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

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INTRODUCTION

We refer to the six randomised controlled trials (RCTs) (PETIT; Natsume et al, [1], HEAP; Bellach et al, [2], BEAT; Tan et al and STEP; Palmer et al. [3] and EAT; Perkin et al, [4], STAR; Palmer et al, [5], published within the last five years. These 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: 12610000535976     | 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 ≥ 20.35 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 random allocation 1:1 to early and standard introduction |
|-------------------------|-----------------------------------------------------------------------------------------------------------------|-------------------------------------------------|------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| Intervention            | Type: Boiled whole hen’s egg powder | Type: Pasteurized Raw hen’s egg white powder | Type: Pasteurized 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 |
|                         | Start: 6 months                          | Start: 4 to 6 months                            | Start: 4 months                          | Start: 4-6.5 months                          | Start: 3 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: Breast milk                          | Type: Rice powder |
|                         | 12 months                               | 12 months                                      | 8 months                                 | 10 months                                 | 6 months |
|                         | 12 months: Sensitisation: IgE, IgG1, IgG4, and IgA ≥ 0.35Ku as egg allergy | 12 months: Sensitisation IgE levels ≥ 0.35Ku as egg allergy | 12 months: Sensitisation EW-SPT responses of 3mm or greater as egg allergy | 12 months: Sensitisation IgE levels ≥ 0.35Ku as egg allergy | 12 months and 36 months Sensitisation SPT ≥5mm or greater |
|                         | Food allergy                            | Food allergy                                    | Food allergy                             | Food allergy                               | Food allergy |
|                         | Oral food challenge (Double blind placebo controlled) | Oral food challenge (Double blind placebo controlled) | Oral food challenge (Double blind placebo controlled) | Oral food challenge (Double blind placebo controlled) | Oral food challenge (Double blind placebo controlled) |
| Age at outcome assessment And outcome types | 8 and 12 months Sensitisation IgE and IgG ≥ 0.35Ku for tested allergens | Food allergy                                  | Food allergy                             | Food allergy                               | Food allergy |
|                         | Oral food challenge (open labelled)      | Oral food challenge (open labelled)             | Oral food challenge (open labelled)     | Oral food challenge (open labelled)        | 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 | -                                             | 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 |
None have stopped due to the adverse reactions to trial powder

IFTA 8% of the intervention group and 38% of the control group was sensitised (p=0.0001)
PAA 4% of the intervention group and 38% of the control group was sensitised (p=0.0001)

At 12 months the control group had a positive egg challenge (OR:0.79 (95%CI-0.51,1.21)
PAA- 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

Adverse reactions

Participants not completing

Non-participants:

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, 1 had repeated illnesses, 1 moved overseas, and 1 did not want to have the raw egg challenge

4 children developed severe adverse reactions due to the study powder

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%CI0.023,0.297). 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 (OR0.79 (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 ratio(p=0.0001)

No difference in the IgE levels between the groups

Egg-specific IgE levels were substantially higher in the egg group at 12 months [median, 1.22 mgA/L vs control 0.07 mgA/L; P < 0.001].

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

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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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