Prevention of Food Allergy

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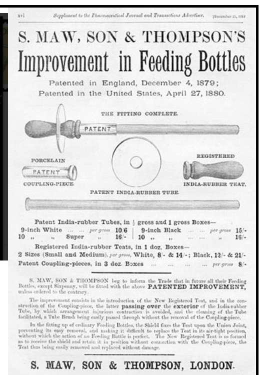
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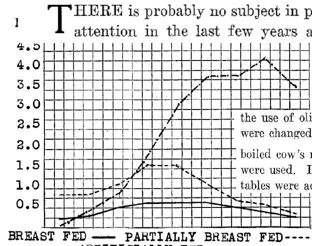
Supplement to the Pharmaceutical Journal and Transactions Advertiser.
S. MAW, SON & THOMPSON'S
Improvement in Feeding Bottles
Patented in England, December 4, 1879;
Patented in the United States, April 27, 1880.
THE FITTING COMPLETE.
PATENT
PORCELAIN
PATENT
COUPLING-PIECE.
REGISTERED
INDIA-RUBBER TEAT.
PATENT INDIA-RUBBER TUBE.
Patent India-rubber Tubes, in ½ gross and 1 gross Boxes—
9-inch White ... ... per gross 10/6 | 9-inch Black ... ... per gross 15/-
10 " " Super " 16/- | 10 " " ... ... " 16/-
Registered India-rubber Teats, in 1 doz. Boxes—
2 Sizes (Small and Medium), per gross, White, 8/- & 14/-; Black, 12/- & 21/-
Patent Coupling-pieces, in 3 doz. Boxes ... ... per gross 8/-
S. MAW, SON & THOMPSON beg to inform the Trade that in future all their Feeding Bottles, except Sixpenny, will be fitted with the above PATENTED IMPROVEMENT, unless ordered to the contrary.
The improvement consists in the introduction of the New Registered Teat, and in the construction of the Coupling-piece, the latter passing over the exterior of the India-rubber Tube, by which arrangement injurious contraction is avoided, and the cleaning of the Tube facilitated, a Tube Brush being easily passed through without the removal of the Coupling-piece.
In the fitting up of ordinary Feeding Bottles, the Shield fixes the Teat upon the Union Joint, preventing its easy removal, and making it difficult to replace the Teat in its air-tight position, without which the action of no Feeding Bottle is perfect. The New Registered Teat is so formed as to receive the shield and retain it in position without connection with the Coupling-piece, the Teat thus being easily removed and replaced without damage.
S. MAW, SON & THOMPSON, LONDON.

In 1865, chemist Justus von Liebig patented an infant formula made of cow's milk, wheat and malt flour, and potassium bicarbonate

THE INFLUENCE OF BREAST AND ARTIFICIAL FEEDING ON INFANTILE ECZEMA

Clifford G. Grulee, M.D., and Heyworth N. Sanford, M.D.
Chicago, Ill.

THERE is probably no subject in pediatrics that has received so much attention in the last few years as that of infantile eczema.



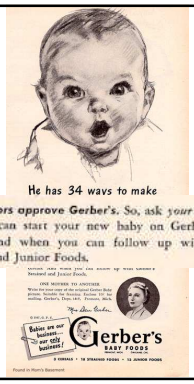
the use of olive oil only for cleansing purposes. None of the feedings were changed in any way. In the artificially fed infants, 1.5 ounces of boiled cow's milk and 0.1 ounce of cane sugar per pound body weight were used. In all infants cod liver oil, orange juice, cereals, and vegetables were added to the diet.

Chart 1.—Monthly incidence of infantile eczema.

Journal of Pediatrics 1936

By 1946, the proportion of newborns exclusively breastfed at hospital discharge was only 38%

Ads from the 1940s from Nestle and Carnation



1947 ad

1949 ad

BRINGING UP BABIES

A FAMILY DOCTOR'S PRACTICAL APPROACH TO CHILD CARE

BY WALTER W. SACKETT, JR., M.D.

1962

64. At 2-3 Days, Cereal is given to babies under my care at twelve noon and at twelve midnight, again because this is the handiest time for nurses in the hospital to get out on the floor and teach

66. At 10 Days, Strained Vegetables are added to the noon meal.

67. At 14 Days, Strained Meats are offered either at noon, along with the vegetables, or at 6:00 P.M. with the cereal feeding. There is

68. At 17 Days, Soups and Meat Combinations, such as lamb and rice or beef and vegetables, are introduced, and we realize now that baby is eating regular little meals. He may have meat and vegetable

72. At 5 Weeks, Eggs are introduced, and this addition provokes a great deal of controversial comment. Some authorities insist that

74. At 9 Weeks, Bacon and Eggs, Just Like Dad! In not-so-strange

By the mid-1960s the typical age at introduction of solids had decreased from 6-7 months to 4-6 weeks

Amy Bentley, **Booming Baby Food: Infant Food and Feeding in Post-World War II America,** *Michigan Historical Review* Vol. 32, No. 2 (Fall, 2006), pp. 63-87

PROPHYLAXIS OF ALLERGIC DISEASE IN THE NEWBORN

Jerome Glaser, M.D.
and
Douglas E. Johnstone, M.D., Rochester, N. Y.

J.A.M.A., Oct. 17, 1953

Incidence of Major Allergy in Children

	No. of Patients	Incidence of Major Allergy	Atopic Dermatitis and Sequelae	Allergy to Cow's Milk and Sequelae
Experimental group	96	14	7	7
Sibling control group	65	42	21	24
Nonrelated control group	91	50		

* 10 asthma, 4 polinosis, and 1
† 11 asthma, 6 chronic atopic d
allergic rhinitis.
‡ 24 asthma and 6 pollinosis.
§ 21 asthma, 1 pollinosis, and 1 pollinosis and perennial allergic rhinitis

hood, and adult life. It is assumed that a physiological immunologic immaturity exists in the early months of life that results in sensitization and clinical symptoms caused by absorption from the intestinal tract of unaltered proteins in potentially allergic children. A poten-

Intervention:

- No cow's milk during first 6 months
- Mother refrains from eating eggs and cheese

Studies of Hydrolyzed Formula, 1988 - 1997

Study	*N*	Follow-up (months)	Diet	Effect of diet
Vandenplas *et al.* 1988 [32]	45	4	pHF	↓ CMPA, atopy
Chandra and Hamed 1991 [34]	263	18	pHF	↓ AD, atopy
Vandenplas *et al.* 1992 [54]	67	12	pHF	CMPA 15.6% Atopy 21.8%
			CMF	CMPA 42.8% Atopy 48.6%
Chandra *et al.* 1989 [33]	221	18	eHF	↓ AD
Zeiger *et al.* 1989 [43]	225	48	eHF	↓ FA
Zeiger *et al.* 1992 [44]				
Halken *et al.* 1993 [35]	141	18	eHF	↓ CMPA (3.6%)
Oldæus 1997	50	18	eHF	↓ Atopic symptoms 51%
	45	18	pHF	↓ Atopic symtoms 64%
	46	18	CMF	Atopic symptoms 84%

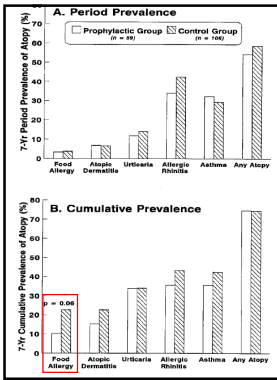
Effect of infants' diet indicated by arrows: ↑ indicates increase, ↓ indicates decrease or → no change in the incidence of disease/symptoms in infant having the diet mentioned.
AD, Atopic dermatitis; BF, breastfeeding compared with formula feeding; CMPA, cow's milk allergy; CMF, cow's milk-based formula; CMPA, cow milk protein allergy; eHF, extensively hydrolysed formula; FA, food allergy; pHF, partly hydrolysed formula.

Halken S[1], Høst A. **Prevention.** Curr Opin Allergy Clin Immunol. 2001 Jun;1(3):229-36.

Fraudulent data on hydrolyzed formula

1: Chandra RK. Five-year follow-up of high-risk infants with family history of allergy who were exclusively breast-fed or fed partial whey hydrolysate, soy, and conventional cow's milk formulas. **J Pediatr Gastroenterol Nutr**. 1997 Apr;24(4):380-8.
2: Chandra RK, Hamed A. Cumulative incidence of atopic disorders in high risk infants fed whey hydrolysate, soy, and conventional cow milk formulas. **Ann Allergy.** 1991 Aug;67(2 Pt 1):129-32..
3: Chandra RK, Singh G, Shridhara B. Effect of feeding whey hydrolysate, soy and conventional cow milk formulas on incidence of atopic disease in high risk infants. **Ann Allergy.** 1989 Aug;63(2):102-6. 4: Chandra RK, Puri S, Hamed A. Influence of maternal diet during lactation and use of formula feeds on development of atopic eczema in high risk infants. **BMJ.** 1989 Jul 22;299(6693):228-30.
5: Chandra RK, Puri S, Suraiya C, Cheema PS. Influence of maternal food antigen avoidance during pregnancy and lactation on incidence of atopic eczema ininfants. **Clin Allergy.** 1986 Nov;16(6):563-9.
6: Chandra RK. Prospective studies of the effect of breast feeding on incidence of infection and allergy. **Acta Paediatr Scand**. 1979 Sep;68(5):691-4.

- **1995: An inquiry conducted by Chandra's former employer, the Memorial University of Newfoundland, concluded that "scientific misconduct has been committed by Dr Chandra."**
- **BMJ 2015: Ranjit Chandra: "How reputation bamboozled the scientific community" (Formal retraction of 1989 paper)**



Clinical trial

- 59 intervention and 106 control
- Mothers avoided cow's milk, egg, and peanut during the last trimester of pregnancy and lactation
- Infants avoided cow's milk until age 1 (casein hydrolysate supplementation before age 1)
- Egg until 2
- Peanut and fish until 3

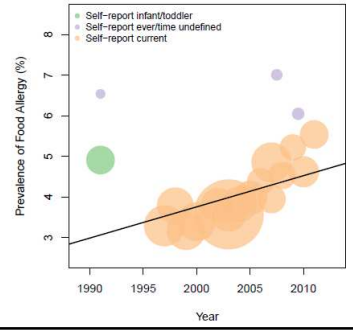
AAP Committee on Nutrition 2000

Infants at high risk for developing allergy, identified by a strong (biparental; parent, and sibling) family history of allergy may benefit from exclusive breastfeeding or a hypoallergenic formula or possibly a partial hydrolysate formula. Conclusive studies are not yet available to permit definitive recommendations. However, the following recommendations seem reasonable at this time:

- **Breastfeeding mothers should continue breast feeding for the first year of life or longer. …. 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.**

Pediatrics Aug 2000, 106 (2) 346-349;

Despite these recommendations, food allergy rates kept rising:



Keet at al: Ann Allergy Asthma Immunol 2014

Original articles

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

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,[a] 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*

Peanut consumption in infants: median 7.1g in Israel vs 0g in UK

Peanut allergy prevalence among Jewish children:
Israel: 0.17% UK: 1.85%

Adjusted RR: 9.8

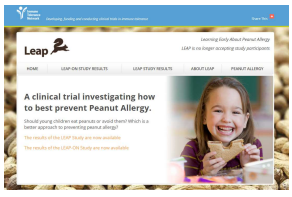
Du Toit JACI 2008

2008 AAP Guidelines

- **At the present time, there is lack of evidence that maternal dietary restrictions during pregnancy play a significant role in the prevention of atopic disease in infants. Similarly, antigen avoidance during lactation does not prevent atopic disease[…]**
- **For infants at high risk of developing atopic disease, there is evidence that exclusive breastfeeding for at least 4 months compared with feeding intact cow milk protein formula decreases the cumulative incidence of atopic dermatitis and cow milk allergy […]. exclusive breastfeeding for at least 3 months protects against wheezing in early life. […]**
- **In studies of infants at high risk of developing atopic disease who are not breastfed exclusively […] there is modest evidence that atopic dermatitis may be delayed or prevented by the use of extensively or partially hydrolyzed formulas, compared with cow milk formula, in early childhood. […]**
- **Although solid foods should not be introduced before 4 to 6 months of age, there is no current convincing evidence that delaying their introduction beyond this period has a significant protective effect on the development of atopic disease regardless of whether infants are fed cow milk protein formula or human milk. This includes delaying the introduction of foods that are considered to be highly allergic, such as fish, eggs, and foods containing peanut protein.**

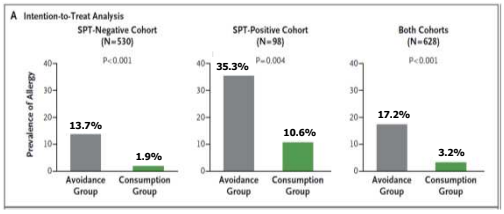
LEAP study

- **640 infants with severe eczema, egg allergy, or both and peanut SPT < 5mm**
- **Enrolled between 4 and 11 months of age**
- **Randomized to 2 groups – peanut avoidance or regular peanut consumption**
- **Final outcome determined by a peanut food challenge at 5 years**
- **Stratified based on baseline peanut skin test**



LEAP Study Design

LEAP Study: Prevalence of Peanut Allergy at Age 5



86% Reduction in SPT negative cohort

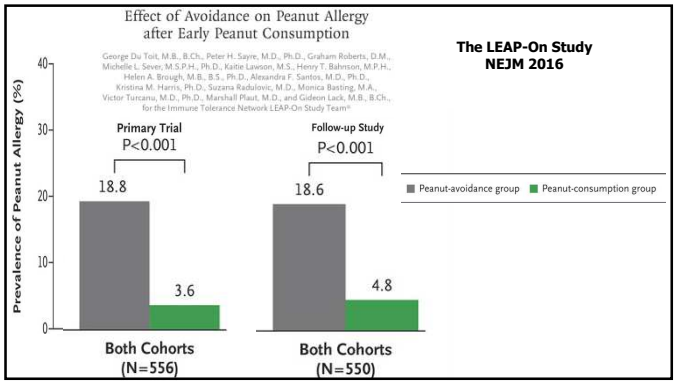
70% Reduction in SPT positive cohort

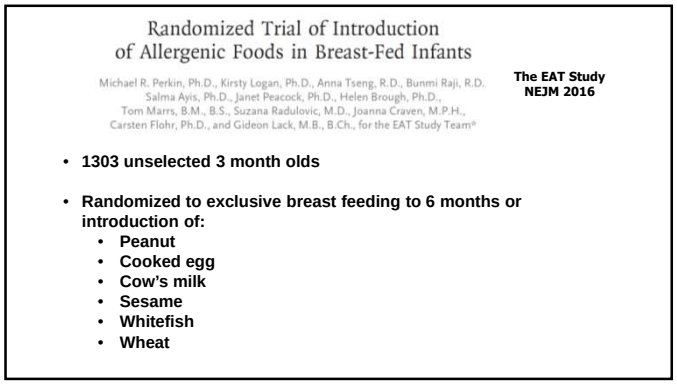
82% Reduction Overall

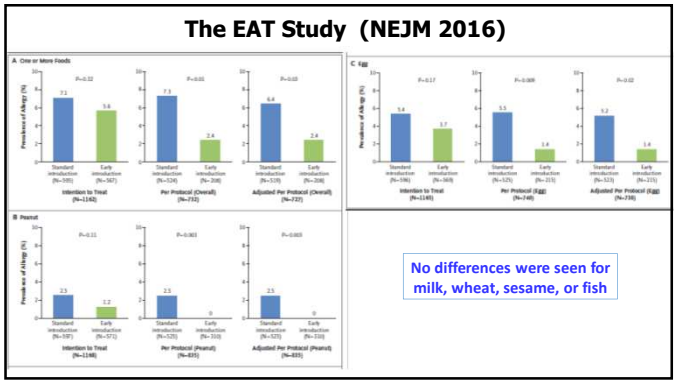
Du Toit NEJM 2015

Preventing Food Allergy Through Early introduction: *Remaining Questions*

- **Duration of Intervention**
- **Duration of Protection**
- **Who to treat**
- **When to intervene**
- **Which foods**
- **How much**


Effect of Avoidance on Peanut Allergy after Early Peanut Consumption
George Du Toit, M.B., B.Ch., Peter H. Sayre, M.D., Ph.D., Graham Roberts, D.M., Michelle L. Sever, M.S.P.H., Ph.D., Kaitie Lawson, M.S., Henry T. Bahnson, M.P.H., Helen A. Brough, M.B., B.S., Ph.D., Alexandra F. Santos, M.D., Ph.D., Kristina M. Harris, Ph.D., Suzana Radulovic, M.D., Monica Basting, M.A., Victor Turcanu, M.D., Ph.D., Marshall Plaut, M.D., and Gideon Lack, M.B., B.Ch., for the Immune Tolerance Network LEAP-On Study Team*
The LEAP-On Study
NEJM 2016
Prevalence of Peanut Allergy (%)
40
30
20
10
0
Primary Trial
P<0.001
18.8
3.6
Both Cohorts (N=556)
Follow-up Study
P<0.001
18.6
4.8
Both Cohorts (N=550)
Peanut-avoidance group
Peanut-consumption group

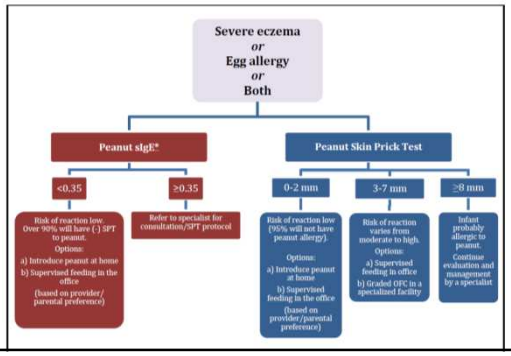

Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants
Michael R. Perkin, Ph.D., Kirsty Logan, Ph.D., Anna Tseng, R.D., Bunmi Raji, R.D., Salma Ayis, Ph.D., Janet Peacock, Ph.D., Helen Brough, Ph.D., Tom Marrs, B.M., B.S., Suzana Radulovic, M.D., Joanna Craven, M.P.H., Carsten Flohr, Ph.D., and Gideon Lack, M.B., B.Ch., for the EAT Study Team*
The EAT Study
NEJM 2016
• 1303 unselected 3 month olds
• Randomized to exclusive breast feeding to 6 months or introduction of:
  • Peanut
  • Cooked egg
  • Cow's milk
  • Sesame
  • Whitefish
  • Wheat


The EAT Study (NEJM 2016)
No differences were seen for milk, wheat, sesame, or fish

Who to treat (and what went wrong with prior guidelines?

- We gave broad-sweeping recommendations based on low quality evidence
  - Caveats were ignored
- We reasoned from faulty mechanistic theories
- We gave into the pressure to "do something"
- We underestimated the possibility of harm

Guidelines for the Prevention of Peanut Allergy in the United States



Summary of Guidelines for the Prevention of Peanut Allergy in the United States

Guideline	Infant Criteria	Recommendation	Earliest Age
1	Severe eczema, egg allergy or both	Strongly consider evaluation by sIgE and/or SPT, and if necessary an oral food challenge; Based on test results, introduce peanut containing foods	4 – 6 months
2	Mild to moderate eczema	Introduce peanut-containing foods	Around 6 months
3	No eczema or any food allergy	Introduce peanut-containing foods	Age appropriate and in accordance with family preferences and cultural practices

Concerns related to screening:

- 11% of those screened in LEAP study were excluded because of large peanut SPT (>4mm)
  - By 5 years of age 78% were peanut allergic but how many were allergic as infants?
- Of those randomized, 2.2% failed the baseline challenge
  - All had predominately mild cutaneous symptoms
- 60% of peanut allergic children have no history of egg allergy or severe eczema
  - ~10% of siblings of peanut allergic children have peanut allergy
  - We don't have good data on those with milder eczema
- Our screening tests are not very good

Koplin JACI 2016, Du Toit JACI 2016

Far more babies (people) are sensitized than allergic to peanut (food) allergens:

- 22% of LEAP participants had positive peanut IgE
  - Remember that only 2.2% failed baseline challenges
- There was no statistically significant relationship between peanut IgE and failing the baseline challenge
  - Of those with positive peanut IgE, 96% passed the oral food challenge
  - If peanut IgE > 2, 95% passed
  - If peanut IgE > 5, 95% passed
  - If peanut IgE > 15, 92% passed
  - Among the 11 with peanut IgE > 20, 100% passed

SPT may be better, but still not great

- Of those with detectable peanut SPT, 87% passed challenge
- If SPT > 1mm, 87% passed
- If SPT > 2mm, 76% passed
- If SPT > 3mm, 70% passed
- Remember that study excluded those with SPT more than 4 mm

Other issues with the Guidelines

- How to best define the "at-risk" population
  - Milk allergy never mentioned as a risk factor
- Feasibility and implementation of the guidelines
- At what age should peanut be started?
  - May contradict WHO Guidelines for exclusive breast feeding through 6 months
- The potential for unintended consequences
- What about other foods?

Wood and Burks: JACI Editorial 2017

Potential for Unintended Consequences

- In a birth cohort study (in Ireland) ~5% of babies had severe eczema or egg allergy (19% had eczema overall)
- From the Editorial:
  - In the United States, even if only babies with severe eczema are screened, this would translate to about 200,000 infants per year for whom screening would be recommended and at least 40,000 who would have a positive peanut IgE based on the LEAP data.
  - The feasibility of guideline implementation may therefore actually be complicated, rather than facilitated, by this approach. Even more importantly, unless these infants with positive IgE testing can access specialty care in a timely manner, they have a true risk of being diagnosed with peanut allergy, unnecessarily avoid peanut, and be placed at higher risk of developing peanut allergy such as those in the avoidance group in the LEAP study.

JAMA | Original Investigation

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

A Systematic Review and Meta-analysis

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

- There was moderate-certainty evidence from 2 trials (1550 participants) that early peanut introduction at 4 to 11 months was associated with reduced peanut allergy (RR, 0.29; 95%CI, 0.11-0.74; $I2$ = 66%; P = .009). Absolute risk reduction for a population with 2.5% incidence of peanut allergy was 18 cases per 1000 population.
- Nine trials studied the effect of egg introduction at 4 to 6 months of age. Of those, five studies with 1915 participants showed moderate-certainty evidence of a lower risk for egg allergy compared with later egg introduction (risk ratio [RR], 0.56; 95% confidence interval [CI], 0.36 - 0.87; P = .009). For a population with a 5.4% incidence of egg allergy, the absolute risk reduction was 24 cases

Negative studies of early egg introduction

Palmer JACI 2013: 86 infants with moderate-to-severe eczema

- No difference in egg allergy (33% vs. 51%, p=0.11)
- 31% of those randomized to egg had an allergic reaction on introduction

Palmer JACI 2016: 820 infants without eczema

- No difference in egg allergy (7% vs 10%, p=0.2)
- 6.1% stopped taking powder due to an allergic reaction

Bellach JACI 2016: 406 infants without egg sensitization

- No difference in egg allergy (5.6% vs. 2.6%, p=0.24) or sensitization (2.1% vs. 0.6%, p=0.35)
- Prior to randomization 16 were egg allergic, including 11 with anaphylactic reactions

Other Foods: We do not have good data

Preventing Food Allergy Through Early introduction: *Remaining Questions*

- Duration of Intervention
- Duration of Protection
- Who to treat
- When to intervene
- Which foods
- How much

Are there approaches other than early feeding that might prevent food allergy?

- Given the difficulties – and even lack of apparent effect – of early feeding of multiple foods, other approaches would be desirable
  - Aggressive control of eczema early in life, based on the dual-exposure hypothesis
  - Manipulation of microbial populations (with pre- or probiotics)
  - Fish oil
  - Vitamin D supplementation (HealthNuts data that infants with vitamin D level ≤50 nmol/L at 12 months had an increased risk of peanut and 99 egg allergies)
  - No published studies in these areas showed an effect and none can be considered useful yet clinically
  - There is no evidence that maternal dietary restrictions or hypoallergenic milk formulas affect the onset of food allergy