Scientific Advisory Committee on Nutrition

Committee on TOXICITY

Evidence on the timing of introduction of peanut into the infant diet and influence on the risk of development of atopic outcomes and autoimmune disease

Background

1. Two randomised controlled trials have been published that describe the introduction of peanut into the infant diet to investigate the influence on the risk of peanut allergy, and the effect of timing of introduction (Du Toit *et al*, 2015; Perkin *et al,* 2016). A summary of the study designs of the LEAP and EAT studies can be found in Figure 2.

2. The LEAP Study randomised 640 UK infants at high risk of peanut allergy to either avoid or consume peanuts until 5 years of age. The study reported introducing peanut into the infant diet between 4-11 months significantly decreased the frequency of the development of peanut allergy ($p<0.001$) (Du Toit *et al*, 2015).

3. The EAT Study recruited 1303 infants from the general population of England and Wales. Infants were randomly assigned to the introduction of six allergenic foods from 3 months of age (peanut, cows' milk, wheat, sesame, white fish and hens' egg) or to the current practice recommended in UK infant feeding advice (exclusively breastfeed to 6 months of age). The EAT study did not show efficacy in an intention to treat analysis. However, a statistically significant reduction in peanut allergy was reported in the per protocol analysis ($p=0.003$).

4. These studies are included in the systematic review and meta-analysis conducted by Ierodiakonou *et al* (2016). The systematic review concluded that there was evidence that introduction of peanut at 4-11 months of age reduces the risk of peanut allergy, compared with the later introduction of peanut. The quality of this evidence was rated as MODERATE using the GRADE system[1]. Figure 1 shows the forest plot of results from the systematic review and figure 3 provides further detail on the GRADE assessment and summarises the finding for this evidence.

[1] http://www.gradeworkinggroup.org/

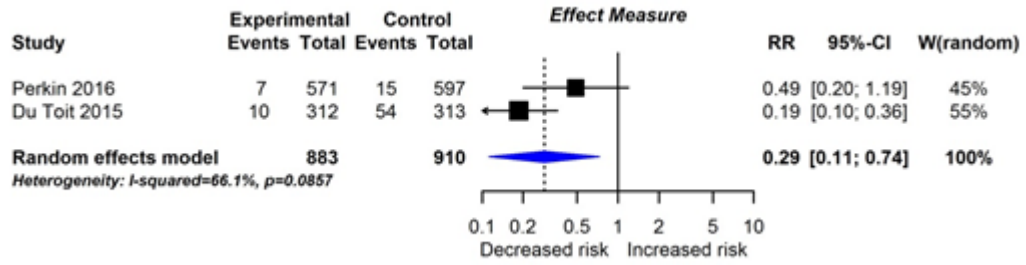

Figure 1: Early nut introduction and risk of FA-Peanut at any age

Figure 2: Summary of study designs of peanut allergy intervention trials

Study	Design	N Int/ Ctrl	Intervention	Population	Country	Disease risk	Age	Outcome assessment
Du Toit, 2015/16 (2, 3)	RCT	319/ 321	6g peanut protein per week, divided between 3 meals, from 4-11 months to 5 years, versus peanut avoidance.	Learning Early About Peanut allergy (LEAP) Study. Infants aged 4-11 months with severe eczema and/or egg allergy and peanut SPT <4mm. Mean 7.8 months.	UK	High	5, 6	Oral food challenge
Perkin, 2016 (16)	RCT	652/ 651	Sequential introduction of six allergenic foods - cow's milk, peanut, egg, wheat, sesame and fish from age 3 months (median 17 weeks milk, 21 weeks wheat, 20 weeks other allergens), versus avoidance to ≥6 months.	Enquiring About Tolerance (EAT) Study. Children exclusively breastfed at 3 months and gestation over 37 weeks.	UK	Normal	3	Oral food challenge

Figure 3: GRADE assessment and summary of finding for timing of introduction of peanut into the infant diet and risk of peanut allergy

GRADE of evidence assessment	
No of studies	2 intervention studies
Design	2 RCTs
Risk of bias	No. Neither study had a high risk of bias or conflict of interest
Inconsistency	Not Serious I^2=66% (P=0.09), study estimates vary from 0.49 to 0.19 but heterogeneity is likely to be explained by differences in participant adherence to the intervention
Indirectness	Serious. 1 study only recruited infants with egg allergy or eczema, and without high-level peanut sensitization; 1 study used multiple allergenic foods
Imprecision	Serious. 95% CI for RR is wide
Publication bias	Insufficient studies to undertake formal testing of publication bias
Other considerations	GRADE of evidence increased due to the strong effect size
Summary of finding	
Estimate	RR = 0.29 (0.11 to 0.74)
GRADE of evidence	⊗⊗⊗○ Moderate
Absolute risk reduction	
Control Risk: Cases per 1000 population	25 (normal risk) 170(high risk)
Risk Difference: Cases per 1000 population	18 cases less (6 to 22) 121 cases less (44 to 151)

Pre-assessment and problem formulation

5. The evidence base suggests that introducing peanut between 4-11 months (and therefore potentially before 6 months of age) may reduce the risk of peanut allergy. In the UK, current dietary practice is for peanut to be introduced into the infant diet later than 6 months: 8% of infants are introduced to peanut between 8-10 months (McAndrew *et al*, 2012).

6. It is proposed that the risk benefit assessment utilises a two scenario approach whereby the current UK dietary advice is the reference scenario and the alternative scenario is based on the finding from Ierodiakonou *et al* (2016):

   Reference scenario: Infants should be exclusively breastfed until around 6 months of age. Complementary foods should be introduced into the infant's diet from around six months of age alongside continued breastfeeding (and/or breast milk substitutes, if used). Common allergenic foods should be avoided until after 6 months of age.

Alternative scenario: Peanut should be introduced into the diet [of all infants?] between 4-11 months of age (unless already sensitised to peanut).

Individual assessment of risks and benefits

7. A number of possible health effects of changing from the reference scenario to the alternative scenario have been identified. These are outlined in figure 4 below.

Figure 4: Possible health effects of changing from the reference scenario to the alternative scenario

Category of effect	Specific effect
Food allergy	IgE-mediated food allergy to peanut
	Non-IgE mediated food allergy and food hypersensitivity
	IgE-mediated food allergy in siblings
Infant growth	Weight, length/height, BMI, head circumference, mid-upper arm circumference, skin fold thickness.
Nutrition and composition of the infant diet	Exclusive breastfeeding duration
	Total breastfeeding duration
	Macronutrient intake
	Micronutrient intake
	Use of formula
	Composition of the infant diet
Infections	Gastrointestinal infections
	Respiratory infections
	Ear infections
Maternal health	Maternal weight loss
	Breast cancer
Safety	Anaphylaxis and allergic reactions
	Mycotoxin exposure
	Choking episodes

References

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Ierodiakonou D, Garcia-Larsen V, Logan A, Groome A, Cunha S, Chivinge J, et al (2016). Timing of Allergenic Food Introduction to the Infant Diet and Risk of Allergic or Autoimmune Disease: A Systematic Review and Meta-analysis. Journal of the American Medical Association. 316(11): 1181-1192

McAndrew F, Thompson J, Fellows L, Large A, Speed M, Renfrew MJ. (2012) Infant Feeding Survey 2010. Health and Social Care Information Centre.

Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, Brough H, Marrs T, Radulovic S, Craven J, Flohr C, Lack G; EAT Study Team. (2016) Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants. New England Journal of Medicine. 374: 1733-1743