology* 2013; 131:1565-73.
- **Chung CS, Yamini S, Trumbo PR. FDA's health claim review: Whey-protein partially hydrolyzed infant formula and atopic dermatitis. *Pediatrics* 2012; 130:e408-14.**

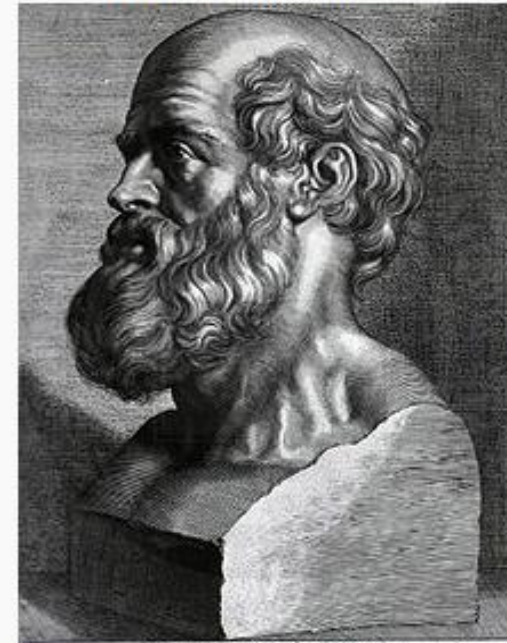
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In Fielding Hudson Garrison, *An Introduction to the History of Medicine* (1929)

Gideon Lack, MD



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

J Allergy Clin Immunol
2008;122:984-9.

George Du Toit, FRCPCH,^a Yitzhak Katz, MD, PhD,^b Peter Sasieni, PhD,^c David Mesher, MSc,^c Soheila J. Maleki, PhD,^d Helen R. Fisher, BSc,^a Adam T. Fox, FRCPCH,^a Victor Turcanu, MD, PhD,^a Tal Amir,^e Galia Zadik-Mnuhin, MD,^f Adi Cohen, MD,^f Irit Livne, MD,^g and Gideon Lack, FRCPCH^a London, United Kingdom, Tel Aviv, Haifa, and Jerusalem, Israel, and New Orleans, La

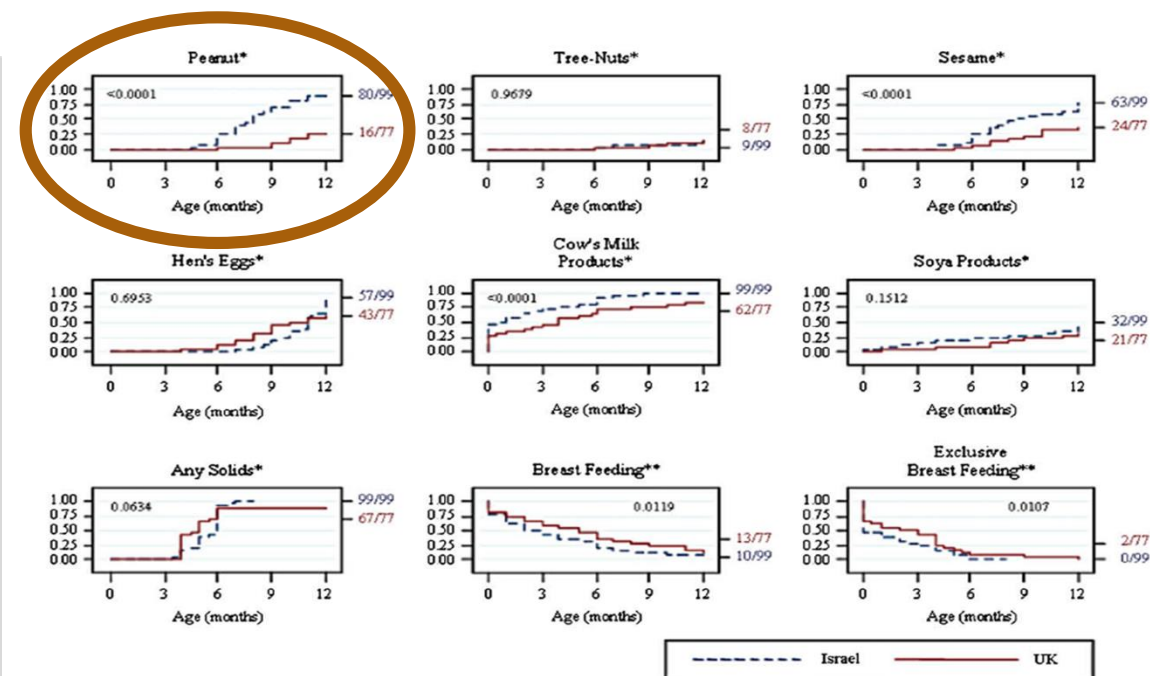
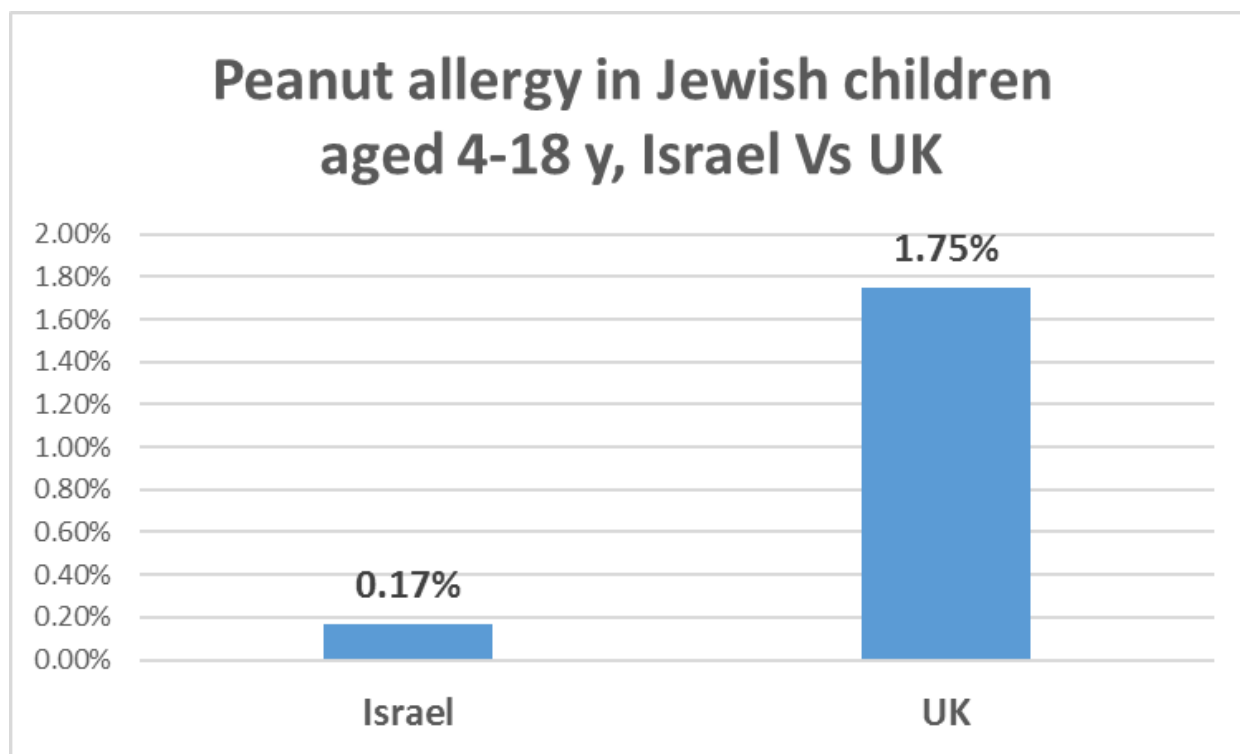


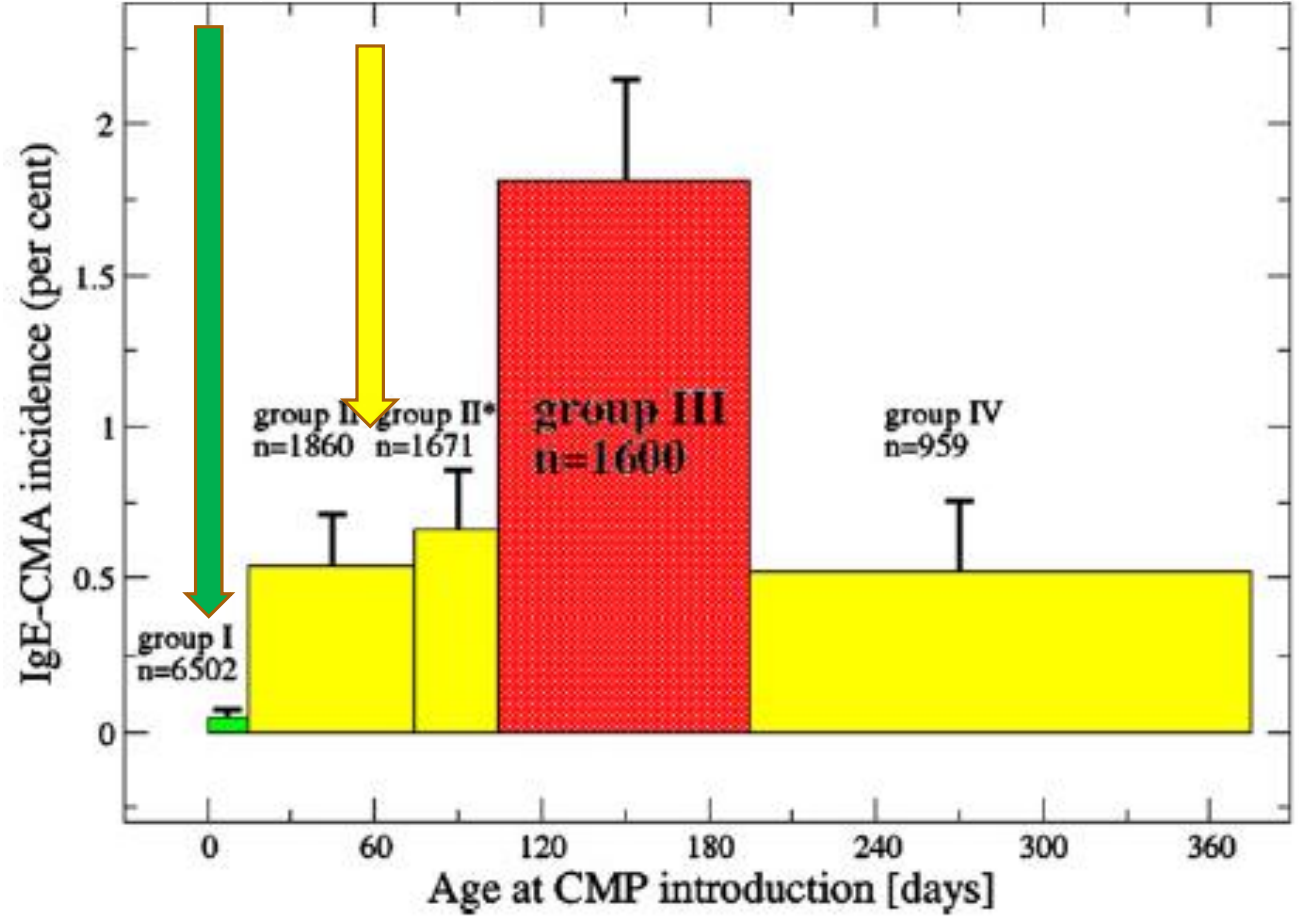
FIG 1. Kaplan-Meier estimates for age at which foods are introduced and duration of breast-feeding and exclusive breast-feeding according to country. *The y-axis represents proportions who have consumed food by age (in months). **The y-axis represents the proportion still breast-feeding/exclusively breast-feeding at various ages (in months). P values are derived by using the log-rank test.

Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy JACI 2010

Yitzhak Katz, MD,^{a,c} Nelly Rajuan, MSc,^{c*} Michael R. Goldberg, MD, PhD,^a Eli Eisenberg, PhD,^d Eli Heyman, MD,^b Adi Cohen, MD,^a and Moshe Leshno, MD, PhD^a *Zerifin and Tel Aviv, Israel*

13019 – newborns (2004-6)
 66 – (0.5%) – IgE CMA
 None of these with soy allergy
 And a surprise !!!!

Age of exposure (days)	1-14	15-103	104-190	> 190
Number of infants	6502	3531	1600	959



Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy

Yitzhak Katz, MD,^{a,c} Nelly Rajuan, MSc,^{c*} Michael R. Goldberg, MD, PhD,^a Eli Eisenberg, PhD,^d Eli Heyman, MD,^b Adi Cohen, MD,^a and Moshe Leshno, MD, PhD^e *Zerifin and Tel Aviv, Israel*

TABLE III. Feeding pattern during the first week

	No.	Exclusively or almost exclusively breast-fed (%)	Partial breast-feeding (%)	No breast-feeding (%)	Total (%) breast-fed	Total (%) CMP fed
Whole population	13,019	6,920 (53.2)	2,925 (22.5)	3,174 (24.4)	9,845 (75.6)	6,099 (46.8)
Jewish	10,135	5,826 (57.5)	1,772 (17.5)	2,537 (25)	7,598 (75)	4,303 (42.5)
Muslim	1,806	511 (28.3)	944 (52.3)	351 (19.4)	1,455 (80.6)	1,295 (71.7)
Other*	1,078	583 (54.1)	209 (19.4)	286 (26.5)	792 (73.5)	495 (45.9)

*Christian, atheists, and not known.

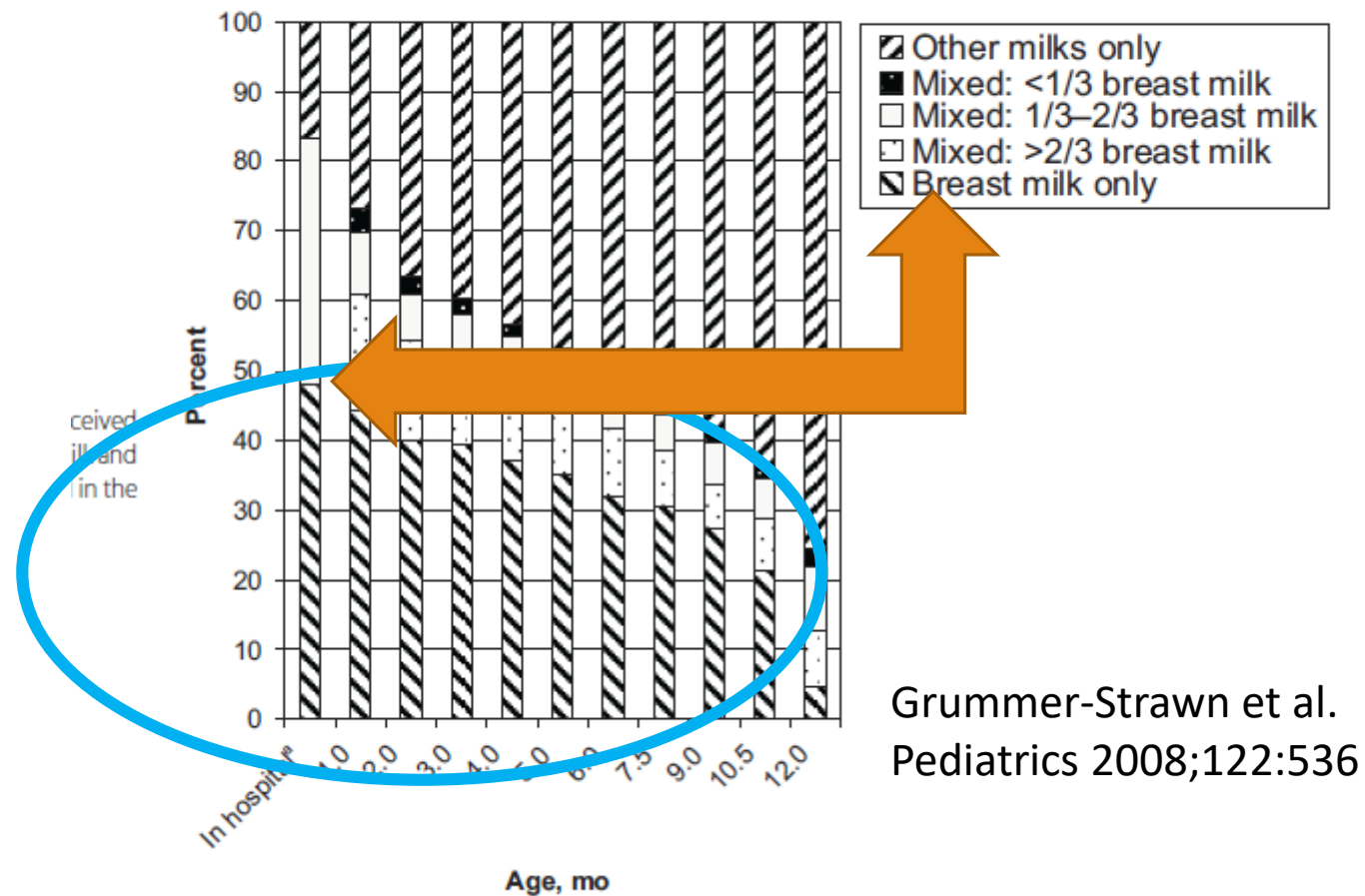
Total	13,019	%	Allergic	66	% CMA
Jewish	10,135	77.8%	Jewish	65	98.5
Non Jewish	2,884	22.2%	Non Jewish	1	1.5%



Similar Data from :

- Israel
- Saud Arabia
- Croatia
- Japan
- The Netherlands
- UK
- And more....

Percentage of milk or formula feeding in which infants received breast milk.



Grummer-Strawn et al.
Pediatrics 2008;122:536

Taken together

Less than 50% practice exclusive breast feeding through the first month

Hardly any case of IgE CMA allergy in the first month of life

The Association of the Delayed Introduction of Cow's Milk with IgE-Mediated Cow's Milk Allergies



Yutaro Onizawa, MD^a, Emiko Noguchi, MD, PhD^b, Masafumi Okada, MD, PhD^c, Ryo Sumazaki, MD, PhD^d, and Daisuke Hayashi, MD^a *Ibaraki, Japan*

What is already known about this topic? A few studies have suggested that the early introduction of cow's milk formula might be protective against IgE-mediated cow's milk allergies. However, these studies have limited data about the factors affecting parental choices regarding feeding patterns.

What does this article add to our knowledge? In this case-control study, the delayed introduction of cow's milk formula was an independent risk factor for an IgE-mediated cow's milk allergy. Most parents chose exclusive or almost exclusive breastfeeding because of reasons other than allergy prevention.

How does this study impact current management guidelines? In contrast to the current guidelines, our result suggests that regular consumption of cow's milk formula might play an important role in preventing IgE-mediated cow's milk allergies.

CONCLUSIONS: The early introduction of cow's milk formula is associated with lower incidence of IgE-CMA. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:481-8)

The ingestion of cow's milk formula in the first 3 months of life prevents the development of cow's milk allergy

Tetsuhiro Sakihara^{1,2,*}, Shiro Sugiura¹, and Komei Ito¹

¹Department of Allergy, Aichi Children's Health and Medical Center, Obu 474-8710, Japan

Table 3. The multivariate logistic regression analysis of the risk factors for the development of cow's milk allergy

Variable	CMA (n = 171)	Non-CMA (n = 203)	aOR	95% CI	p-value
Male sex	114 (66.7)	130 (64.0)	1.20	0.75–1.93	NS
Preterm	3 (1.8)	18 (8.9)	0.18	0.04–0.80	0.024 [†]
Low birth weight	11 (6.4)	16 (7.9)	1.58	0.53–4.69	NS
Cesarean section	20 (11.7)	38 (18.7)	0.83	0.43–1.61	NS
Atopic dermatitis	138 (80.7)	144 (70.9)	1.40	0.82–2.37	NS
Bronchial asthma	48 (28.1)	41 (20.2)	1.52	0.89–2.59	NS
Family history	158 (92.4)	187 (92.1)	1.01	0.44–2.32	NS
EW-sIgE >50 U _A /mL	80 (46.8)	65 (32.0)	1.61	1.01–2.58	0.044
Daily CMF ingestion [†]	11 (6.4)	64 (31.5)	0.16	0.08–0.32	<0.001 [†]

Values are presented as number (%). CMA, cow's milk allergy; aOR, adjusted odds ratio; CI, confidence interval; family history, family history of allergic diseases; EW-sIgE, maximum egg white-specific IgE titer at <72 months of age; CMF, cow's milk formula; NS, nonsignificant. *p < 0.05, statistically significant. [†]CMF ingestion at least once daily until first 3 months of age.

Conclusion: Ingestion of CMF during the first 3 months of life might prevent the development of CMA in high-risk infants.



Can early introduction of egg prevent egg allergy in infants? A population-based study

Jennifer J. Koplin, BSc (Hons),^{a,b} Nicholas J. Osborne, PhD,^{a,b,c} Melissa Wake, MD, FRACP, MBBS,^{a,b,d} Pamela E. Martin, BBiomedSc (Hons),^{a,b} Lyle C. Gurrin, PhD,^{a,c} Marnie N. Robinson, MBBS, FRACP,^e Dean Tey, MBBS, FRACP,^e Marjolein Slaa, MBBS,^a Leone Thiele, BA, RN, RM, MNSc,^a Lucy Miles, BNurs,^a Deborah Anderson, BNurs/BAppSc,^a Tina Tan, BSc,^{a,b} Thanh D. Dang, BBiomedSc (Hons),^{a,b} David J. Hill, MBBS, FRACP,^a Adrian J. Lowe, PhD,^{a,c} Melanie C. Matheson, PhD,^c Anne-Louise Ponsonby, MBBS, FAFPHM, FRACP, PhD,^{a,b} Mimi L. K. Tang, MBBS, FRACP, FRCPA, FAAAAI, PhD,^{a,b,e} Shyamali C. Dharmage, MBBS, MD, PhD,^c and Katrina J. Allen, MBBS, FRACP, PhD^{a,b,e} *Melbourne, Australia*

Conclusions: Introduction of cooked egg at 4 to 6 months of age might protect against egg allergy. Changes in infant feeding guidelines could have a significant effect on childhood egg allergy and possibly food allergy more generally. (J Allergy Clin Immunol 2010;126:807-13.)



The Effects Of Infant Feeding Practices On Food Sensitization In A Canadian Birth Cohort

M. M. Tran¹, W. Dai¹, D. L. Lefebvre¹, P. Subbarao², A. B. Becker³, P. J. Mandhane⁴, S. E. Turvey⁵, W.-Y. Lou⁶, M. R. Sears¹

¹Firestone Institute, Hamilton, ON, Canada, ²The Hospital For Sick Children, Toronto, ON, Canada, ³University of Manitoba, Winnipeg, MB, Canada, ⁴University of Alberta, Edmonton, AB, Canada, ⁵University of British Columbia, Vancouver, BC, Canada, ⁶University of Toronto, Toronto, ON, Canada

and the CHILD Study Investigators

Exclusive breastfeeding to 6 months did not significantly alter the risk of sensitization to egg or peanut at age 1 year, but increased the risk of sensitization to cow's milk. In contrast, early introduction of solid foods reduced the risk of food sensitization, as did an increased diversity of these "allergenic" foods introduced during the first year. The findings from this study reaffirm the paradigm shift from delayed food introduction and food avoidance to earlier introduction of diverse foods for allergy prevention.



Fish Allergy – The Singapore Story



The screenshot shows a web browser window displaying the NUS Department of Paediatrics website. The header includes the NUS logo and navigation links for 'NUS Home', 'Search', and 'NUS Websites'. The page title is 'Department of Paediatrics, Yong Loo Lin School of Medicine'. A breadcrumb trail reads 'Home > Academic Programmes > Postgraduates'. The main content area features a title 'FISH ALLERGY - THE SINGAPORE STORY' by 'Dr Dawn Lim Li-Chern', who is identified as an Assistant Professor and Registrar. The text discusses the prevalence of fish allergy in Western populations and its significance in Singapore, where fish consumption is high. A sidebar on the left lists various medical specialties under the heading 'Lecture series'.

NUS Home Search: in NUS Websites Go

NUS National University of Singapore

Department of Paediatrics
Yong Loo Lin School of Medicine

Home > Academic Programmes > Postgraduates

FISH ALLERGY - THE SINGAPORE STORY

Dr Dawn Lim Li-Chern

Assistant Professor, Department of Paediatrics, National University of Singapore
Registrar, The Children's Medical Institute, National University Hospital

Introduction

Fish is an important component of the world's food supply. However, it is also one of the most common causes of food allergy in Western populations¹, especially in countries where fish consumption is high. Three percent of Finnish children have fish allergy² and it affects 1/1000 Swedish adults³. It has been reported to account for 18% of food allergy in Spanish children⁴ and 39% in Swedish children⁵. Up to 39% of children with atopic dermatitis have shown to be sensitized to fish^{6,8}. Moreover, it accounts for a significant proportion of food-induced anaphylactic reactions in many countries⁹⁻¹¹.

The major allergen from the cod fish (*Gadus callarius*) Gad c 1, has been extensively studied and is well characterized¹². It is a 12kDa calcium binding sarcoplasmic protein belonging to parvalbumin subfamily, involved in muscle relaxation and is recognised as the "prototype" fish allergen¹². Parvalbumin is also the major allergen for other fish whose allergens have been characterized, namely salmon¹³, mackerel¹⁴ and carp¹⁵.

Asia has one of the highest rates of fish consumption in the world. The average world annual fish consumption is calculated to be 16 kg per capita¹⁶ as compared to 24.9 kg per capita in Asia. Fish is also an important element of the Singaporean diet with a high local per capita consumption¹⁷.

Lecture series

- Allergy & Pulmonology/ Immunology
- Ambulatory & Developmental Paediatrics
- Cardiology
- Emergency & Critical Care
- Endocrinology & Metabolism
- Ethics
- Gastroenterology & Hepatology
- Haematology & Oncology
- Neonatology
- Nephrology
- Neurology

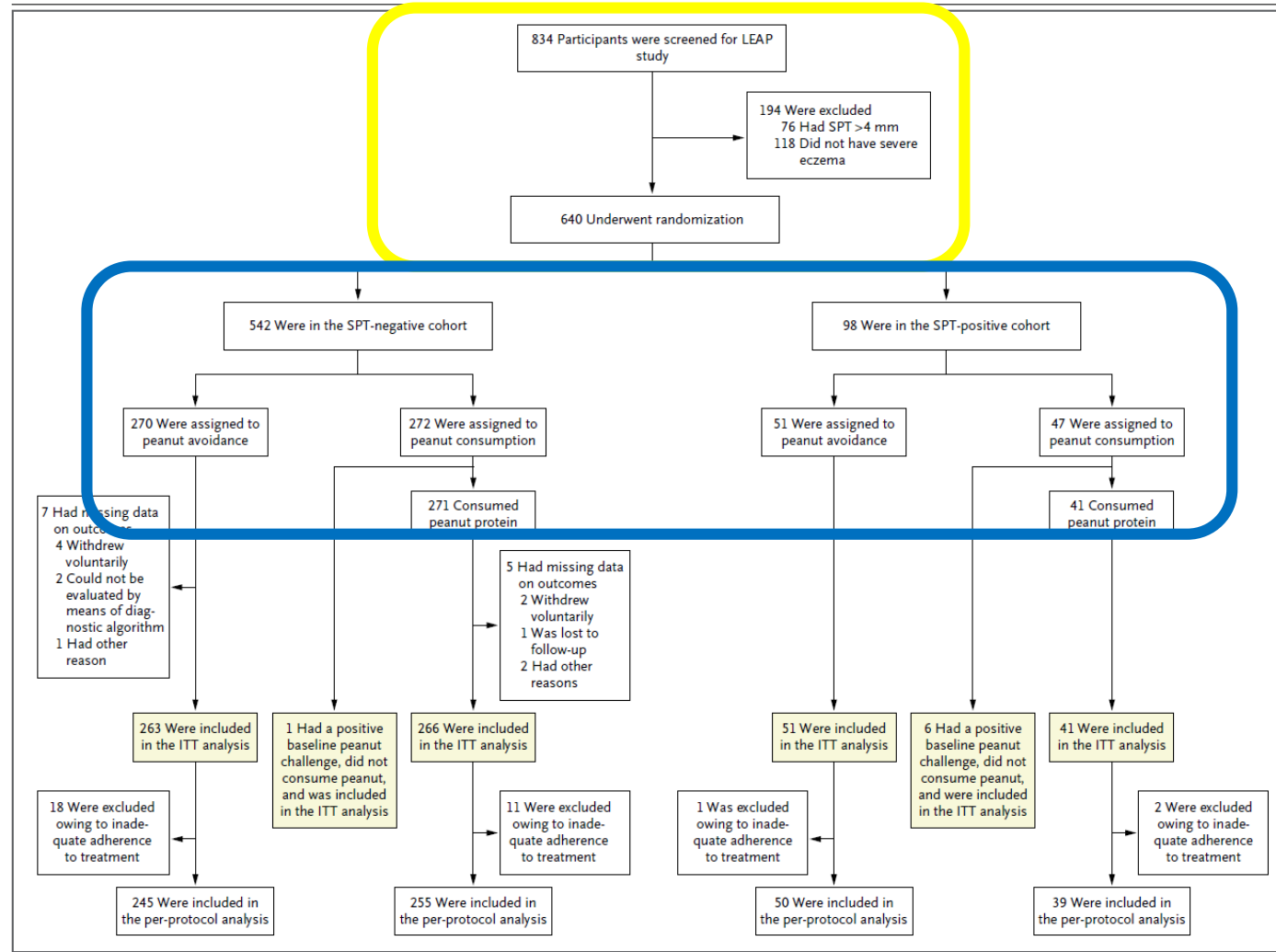
From observations

TO INTERVENTION STUDIES

ORIGINAL ARTICLE

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*



834 participants were selected for LEAP study

194 Were Excluded

76 Had SPT > 4mm

118 Did NOT have severe enough eczema

640 Underwent randomization

542 SPT Negative cohort

270 peanut avoidance

272 peanut consumption

98 Were in the SPT positive

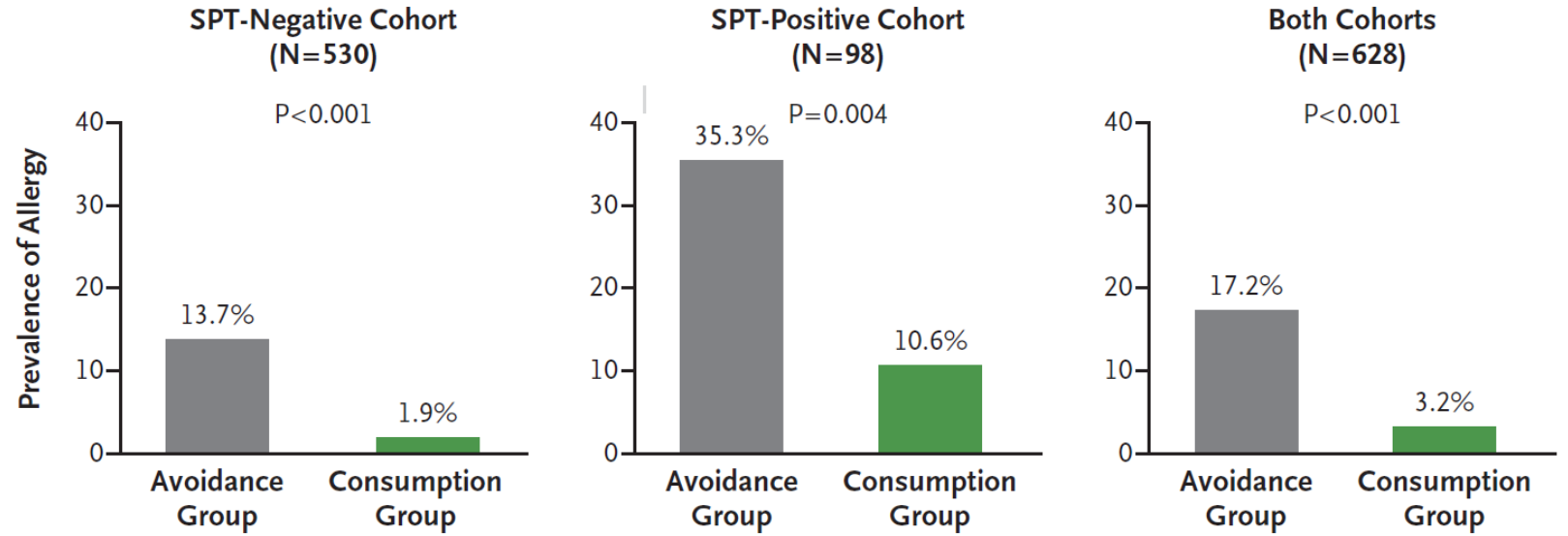
51 – Peanut avoidance

47 – Peanut consumption -

6 had a positive baseline challenge (12.7%!!)

LEAP RESULTS

A Intention-to-Treat Analysis



B Per-Protocol Analysis

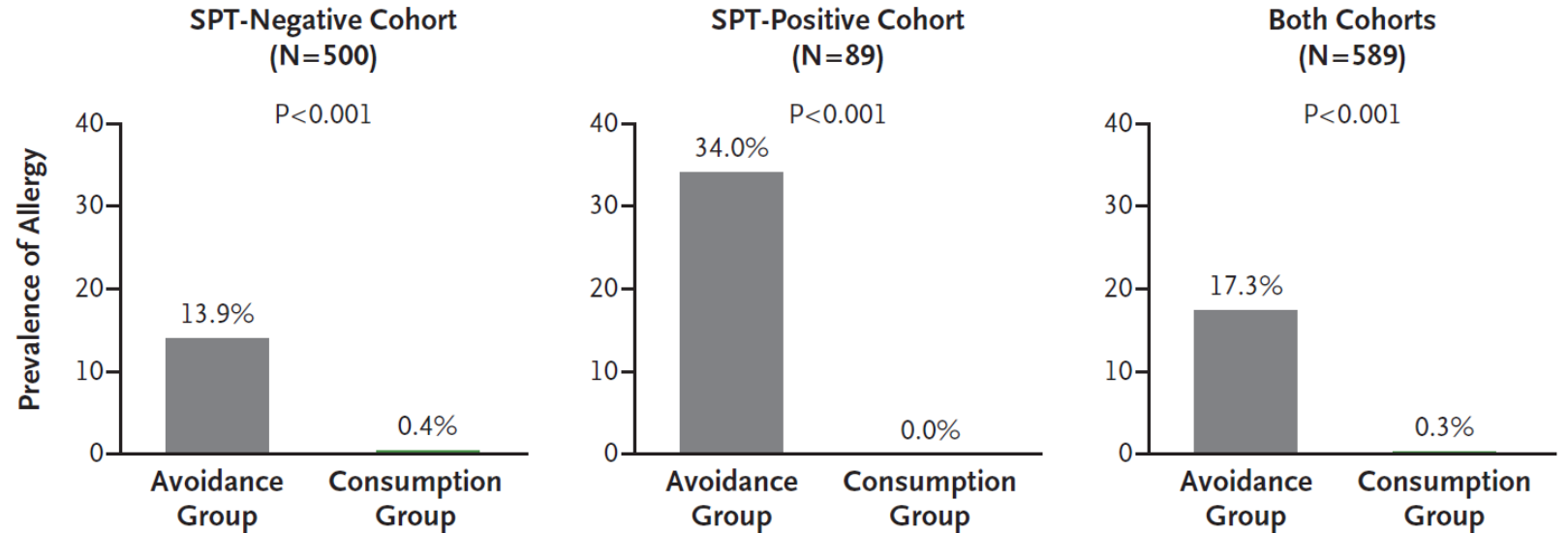


Figure. Suggested Algorithm for the Introduction of Peanut

Children younger than 1 y with history of severe

An old joke.

Hans, a merchant from Germany went to the market in Galicia. While examining some wares, a local storekeeper asked him, "Tell me Hans, how many eggs you can eat on an empty stomach? After thinking for a while, he replied, "ten". The storekeeper promptly asked, how can you? After the first egg your stomach is not empty anymore....Upon his return home he met his friend Franz. "Tell me Franz, how many eggs can you eat on empty stomach"? "Eight" replied Franz. Hans was disappointed and said "too bad Franz" he said, if you would have answered "ten" I had a good joke for you.



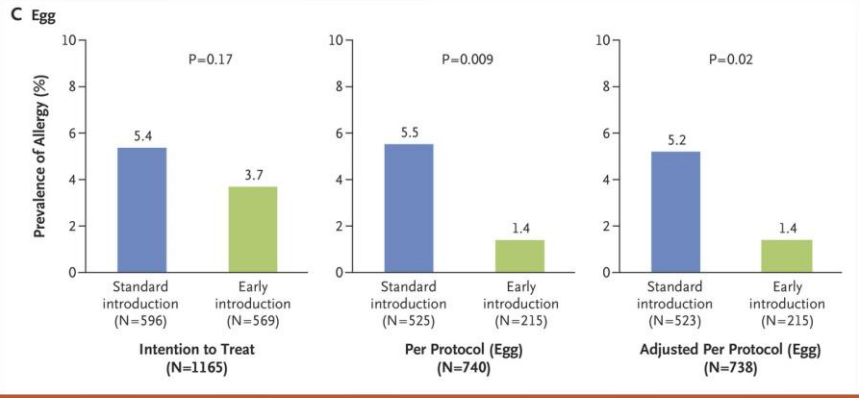
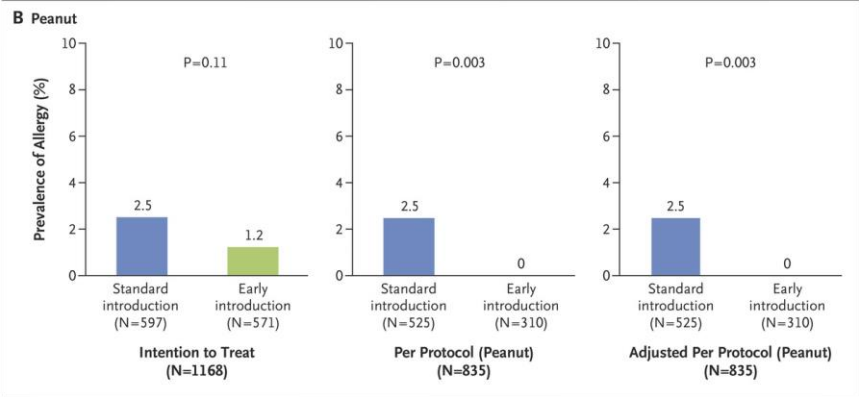
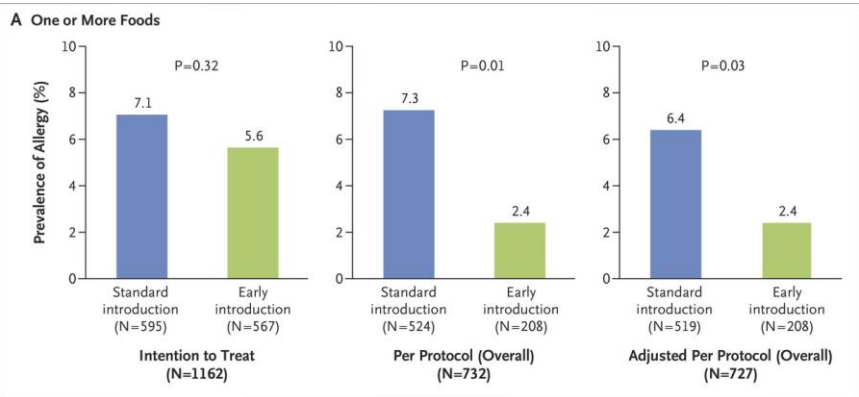
ORIGINAL ARTICLE

N ENGL J MED 374;18 NEJM.ORG MAY 5, 2016

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

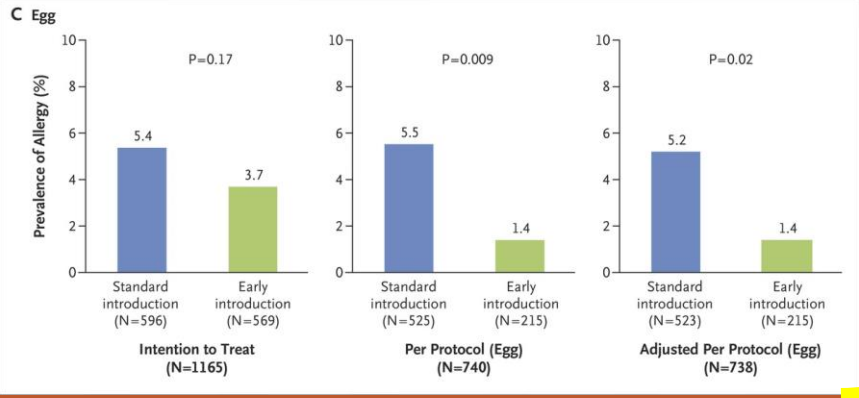
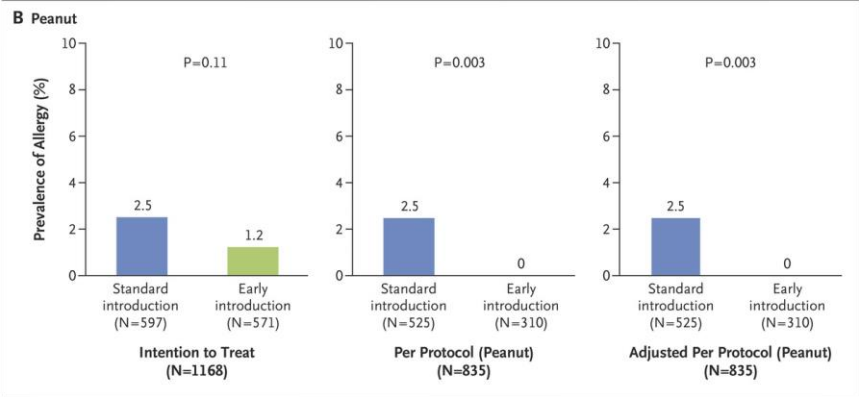
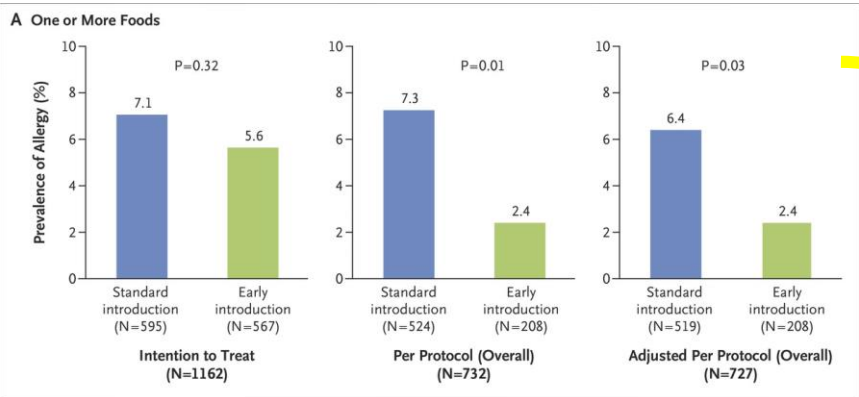
CONCLUSIONS

The trial did not show the efficacy of early introduction of allergenic foods in an intention-to-treat analysis. Further analysis raised the question of whether the prevention of food allergy by means of early introduction of multiple allergenic foods was dose-dependent. (Funded by the Food Standards Agency and others;

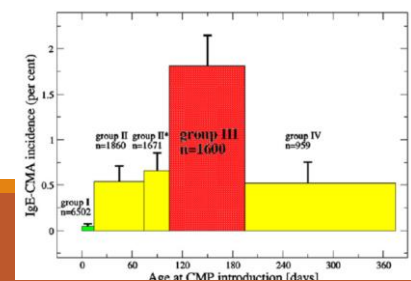


	Standard Introduction	Early Introduction	p	drop
ITT - All (1162)	42/595, 7.1%	32/567, 5.6%	0.32	430:1162, 37%
PP (732)	7.3%	2.4%	0.01	
ITT Peanut (1168)	15/597, 2.5%	7/571 (1.2%)	0.11	
PP Peanut	5/525, 2.5%	0/310, 0	0.003	
ITT Egg	32/596, 5.4%	21/569 3.3%	0.17	
PP Egg	29/525, 5.5%	3/215 1.4%	0.009	
ITT Milk	0.7%	0.5%	1	
PP Milk	0.6%	0.2%	0.63	
ITT Sesame	0.5%	0.5%	1	
PP Sesame	0.6%	0	0.56	

Only 42% compliance !!!




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Hen's Egg The Most Common Food Allergen – Australia









EARLY INTRODUCTION OF EGG TO PREVENT EGG ALLERGY

Name	STAR	EAT	HEAP	STEP	BEAT	PETIT
Year Published(J)	2013 (JACI)					
Year Born	2009-2011					
Country	Australia					
Study Type						
Exclusion						
Risk/Participants	Eczema					
No partici	86					
Egg Q/Q	900 mg/d					
Age start	4-8m					
Sensitized at screening	36% (Egg sIgE>0.35 kU _A /L)					
Allergy at screening	15/49 31% *, 3/37					
Egg sensitization	45% 63%					
Egg Allergy End	33%, 51%					
Conclusion/ remarks	NS					

Embargo

EARLY INTRODUCTION OF EGG TO PREVENT EGG ALLERGY

Name	STAR	EAT	HEAP	STEP	BEAT	PETIT
Year Published(J)	2013 (JACI)	2016(NEJM)	2016 (JACI)	2016 (JACI)	2016 (JACI)	2016 (Lancet)
Year Born	2009-2011	2009-12	2012-13	2010-14	2011-13	2012-2014
Country	Australia	UK	Germany	Australia	Australia	Japan
Study Type						
Exclusion		Prev Egg, positive challenge	SPT >2mm, EslgE>0.35kU _A /L	Eczema, prev egg	SPT >2mm	Prior egg consu
Risk/Participants	Eczema	3m, Exc BF	NONE	Atopic Mother	Atopic 1 st degree	Eczema
No partici	86	1303	406 S,	820(407/413)	319	121(ITT)/
Egg Q/Q	900 mg/d	>1000mg/d	833mg/d (1 st week), 1650, 2500mg.	400mg/d	350 mg/d	Embargo
Age start	4-8m	3.4	4-6m	4.5-6m	3.8m	
Sensitized at screening	36% (Egg slgE>0.35 kU _A /L)	5.1%	23(5.7%)	5% (Egg slgE>0.35 kU _A /L)	13/332 (3.9)	
Allergy at screening	15/49 31% *, 3/37		3.9% +4%	36/407), 19/413 P 25/407 6/413 c	(14)8.5%+	
Egg sensitization	45% 63%		5.6% 2.6%	10.8% vs 15.1%	11% 20%	
Egg Allergy End	33%, 51%	1.4% vs 5.5%	2.1% 0.6%	26/371, 39/377* 7% 10.3% ns	8 13	8.3% vs 37.7%
Conclusion/ remarks	NS	Favor (PP)	NEGATIVE	Pp	NS	P=0012

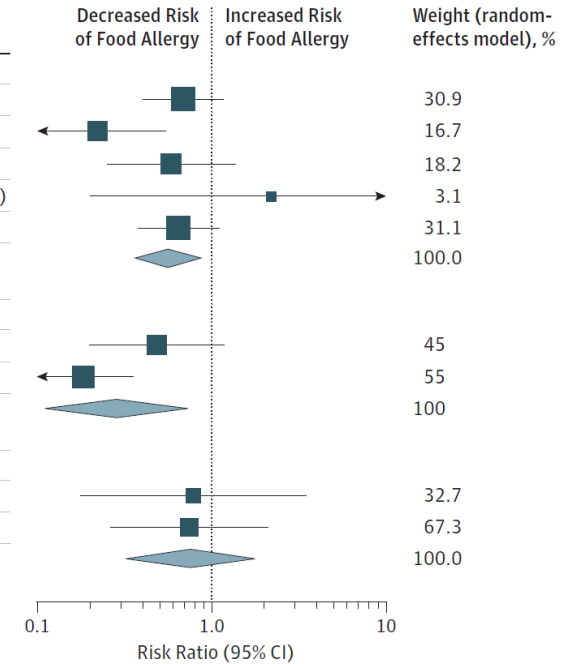
Timing of Allergenic Food Introduction to the Infant Diet and Risk of Allergic or Autoimmune Disease

A Systematic Review and Meta-analysis

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

A Risk of food allergy

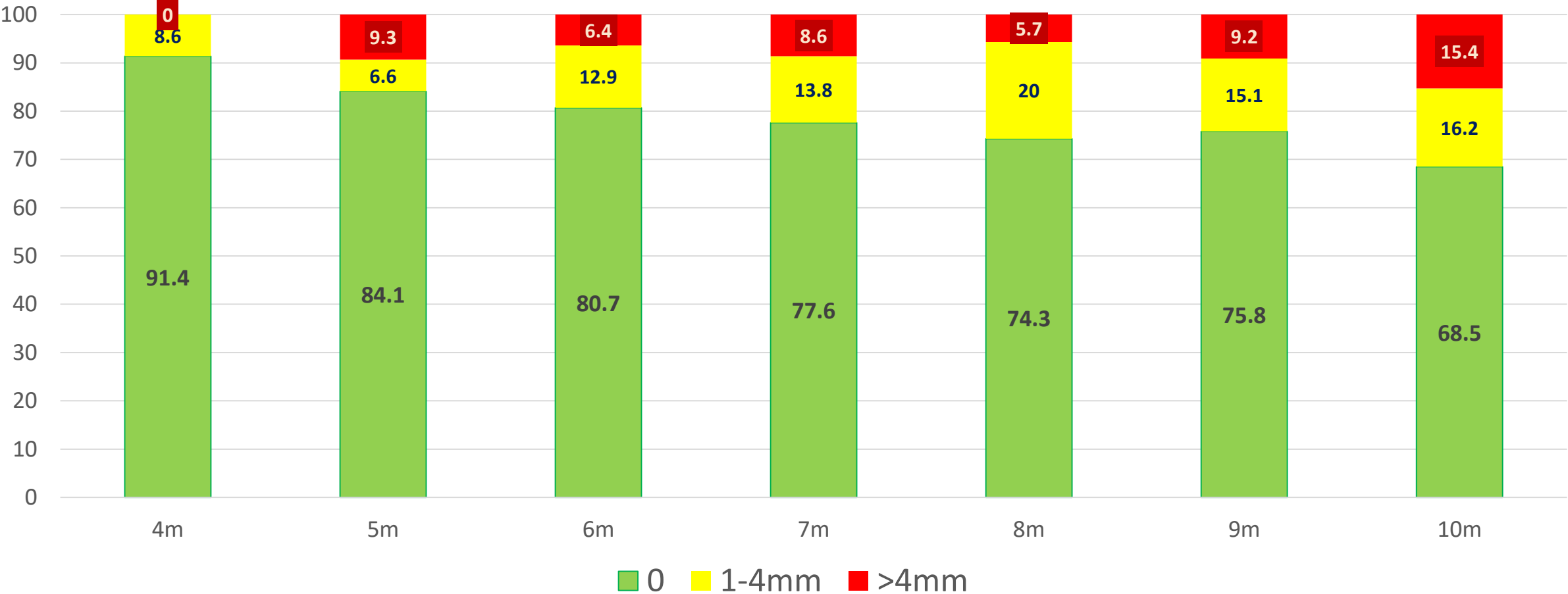
Outcome	Dietary Introduction of Allergenic Food				Risk Ratio (95% CI)
	Early		Late		
	No. of Events	Total No.	No. of Events	Total No.	
Egg allergy					
Perkin et al, ⁶ 2016	21	569	32	596	0.69 (0.40-1.18)
Natsume et al, ¹⁷ 2016	5	60	23	61	0.22 (0.09-0.54)
Tan et al, ¹⁸ 2016	8	130	13	124	0.59 (0.25-1.37)
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: $I^2 = 35.8\%$; $P = .18$					
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		883		910	0.29 (0.11-0.74)
Heterogeneity: $I^2 = 66.1\%$; $P = .09$					
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		762		788	0.76 (0.32-1.78)
Heterogeneity: $I^2 = 0\%$; $P = .95$					



CONCLUSIONS AND RELEVANCE In this systematic review, early egg or peanut introduction to the infant diet was associated with lower risk of developing egg or peanut allergy. These findings must be considered in the context of limitations in the primary studies.


FROM the LEAP study – (peanut NEJM 2015)

Peanut SPT Wheal Size by Age



The most important factors are : Timing, Timing, and TIMING

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The results of sensitisation rates on specific IgE measurements at enrolment to three of the major food allergens: egg, peanut and cow's milk are shown in Figure 2. 22% of 4 month olds are sensitised to peanut with IgE levels greater than 0.35 KU/L. However, the figure for any specific IgE to peanut is even higher with 40% of 4 month olds having levels greater than 0.1 KU/L).

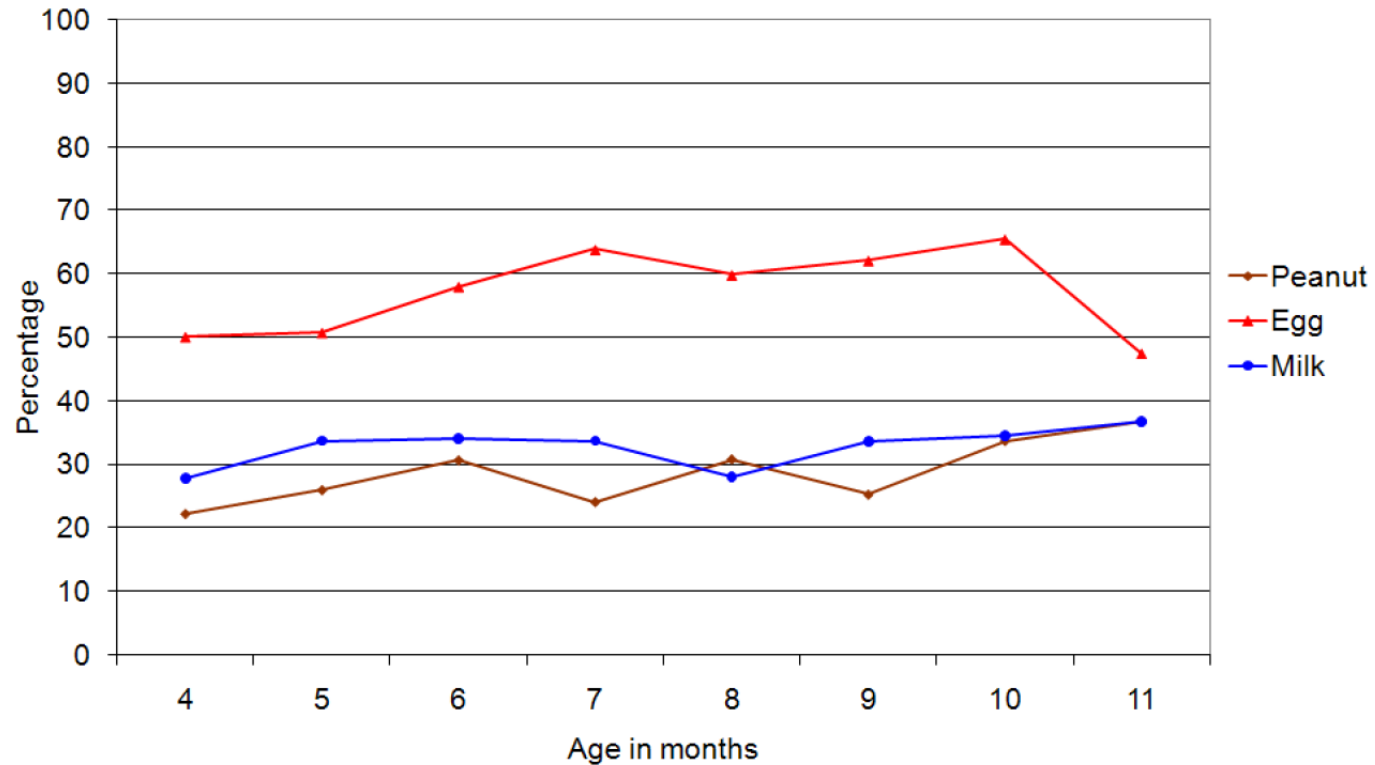


Figure 2. Sensitisation to allergenic foods (IgE>0.35KU/L) at enrolment onto the LEAP Study.

Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Perkin MR, Logan K, Tseng A, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med* 2016;374:1733-43. DOI: 10.1056/NEJMoa1514210

1.2 AETIOLOGY OF FOOD ALLERGY

1.2.1 Increased Prevalence of Food Allergy

With regard to the introduction of mixed feeding there has been a significant trend since 1975 towards later introduction. The proportion of infants given solids by 8 weeks of age has decreased: 49% in 1975, 24% in 1980 & 1985, and 19% in 1990.¹² It is a simple ecological observation that this decrease to a third of what it was has coincided with up to a three-fold increase in allergy in children.¹¹ This change has been compounded by a number of different bodies recommending delayed introduction of foods. The American Academy of Pediatrics

- ❖ With regard to the introduction of mixed feeding there has been a significant trend since 1975 toward late introduction.
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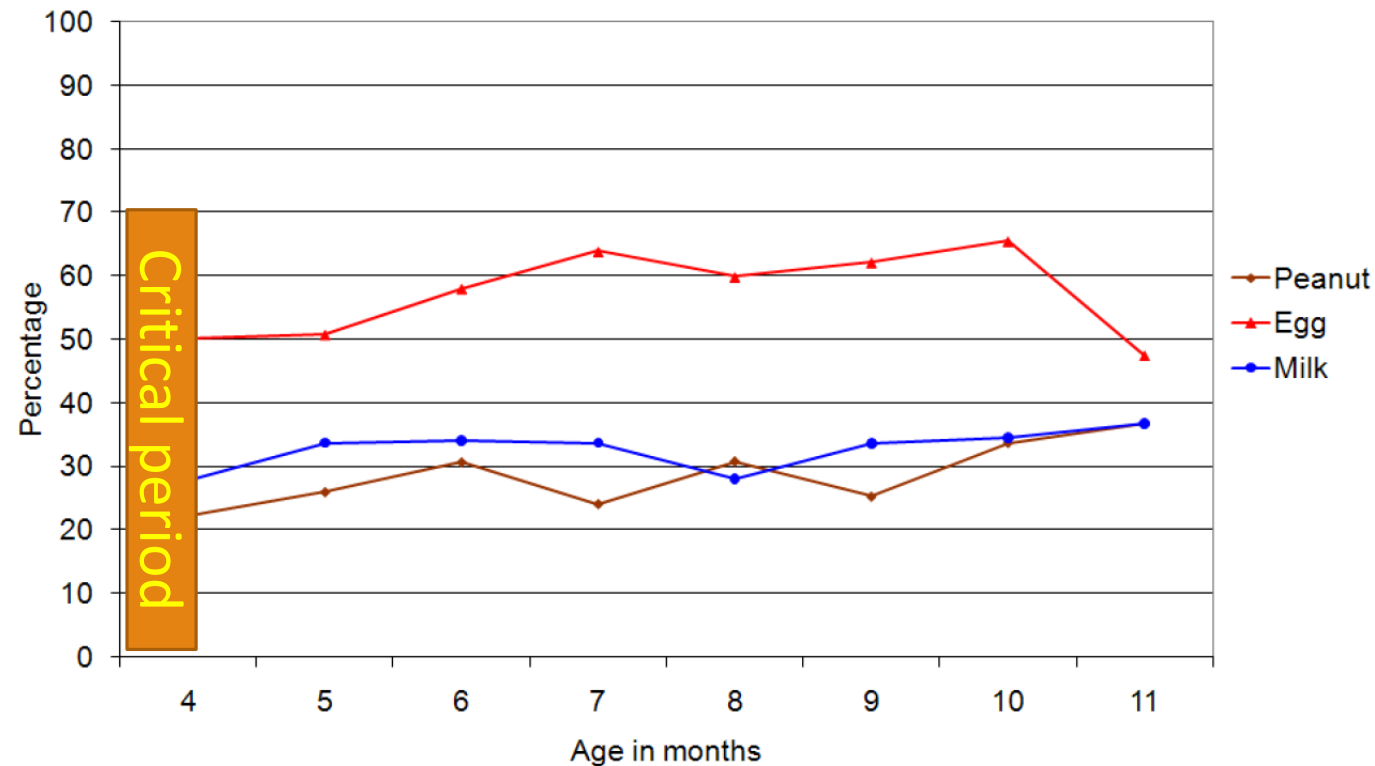


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Safety - Peanut challenges

- **Baseline challenge**

- 2 g peanut protein or if sensitized to peanut, 3.85 g.
- Challenge foods well accepted, no incomplete challenges due to feeding or choking issues.
- 7 positive challenges
- Reactions:
 - Predominantly cutaneous
 - No epinephrine required



- **Month 60 challenge**

- 5 g peanut protein open challenge or 9.35 g DBPCFC
- 57 positive challenges
- Reactions:
 - Respiratory and/or cardiovascular signs 14 (24.5%)
 - IM epinephrine administered to 9 (16%)



CORRESPONDENCE

Introducing Allergenic Foods in Infants

added at 4 months. Their whole generation grew up without a lot of food allergy.

Then opinion changed, on the basis of scant evidence,¹ and by 1991 less than 20% of 2-month-old infants were getting semisolid food, as compared with more than 70% in 1976.² When my daughters visited, I could not feed my grandchildren bananas at 6 weeks of age, even though their mothers enjoyed them in their infancy. An entire generation attests to the safety and benefits of early introduction of solid foods.

Robert S. Bobrow, M.D.

trial to resolve. We believe that the body of evidence is moving toward the early introduction of allergens to prevent food allergies. Perhaps grandparents know best after all!

Michael R. Perkin, Ph.D.

St. George's, University of London
London, United Kingdom

Gideon Lack, M.B., B.Ch.

King's College London
London, United Kingdom
gideon.lack@kcl.ac.uk

- ✓ **Food allergy is mostly an iatrogenic disease ?**
- ✓ **The bright side of story : we can reverse the trend of the food allergy epidemic.**
- ✓ **Israel has contributed a great deal to the new trend in infant feeding.**

LEM-Media, Inc.
gideon.lack@kcl.ac.uk

GENETICS OF PEANUT ALLERGY: A TWIN STUDY

SICHERER ET AL. J ALLERGY CLIN IMMUNOL 2000;106:53-56

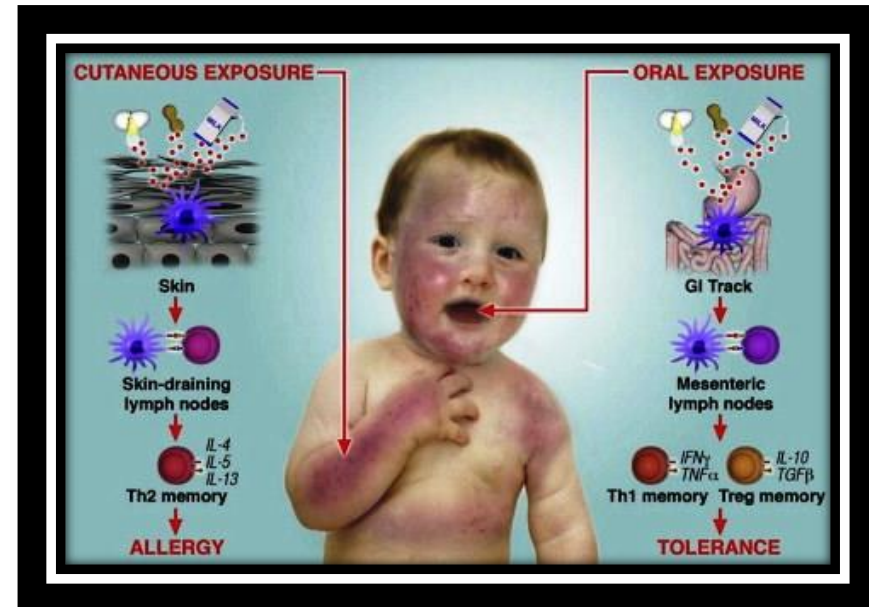
UPDATE ON RISK FACTOR FOR FOOD ALLERGY

LACK G. J ALLERGY CLIN IMMUNOL 2012;129:1187-1197

TABLE I. Concordance rates for peanut allergy

	Monozygotic	Dizygoti
Concordant	9	3
Discordant	5	41
Pairwise concordance rate*	64.3%	6.8%

* $\chi^2 = 21.38$; $P < .0001$.



Don't trust the story and the test – perform OFC when ever possible

Very few foods cause the vast majority of reactions !!

RESULTS OF DOUBLE-BLIND, PLACEBO-CONTROLLED FOOD CHALLENGES IN CHILDREN

Patients undergoing DBPCFC	630
Patients with positive DBPCFC	235 (37%)
Number of food challenges - DBPCFC	1419
Number of positive DBPCFC	313 (22%)

Foods:	Egg	85	Chicken	2	
	Peanut	74	Turkey	1	
	Milk	69	Banana	1	<input type="checkbox"/> Sesame
	Nuts	32	Rye	1	<input type="checkbox"/> Kiwi
	Soy	17	Squash	1	<input type="checkbox"/> Buckwheat
	Fish	10	Hot dog	1	
	Wheat	7	Crab	1	
	Pea	5	Corn	1	
	Shrimp	3			

TOTAL: 313

Egg, Milk, Peanut, Wheat, Soy = 252 or 81% of total