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Does Early Egg Consumption Reduce Egg Allergy? Evidence from Randomised Controlled Trials

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ABSTRACT

We refer to the six randomised controlled trials (RCTs) (PETIT; Natsume et al, HEAP; Bellach et al, BEAT; Tan et al and STEP; Palmer et al, EAT; Perkin et al, STAR; Palmer et al, published within the last five years. These trials reported on early egg introduction and risk of later egg sensitization and egg allergy at 12 months of age. Based on these trial results, it is clear that RCT results need to be critically appraised and interpreted. We found that the methodological differences among the studies may have influenced the study results. Therefore, critical interpretation of RCT results is required to understand the evidence.

Keywords: Randomised controlled trials; Egg; Sensitisation; Allergy

Introduction

We refer to the six randomised controlled trials (RCTs) PETIT; Natsume et al. [1], HEAP; Bellach et al. [2], BEAT; Tan et al. [3] and STEP; Palmer et al. [4], EAT; Perkin et al. [5], STAR; Palmer et al. [6] published within the last five years. The trials reported on early egg introduction and risk of later egg sensitisation and allergy at 12 months of age. Although these six trials were very similar in several respects, we have concerns regarding the consistency of the findings. The Japanese PETIT trial was the only one to find a protective effect for egg allergy diagnosed using oral food challenge testing (OFC). Although the EAT and STAR trials concluded that early introduction of egg was protective against food allergy, neither showed good evidence on OFC testing. In terms of sensitisation, the BEAT trial found reduced sensitisation when whole egg was introduced to high risk infants. The STEP and HEAP found no protection for either sensitisation or food allergy.

RCTs provide the highest level of evidence for a causal effect from an intervention [7]. However, belief in the RCT as a study design may lead to the results being accepted as unarguable evidence and a failure to critically appraise individual studies. This can lead to confusion when similar RCTs present conflicting results as is the case here. There are several methodological differences between the studies which may have influenced the results. PETIT was based on high risk children in Japan. The other studies on high allergy risk populations, the BEAT, STEP and STAR, all used Australian birth cohorts, and the allergy risk was defined differently. In the BEAT study, high risk was defined as any immediate family member (father, mother, older sibs) with food allergy, asthma, atopic eczema or allergic rhinitis. In STEP it was based on the "atopic status" of the mother only (medically diagnosed allergic disease with sensitisation to at least one common aero allergen), and results were adjusted for paternal allergic disease. The STAR trial recruited babies with severe eczema. In all three trials the intervention was similar (whole egg) and, all assessed the outcome at 12 months. However, the intervention timing and duration differed. In STAR and BEAT the intervention began at 4 and ended at 8 months with a duration of 4 months. In STEP, the intervention began at 4.5-6 months continuing until 10 months with a variable duration of 4.5-6 months. They also differed with respect to analysis. Although both BEAT and STEP provided an intention-to-treat analysis, STEP adjusted for baseline factors which appeared different between the groups while BEAT controlled only for region of origin of parents. All 3 trials may have been underpowered (Table 1). The STEP

trial which reportedly failed to reach the planned sample size was almost twice the sample size of BEAT and 10 times the size of STAR.

In contrast, the HEAP and EAT trials were selected from the general population. The intervention in HEAP was egg white, as opposed to whole egg, and in EAT it was a combination of 6 allergenic foods, making it distinctly different from all the other trials. In HEAP egg introduction commenced at 4-6 months and continued until 12 months of age with an intervention duration of 6-8 months, substantially longer than the other trials, and extending into a different developmental period of infancy (12 months as opposed to 8 or 10 months in BEAT and STEP and 4 to 8 months in STAR).

Table 1: A comparison of the methodology of included trials and the message from each trial.

	PETIT Trial Natsume et al. [1]	**HEAP Trial Bellach et al. [2]**	**BEAT Trial Tan et al. [3]**	**STEP Trial Palmer et al. [4]**	**EAT trial Perkin et al. [5]**	**STAR Trial Palmer et al. [4]**
Country	Japan	Germany	Australia	Australia	United Kingdom	Australia
Clinical trial registry number	UMIN: 000008673	DRKS: 00005668	ACTRN: 12611000535976	ACTRN: 12610000388011	ISRCTN: 14254740	ACTRN: 12609000415202
Population	High risk population	General population	High risk population	High risk population	General population	High risk population
Inclusion criteria	4-5 months of age With Atopic dermatitis Born after 38 weeks of gestation Not ingested eggs no immediate allergic reaction to eggs or not having severe illnesses	Gestational age > 34 weeks Birth weight >2.5Kg Maternal age > 18 year Sufficient language skills	Healthy Full term	Singleton infants Children without allergic diseases such as eczema Eggs were not introduced before the age of 4 months Children without congenital or developmental disorders >35 weeks of gestation Birth weight between 2.0-4.5Kg	Singleton infants Three months of age Exclusively breastfed	Singleton infants With moderate to severe eczema Eggs or solids introduced before 4 months of age were excluded
High-risk population definition	Atopic dermatitis diagnosed based on Hannifin and Rajka criteria	NA	At least one first degree relative with atopic disease (food allergy, asthma, atopic eczema, or allergic rhinitis)	Maternal atopy diagnosed as history of a medically diagnosed allergic disease with sensitisation to at least one common aeroallergen	NA	Moderate to severe eczema determined by using a standardized SCORAD
Sample size (intervention/ control)	Intervention: 73 Control: 74	Intervention: 142 Control: 156	Intervention: 122 Control: 122	Intervention: 407 Control: 413	Intervention :567 Control :595	Intervention :49 Control:37
Method used for exclusion of sensitized infants at baseline	NA (IgE for Hen's egg was tested but has not led to exclusion)	Hen's egg specific IgE ≥0.35 Kilounits Number excluded 23(Due to increased IgE)	SPT to commercial egg white of 2 mm or greater Number excluded 13 (70% of these had eczema)	Infants who had a history of allergic disease Number excluded 396	SPT greater than zero and OFC to check whether they are allergic to exclude Number excluded 16 (50% had major health issues)	NA (Although blood samples were tested for egg specific IgE and IgG this had not led to exclusion)

Randomisation procedure	Double blind 1:1 randomisation Using permuted blocks of 4 randomisation and participants stratified based on institution and sex	Double blind 1:1 randomisation at a single site	Double blind randomisation based on permuted blocks stratified by sex	Double blind randomly permuted blocks 4, 6 and 8 with stratification for city, infant sex, and feeding mode	Double blind randomly allocated 1:1 to early and standard introduction	Double blind random allocation stratified by infant sex and feeding mode (breastfed or formula fed >200ml per day)
Intervention	Type: Boiled whole hen's egg powder	Type: Pasteurized Raw hen's egg white powder	Type: Pasteurized whole hen's egg powder	Type: pasteurized raw whole hen's egg powder	Type: Allergen protein (peanut, cooked whole hen's egg, cow's milk, sesame, white fish and wheat)	Type: Pasteurized raw whole hen's egg powder
	Quantity: 25mg of hen's egg protein daily	Quantity: 2.5g hen's egg protein (building up over three weeks	Quantity: 0.35g egg protein	Quantity: 0.4g egg protein daily (0.9g egg powder (1/2 egg per week)	Quantity: 2 g	Quantity: 0.9 g egg protein equivalent to 1/2 of an egg
	Start: 6 months	Start: 4 to 6 months	Start: 4 months	Start: 4-6.5 months	Start: 3 months	Start: 4 months
	End: 12 months	End: 12 months	End: 8 months	End:10 months	End:6 months	End: 8 months
	Intervention duration: 6 months	Intervention duration: 6-8 months	Intervention duration: 4 months	Intervention duration: 4.5-6 months	Intervention duration: 3 months	Intervention duration: 4 months
	Frequency: daily	Frequency- three times a week	Frequency- daily	Frequency- daily	Frequency: twice weekly	Frequency: daily
Control	Type- pumpkin powder	Type: Rice powder	Type: Rice powder	Type: Rice powder	Type-Breast milk	Type: Rice powder
When encouraged to introduce egg to controls	12 months	12 months	8 months	10 months	6 months	8 months
Age at outcome assessment And outcome types	12 months: Sensitisation: IgE, IgG1, IgG4, and IgA ≥ 0.35Ku Food allergy Oral food challenge (open labelled)	12 months: Sensitisation IgE levels ≥ 0.35Ku as egg allergy Food allergy Oral food challenge (Double blind placebo controlled	12 months: Sensitisation EW-SPT responses of 3mm or greater as egg allergy Food allergy Oral food challenge (Double blind placebo controlled	12 months: Sensitisation IgE levels ≥ 0.35Ku as egg allergy SPT 3mm or greater Food allergy Oral food challenge (open labelled)	12 months and 36 months Sensitisation SPT >5mm or greater Food allergy Oral food challenge (Double blind placebo controlled	8 and 12 months Sensitisation IgE and IgG ≥ 0.35Ku for tested allergens Food allergy Oral food challenge (open labelled)
Did the authors consider and adjust for potential imbalance in baseline factors or adjust for other factors	Adjusted for allergic history of father and mother and start of solid foods	-	Fathers region of birth (Australian or New Zealand)	Adjusted for city, infant sex, breast-feeding status, and paternal history of allergic disease	Age	Checked for baseline disparities and there were no significant differences

Non-participants/ Participants not completing Adverse reactions	119 excluded at randomisation 37 -no atopic dermatitis 69-parental decline 13- not registered During the follow up 24 form the placebo arm and the 27 from the intervention arm were excluded None have stopped due to the adverse reactions to trial powder	23 at randomisation 42 in the intervention arm and the 43 in the control arm were lost 18 from the intervention arm excluded due to inadequate or impossible adherence to the study powder	28 at randomisation 14 reacted to egg powder and stopped (14/152) 7 lost to follow-up in the intervention arm and 8 lost to follow up in the control arm 14 infants reacted to study powder and did not continue	1200 at randomisation 25 in the intervention arm and the 6 in the control arm had reactions to study powder 12 in each arm was lost to follow-up 6 infants had reactions to study powder	1303 were randomised and 651 were in the standard introduction group and 652 were in the early introduction group. From the standard introduction group 56 had missing data 7 has exceeded the visit window and 5 could not be evaluated from the early introduction group 81 had missing data None have stopped due to adverse effects	9 did not attend the final appointment 4 as their parents were busy from this 1 was in the rice group, two did not like the rice powder, I had repeated illnesses, I moved overseas, and I did not want to have the raw egg challenge) 4 children developed severe adverse reactions due to the study powder
Results- sensitisation	ITA 8% of the intervention group and 38% of the control group was sensitized (p=0.0001) PPA 4% of the intervention group and 38% of the control group was sensitized 9p<0.0001)	ITA 5.6% in the intervention group and 2.6% of the placebo group was sensitised to egg (p=0.24) PPA 4.8% in the intervention group and 2.6% of the placebo group was sensitised to egg RR,1.84 95%CI:0.53,6.37 (p=0.35)	ITA 10.7% in the intervention group and 20.5% of the placebo group was sensitised to egg (OR) of 0.46 (95% CI, 0.22-0.95; p=0.03 PPA- (OR, 0.24; 95% CI, 0.09-0.61; P 0.015).	ITA 7% of the intervention group and 10.3% of control group was sensitised to egg (OR of 0.75 95%CI, 0.48,1.17) p=0.20 SPT results- 0.77 (0.54-1.10) p=0.15 PPA- The per-protocol analysis found a lower percentage of infants in the egg group, 9 of 305 (3.0%), compared with the control group, 31 of 312 (9.9%) (aRR, 0.32; 95% CI, 0.16-0.65; P 0 .002), had IgE-mediated egg allergy	ITA- at 12 months 13% in the standard introduction group and 10.4% in the early introduction group (p=0.17) and at 36 months 6.2% in the standard introduction group and 5.1% in the early introduction group (p=0.43).	ITA- 45% in the egg group and the 63% of the control group was sensitised to egg (RR:0.72 95%CI, 0.47,1.09) p=0.12 PPA – at 12 months 12.5% in the standard introduction group and 6.1% in the early introduction group (p=0.009) and at 36 months 6.3% in the standard introduction group and 3.3% in the early introduction group (p=0.10)
Results- Oral food challenge	At 12 months Oral food challenge 9% of the egg group and 38% of the placebo group (OR:0.083, 95%CI:0.023,0.297). IgE levels in the ITA among the non-sensitised group placebo vs egg the p=0.31 Among the sensitised group 0.001.	At 12 months Oral food challenge 2.1% from the intervention group and the 0.76% of the control group had a positive challenge and there was no difference between groups	At 12 months - Oral food challenge or described reaction to powder 8/24 vs 13/124 – no difference between groups	At 12 months Oral food challenge 7.7% of the egg group and the 41% of the control group had a positive egg challenge (OR:0.79(95%CI-0.51,1.21) p=0.28 no difference between groups	At 12 months In the standard introduction group 5.4% and 3.7% in the early introduction group (p=0.17).	At 12 months- Oral food challenge 33% had a positive egg challenge
Further analyses available	In the PPA among the non-sensitised group placebo vs egg it is p=0.063 and in the sensitised group p=0.00251% from the control group	Egg challenge test Among the children with eczema hens' egg specific IgE was high at baseline (p,0.001)	Intervention group higher IgG4 an higher IgG4/IgE ratios(p<0.0001) No difference in the IgE levels between the groups	Egg-specific IgG4 levels were substantially higher in the egg group at 12 months (median, 1.22 mgA/L vs control 0.07 mgA/L; P < .0001).	Adjusted per protocol analysis -5.2% in the standard introduction group and 1.4% in the early introduction group (p=0.02).	Lower proportion in the egg group had IgE mediated egg allergy at 12 months in the egg group (RR:0.65(0.38,1.11) p=0.11

Overall conclusion of the trial	Heated egg introduction to high risk children will help prevent development of egg allergy.	No evidence of protection	A protective effect towards egg sensitisation	No evidence of protection	Early introduction of allergenic food is protective against food allergy	A reduction in egg allergy can be achieved by early regular introduction of eggs in infants with eczema

Note: NA: not applicable.

Results from HEAP, although not significant at the 5% level, suggested an increased risk of sensitisation to egg in the intervention group. Similarities in results from STEP and HEAP (no associations found) may be related to the longer duration of the intervention in these two trials.

A major difference between the trials which may explain the different outcomes is the timing of egg introduction to the control groups with respect to the commonly measured outcome time of 12 months. BEAT and STAR controls were encouraged to consume egg from 8 months, STEP controls from 10 months, and HEAP and PETIT controls from 12 months. This difference may have influenced the timing of IgE response to egg introduction in the controls which may in turn have changed the magnitude and direction of association when compared to the intervention group. For example, if children in the HEAP trial had not been exposed to egg prior to egg allergy testing, then they may appear less "sensitised" compared to exposed populations.

In summary, the methodological differences which may have resulted in different findings include: the trial population, the sample size, the start and end date of the intervention, the treatment of the control group with respect to the intervention and how the outcomes were analysed.

The main drawback of RCT's is external validity or how generalizable the trial results are [7]. The best way to overcome questions related to external validity is to recruit a representative sample form the general population. Therefore, a random selection of a sample from the general population is the first step followed by randomisation of the enrolled participants. Based on these two factors it can be decided whether the results are truly generalizable and how the results could be incorporated into policy. Furthermore, there is evidence that the external validity determines where the trial sits truly in the evidence hierarchy [7].

Evidence from RCTs cannot be taken at face value. All evidence, regardless of study type, needs to be critically evaluated with respect to methodology even though RCT's are considered the highest level of evidence. We suggest that the evidence presented by these RCTs is insufficient to confirm that early egg consumption reduces future egg sensitisation and allergy. Larger trials based on the general population accounting for baseline disparities among the trial arms should be our future focus.

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