

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

Background

1. Six randomised controlled intervention studies have been published in which egg was introduced into the infant diet, the aim being to investigate the influence of introduction on risk of developing egg allergy, and the effect of timing of introduction (Halpern *et al*, 1973; Palmer *et al*, 2013; Bellach *et al*, 2016; Natsume *et al*, 2016; Perkin *et al*, 2016; Tan *et al*, 2016). Table 1 provides a summary of the study designs employed in these trials.
2. These studies frequently utilised different forms of egg for the intervention, different doses, and administration to non-equivalent cohorts of differing risks.
3. Four studies found no statistically significant effect of timing of introduction of egg into the infant diet on risk of egg allergy from intention to treat data (Bellach *et al*, 2016; Halpern *et al*, 1973¹; Palmer *et al*, 2013; Tan *et al*, 2016). Perkin *et al* (2016) did not show efficacy in an intention to treat analysis. However, a statistically significant reduction in egg allergy was reported in the per protocol analysis ($p=0.003$). Natsume *et al* (2016) reported a statistically significant reduced risk of egg allergy with introduction of egg (alongside management of eczema) from six months of age ($p=0.013$).
4. These studies (except Halpern) 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 egg at 4-6 months of age reduces the risk of egg allergy, compared with later egg introduction. The quality of this evidence was rated as MODERATE using the GRADE system². Figure 1 (below) shows the results from the meta-analysis. Figure 2 provides further detail on the GRADE assessment and summarises the findings for this evidence. A further study has been published since the meta-analysis by Imperial College in which infants were randomly allocated to receive pasteurised raw whole egg

¹ This study was excluded from the Imperial meta-analysis, because the denominators were not reported.

² <http://www.gradeworkinggroup.org/>

powder (n = 407) or rice powder (n = 413) from ages 4-6 months to 10 months when cooked egg was introduced in all subjects. The authors found no differences in the incidence of IgE-mediated egg allergy between test and control groups (Palmer *et al*, 2016).

Figure 1: Early egg introduction and risk of FA-Egg at age ≤ 4 years

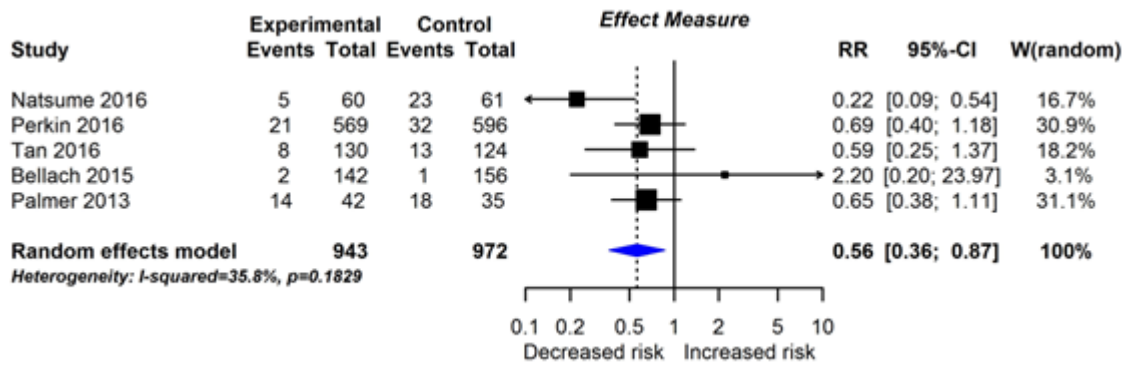


Figure 2: Summary of study designs of egg allergy intervention trials

Study	Design	N Int/ Ctrl	Intervention	Population	Country	Disease risk	Age	Outcome assessment
Bellach, 2016	RCT	184/ 199	Pasteurised egg white powder (~2.5g protein, equivalent to 5g whole egg protein) versus rice powder 3 times per week from 4-6 months to 12 months	HEAP Study. Infants aged 4-6 months with specific IgE to egg <0.35 kU/L	Germany	Normal	1	Oral food challenge
Halpern, 1973	RCT	~875/ 875	Egg yolk given before 3 weeks, versus after 6 months.	Caucasian infants seen at birth by one of 11 private paediatricians in Dallas.	USA	Normal	5	Oral food challenge
Natsume, 2016	RCT	60/ 61	Pulverised boiled egg (50mg daily from 6-9 months; 250mg daily from 9-12 months) versus placebo from 6 to 12 months. Eczema management.	Infants with atopic dermatitis by 4-5 months.	Japan	High	1	Oral food challenge
Palmer, 2013	RCT	49/ 37	1 teaspoon (900mg whole egg protein) per day of pasteurized raw whole egg powder, versus rice flour powder, given daily from randomization at 4 months to 8 months age.	Singleton term infants with symptoms of moderate-to-severe eczema.	Australia	High	1	Oral food challenge

Study	Design	N Int/ Ctrl	Intervention	Population	Country	Disease risk	Age	Outcome assessment
Perkin, 2016	RCT	652/ 651	Sequential introduction of six allergenic foods - cow's milk, peanut, egg, wheat, sesame and fish – target 2g protein for each food, twice weekly 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
Tan, 2016	RCT	165/ 154	Pasteurised whole egg powder (350mg whole egg protein) daily versus rice powder from the time of solid food introduction (median 4 months) until 8 months age.	BEAT Study. Infants with a first degree relative with allergic disease, and egg SPT < 2 mm at age 4 months.	Australia	High	1	Oral food challenge

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

GRADE of evidence assessment	
No of studies	6 intervention studies (5 of which provided data for meta-analysis)
Design	6 RCT
Risk of bias	Not Serious 1 study at high risk of bias, no studies at high risk of conflict of interest
Inconsistency	Not serious $I^2=36%$ ($P=0.18$). Study estimates vary from 0.22 to 0.69 for the studies at low risk of bias
Indirectness	Serious 3 studies only recruited infants without egg sensitization; 1 study only infants with eczema; 1 study used multiple allergenic foods
Imprecision	Not serious 95% CI for RR is wide. Trial sequential analysis suggests that optimum information size has not yet been reached
Publication bias	Insufficient studies to undertake formal testing of publication bias
Summary of finding	
Estimate	RR = 0.56 (0.36 to 0.87)
GRADE of evidence	⊗⊗⊗○ Moderate
Absolute risk reduction	
Control Risk: Cases per 1000 population	54 (normal risk)
Risk Difference: Cases per 1000 population	44 cases less (13 to 64) 220 cases less (65 to 320)

Pre-assessment and problem formulation

- The evidence base suggests that introducing egg between 4-6 months of age may reduce the risk of egg allergy. In the UK, 54% of infants are introduced to egg before 6 months of age (McAndrew *et al*, 2012).
- It is proposed that the risk benefit assessment utilises a three scenario approach. The current UK dietary advice is proposed as the reference scenario, and two alternative scenarios could be explored. Four of the six studies in this evidence base used egg powder as the intervention, which may limit direct application to UK dietary recommendations that focus on whole foods. An alternative scenario which assesses the effects of egg in both powder and whole form may be assessed alongside a second alternative scenario where egg is introduced only

in its whole form (e.g. boiled egg). The finding from Ierodiakonou *et al* (2016) will form the basis for the alternative scenario:

Reference scenario: Infants should be exclusively breastfed for 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 1: Egg protein (of any kind) should be introduced into the diet [of all infants?] between 4-6 months of age.

Alternative scenario 2: Whole (not powdered), cooked egg should be introduced into the diet [of all infants?] between 4-6 months of age

Individual assessment of risks and benefits

7. A number of possible health effects of changing from the reference scenario to the alternative scenarios have been identified. These are outlined in Table 3 below.

Table 3: Possible health effects of changing from the reference scenario to the alternative scenarios

Category of effect	Specific effect
Food allergy	IgE-mediated food allergy to egg
	Non-IgE mediated food allergy and food hypersensitivity
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
Infections	Composition of the infant diet
	Gastrointestinal infections
	Respiratory infections
	Ear infections
Maternal health	Maternal weight loss
	Breast cancer
Safety	Anaphylaxis and allergic reactions
	Microbial exposure (salmonella)

References

- Bellach J, Schwarz V, Ahrens B, Trendelenburg V, Aksunger O, Kalb B Niggemann B, Keil T, Beyer K (2016) Randomized placebo-controlled trial of hen's egg consumption for primary prevention in infants. *Journal of Allergy and Clinical Immunology*. DOI: <http://dx.doi.org/10.1016/j.jaci.2016.06.045>
- Halpern S, Sellars W, Johnson R, Anderson D, Saperstein S, Reisch J (1973). Development of childhood allergy in infants fed breast, soy, or cow milk. *Journal of Allergy and Clinical Immunology*. 51(5) 139-151
- Ierodiakonou D, Garcia-Larsen V, Logan A, Groome A, Cunha S, Chivinge J, Robinson Z, Geoghegan N, Jarrold K, Reeves T, Tagiyeva-Milne N, Nurmatov U, Trivella M, Leonardi-Bee J, Boyle RJ (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.
- Natsume O, Kabashima S, Nakasato J, Yamamoto-Hanada K, Narita M, Kondo M, Saito, M; Kishino, A; Inoue, E; Shinahara, W; Kido, H; Saito, H; Ohya Y (2016). Early introduction of egg for infants with atopic dermatitis to prevent egg allergy: A double-blind placebo-controlled randomized clinical trial. *Journal of Allergy and Clinical Immunology*. 137(2 SUPPL. 1):AB98
- Palmer DJ, Sullivan TR, Gold MS, Prescott SL, Makrides M. (2016) Randomized controlled trial of early regular egg intake to prevent egg allergy. *J Allergy Clin Immunol*. Aug 20. pii: S0091-6749(16)30793-X. doi: 10.1016/j.jaci.2016.06.052. [Epub ahead of print]
- Palmer DJ, Metcalfe J, Makrides M, Gold MS, Quinn P, West CE, Loh R, Prescott SL (2013). Early regular egg exposure in infants with eczema: A randomized controlled trial. *Journal of Allergy and Clinical Immunology*. 132(2):387-92.e1.
- 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
- Tan J, Valerio C, Barnes E, Turner P, Van Asperen P, Kakakios A et al (2016) A randomized trial of egg introduction from 4 months of age in infants at risk for egg allergy. *Journal of Allergy and Clinical Immunology*. DOI: <http://dx.doi.org/10.1016/j.jaci.2016.08.035>