

Early Introduction of Egg and the Development of Egg Allergy in Children: A Systematic Review and Meta-Analysis

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Keywords

Food allergy · Food hypersensitivity · Atopic dermatitis · Primary prevention · Atopy

Abstract

Background: The timing of the introduction of egg to an infant's diet is of current interest, as new evidence raises questions regarding the benefit of delaying egg introduction. The objective of this study was to systematically review the existing literature regarding the effect of the early introduction of egg on the development of egg allergy. **Methods:** Literature searches were conducted in MEDLINE, EMBASE, and CENTRAL, and trial protocols were searched in Meta Register and OpenGREY. Only randomized controlled trials (RCTs) comparing early (between 3 and 6 months of age) egg introduction to no early introduction were included. The primary outcome was the development of egg allergy. **Results:** Of the 416 articles identified and screened, 6 RCTs met the eligibility criteria for data extraction. Allergic outcomes were evaluated in a total of 3,032 participants. A low to moderate level of evidence showed a benefit of the early introduction of egg (relative risk, RR 0.60, 95% CI 0.44–0.82, $p = 0.002$, mild heterogeneity, $I^2 = 23\%$). The absolute risk reduction for a population with an incidence of egg allergy of 9.3% was 37

fewer cases (95% CI 17–52) per 1,000 people. Consumption of <4,000 mg/week of egg protein had a greater preventive effect than a higher dose. **Conclusion:** This systematic review and meta-analysis showed an association between the early introduction of egg and a lower risk of egg allergy. Furthermore, the nature and dose of egg protein exposure may play a role. These findings should be addressed in the context of primary studies.

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Introduction

Food allergy is an atopic disease that results from an immediate hypersensitivity reaction upon reexposure to a food allergen. The prevalence of food allergy varies from 1 to 8% worldwide and is dependent on a genetic predisposition as well as geographical and environmental factors [1]. The timing of the exposure of an infant to a food allergen may play a role in the development of food allergy later in life. Historically, the recommendation has been to delay the introduction of the most common food allergens to the diet of an infant, including egg, cow's

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milk, peanut, tree nuts, wheat, soy, fish, shellfish, and sesame [2]. This practice was especially emphasized in atopic infants who are at high risk for developing food allergies. However, this was revised in the recent guidelines, which recommend breastfeeding exclusively for the first 4–6 months of an infant's life and recommend against the avoidance of any type of food [3, 4]. This change was a result of multiple observational studies that showed that the earlier an allergenic food is introduced to the diet, the less likely the child is to develop a food allergy [5–8]. One study by Du Toit et al. [5] showed that the incidence of peanut allergy is significantly higher in populations that avoid peanuts (1.85%) compared to populations that consume peanuts (0.17%) early in life between the ages of 8 and 14 months. Another study investigating the early introduction of cow's milk protein (CMP) found that the mean age of CMP introduction was significantly lower ($p < 0.001$) in healthy infants (61.6 ± 92.5 days) than those with IgE-mediated CMP allergy (116.1 ± 64.9 days), implying that early exposure to CMP as a supplement to breastfeeding may prevent CMP allergy [6]. Koplin et al. [7] found similar results; introducing egg into the diet between 10 and 12 months was associated with a lower risk of developing egg allergy (odds ratio, OR 1.6, 95% CI 1.0–2.6) than egg introduction after 12 months (OR 3.4, 95% CI 1.8–6.5). This finding was supported by randomized controlled trials (RCTs) of peanut exposure [9, 10] and a single meta-analysis [11]. By intention to treat analysis, Perkin et al. [10] found no difference in the decrease in egg allergy in UK infants fed with egg from 3 months of age compared to only breast-fed infants (3.7 vs. 5.4%, respectively), representing a 31% lower relative risk (RR). However, a significant decrease was observed when per protocol analysis was applied (1.4 vs. 5.5%, $p = 0.009$). In an Australian study of high-risk infants with moderate to severe atopic dermatitis, the subjects were randomized to receive early egg introduction or late egg introduction. At 12 months of age, a lower proportion of infants in the early egg introduction group (33%) compared to the late egg introduction group (51%) were diagnosed with egg allergy; however, this difference was not statistically significant (RR 0.65, 95% CI 0.38–1.11, $p = 0.11$) [12]. The same research group published a larger study of healthy high-risk infants randomized to receive either raw egg or rice powder from 4 to 6 months of age and found a non-significant difference between the groups in IgE-mediated egg allergy: egg 7.0% versus control 10.3% (adjusted RR 0.75, 95% CI 0.48–1.17, $p = 0.20$) [13]. In the third Australian RCT, healthy high-risk infants were randomized to receive either raw egg or rice powder from 4

months of age. Sensitization to egg at 12 months was 20 and 11% in infants randomized to placebo and egg, respectively (OR 0.46, 95% CI 0.22–0.95, $p = 0.03$) [14]. Belach et al. [15] also found no evidence that the consumption of raw egg starting at 4–6 months of age prevents egg allergy, as 2.1% in the treated group versus 0.6% in the placebo group developed egg allergy (RR 3.30, 95% CI 0.35–31.32, $p = 0.35$). In contrast, another recent study by Natsume et al. [16] found that the introduction of heated egg in a stepwise dose was safe and effective in preventing egg allergy (RR 0.22, 95% CI 0.09–0.54, $p = 0.0001$). The evidence from the above observational studies and RCTs is not conclusive and has not led to a change in the guidelines to recommend the early introduction of egg to an infant's diet as a primary prevention of egg allergy. Therefore, to help advance the knowledge of researchers, clinicians, and policy makers, a systematic review and meta-analysis was conducted to evaluate whether the early introduction of egg to the diet of an infant influences the development of egg allergy, and whether the dosage of the allergen can influence the results.

Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [17]. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO 2017:CRD42017051345).

Study Type

Only RCTs evaluating the early (as early as 3 months of age) introduction of egg to the diet of an infant and the development of egg allergy later in life were included. The control groups consisted of infants who were exclusively breastfed until the age of 6 months or infants who received placebo. The primary outcome of interest was the diagnosis of egg allergy by an oral food challenge. The secondary outcome was food sensitization defined by the presence of allergen-specific IgE, confirmed by a positive allergy skin prick test or a positive ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden). Other secondary outcomes were diagnoses of asthma, allergic rhinitis, eczema, and anaphylaxis.

Information Sources and Search Strategy

Literature searches were conducted in MEDLINE (OVID interface, publications after 1948), EMBASE (OVID interface, publications after 1980), and the Cochrane Central Register of Controlled Trials (Wiley interface, current issue). Supplemental searches were conducted for trial protocols (<http://www.controlled-trials.com/mrct/> and the OpenGREY Repository) and abstracts from major conferences. The literature search was limited to studies on human subjects, and no language restrictions were applied. The search was initially conducted up to November 2016 and was subsequently updated in March 2017. The terms used for

the literature searches are included in online supplementary Appendix 1 (see www.karger.com/doi/10.1159/000492131 for all online suppl. material).

Study Selection and Data Extraction

The authors B.A.-S. and S.T.S. independently screened the titles and abstracts (online suppl. Appendix 2) and obtained the full texts for all articles that appeared to meet the inclusion criteria. They screened the full text of each article (online suppl. Appendix 3) to determine eligibility based on the inclusion criteria. Disagreements were resolved through discussion to reach a consensus. Using a standardized data extraction form (online suppl. Appendix 4), both authors extracted data from each eligible study independently.

Risk of Bias in Individual Studies

As only randomized controlled studies were included in this systematic review, the risk of bias was assessed using the Cochrane Collaboration Tool. The judgment of risk for each eligible study based on the independently extracted information by the authors was rated as high, low, or unclear. Disagreements were resolved by discussion. Computed graphics were created to represent potential bias within and across studies using RevMan 5.1 (<http://tech.cochrane.org/revman/download>).

Data Synthesis

As the clinical, methodological, and statistical heterogeneity among the eligible studies was low, a quantitative synthesis of the results was conducted. The meta-analysis was conducted using a random-effects model. Dichotomous data including the occurrence of egg allergy, egg sensitization, and eczema were determined by using RR with a 95% CI. Individual outcomes were stratified using the Mantel-Haenszel (M-H) method. The RevMan 5.1 statistical software was used.

Quality of Evidence

The quality of evidence in the domains of risk of bias, consistency, directness, and precision were evaluated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

Results

Study Selection

Our search strategy identified 416 articles, 56 of which were excluded because of duplicates; therefore, the titles and abstracts of 360 articles were screened. A total of 24 out of the 360 articles were found to be eligible for the full-text review. Eighteen studies were excluded, most commonly because the studies were not RCTs. Ultimately, 6 studies were included in the systematic review (see online suppl. Appendix 5 for the PRISMA flow diagram).

Study Characteristics

The 6 interventional RCTs included in the review were all published as full texts and included a total of 3,032 par-

ticipants (Table 1). The proportion of infants with atopic dermatitis was reported in 5 studies (Bellach et al. [15], Palmer et al. [12], Perkin et al. [10], Tan et al. [14], Natsume et al. [16]) and ranged from 9 to 100%, while 1 study that had no infants with atopic dermatitis (Palmer et al. [13]). A family history of atopic diseases was reported in 62–100% of the participants. The intervention group received pasteurized raw whole egg or egg white powder in 4 studies [12–15] and heated eggs in 2 studies [10, 16]. There were variable doses of egg protein exposure, with a median dose of 2,800 mg/week (range 350–7,500; Table 1). The placebo group received rice powder in 4 studies [12–15], squash powder in 1 study [16], and exclusive breastfeeding in the remaining study [10]. All studies determined the primary outcome of the development of egg allergy using an oral food challenge, except in the study by Tan et al. [14] in which the primary outcome was egg sensitization determined by a positive allergy skin test (Table 1).

Risk of Bias within Studies

The assessment of risk of bias is summarized in Figure 1. The risks of bias were as follows: unclear regarding allocation concealment (selection bias) in 2 studies (Palmer et al. [12, 13]), unclear regarding the blinding of participants and their parents (performance bias) in 1 study (Perkin et al. [10]), and unclear and high regarding the blinding of outcome assessments (detection bias) in 2 studies each (Palmer et al. [13] and Natsume et al. [16], and Bellach et al. [15] and Perkin et al. [10]).

Egg Allergy

All 6 interventional RCTs reported the development of egg allergy in their participants. One study, by Natsume et al. [16], showed that the early introduction of egg to the diet of an infant between the ages of 4 and 6 months compared to no early introduction may prevent the development of an egg allergy. The study by Bellach et al. [15] did not show any benefits of early egg protein introduction, and rather showed a trend toward increased egg allergy. Although the other 4 studies showed a trend towards protection, it was not significant on intention to treat analysis. The combined effect of early egg introduction from all 6 RCTs (2,663 participants) showed a benefit for the intervention group compared to the control group (RR 0.60, 95% CI 0.44–0.82, $p = 0.002$, mild heterogeneity, $I^2 = 23\%$; Fig. 2a) [10, 12–16]. The absolute risk reduction for a population with an incidence of egg allergy of 9.3% was 37 fewer cases (95% CI 17–52 cases) per 1,000 people (Table 2).

Table 1. Characteristics of the RCTs included in the systematic review

Author [Ref]/ year of publication	Country	Randomized participants, <i>n</i> inter- control vention	Participant inclusion criteria	First-degree relative with history of allergic disease, <i>n</i> (%)	Participants with eczema, <i>n</i> (%)	Intervention	Total dose, mg/week	Compa- rison	Outcome reported	Age at outcome assess- ment, years
Bellach [15], 2017	Germany	184 199	Gestational age of 34 weeks or greater and birth weight of 2.5 kg or greater	259 (68)	34 (9)	Pasteurized raw egg white powder 2.5 g, 3 days a week starting at 4–6 months until 12 months	7,500	Rice powder	Egg allergy by oral food challenge and egg-specific IgE ≥ 0.35 kU/L	1
Natsume [16], 2017	Japan	60 61	Infants aged 4–5 months who were diagnosed with atopic dermatitis	75 (62)	121 (100)	Heated whole egg powder, 50 mg/day, from age 6–9 months; 250 mg/day from age 9–12 months	350 (6–9 months); 1,750 (9–12 months)	Squash powder	Egg allergy by oral food challenge	1
Palmer [12], 2013	Australia	49 37	Singleton term infants with moderate to severe eczema (SCORAD20 score of >15)	79 (92)	86 (100)	Pasteurized raw whole egg powder, 0.9 g once a day starting at 4–8 months	6,300	Rice powder	Egg allergy by oral food challenge and allergy skin test ≥ 3 mm of negative control	1
Palmer [13], 2017	Australia	407 413	Singleton infants with atopic mothers, age <6.5 months who were born at more than 35 weeks' gestation with a birth weight of more than 2,000 g	820 (100)	0	Pasteurized raw whole egg powder, 0.4 g daily starting at 4–6.5 months	2,800	Rice powder	Egg allergy by oral food challenge, allergy skin test ≥ 3 mm of negative control, and egg-specific IgE ≥ 0.35 kU/L	1
Perkin [10], 2016	UK	652 651	Singleton infants who were 3 months of age and exclusively breastfed	814 (62)	317 (24)	Six allergenic foods (milk, eggs, sesame, peanut, fish, and wheat), 2 g of protein twice a week starting from 3 months	4,000	Exclusive breast- feeding	Food allergy by oral food challenge and egg-specific IgE ≥ 0.35 kU/L	3
Tan [14], 2017	Australia	165 154	Healthy term infants with at least 1 first- degree relative with a history of any atopic disease	319 (100)	82 (26)	Pasteurized raw egg powder starting from 4 months	2,450	Rice powder	Egg allergy by allergy skin test ≥ 3 mm of negative control	1

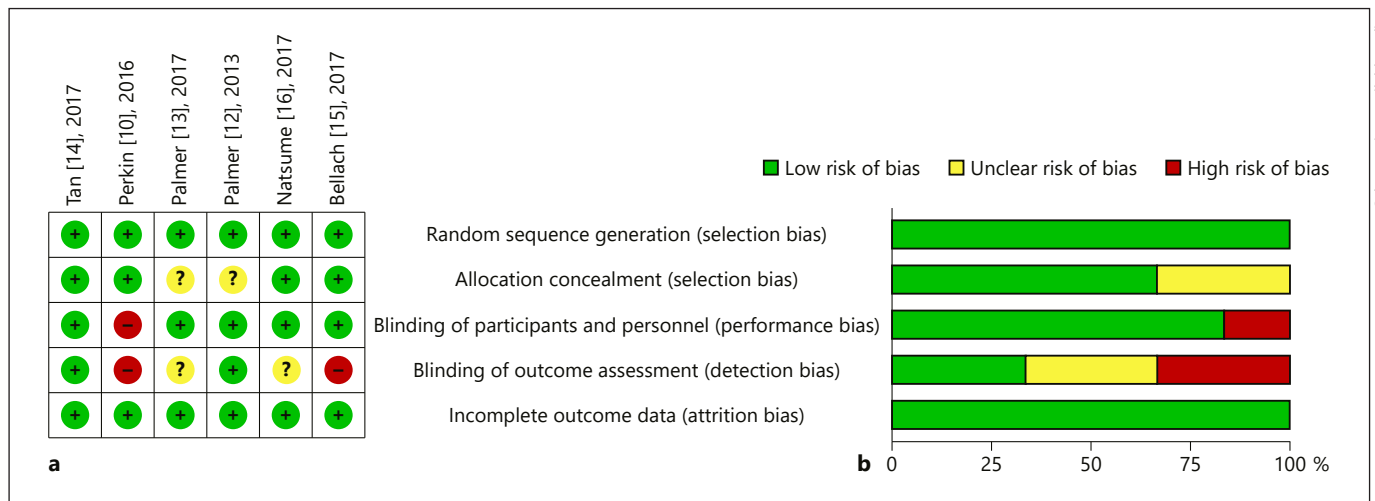


Fig. 1. Risk of bias. **a** Level of risk of bias for each study. **b** Level of bias in percentages across all studies.

Allergy Sensitization

Five RCTs reported the development of egg sensitization by either a positive skin test or a positive ImmunoCAP test in infants with early introduction versus no early introduction of egg. All 5 studies showed a decrease in sensitization in the early intervention group compared to the no early intervention group, except for the study by Bellach et al. [15], which showed the opposite association. However, the overall analysis was in favor of the early introduction of egg, showing less sensitization in children with early introduction compared to no early introduction of egg (RR 0.74, 95% CI 0.58–0.95, $p = 0.02$, unimportant heterogeneity, $I^2 = 17\%$; Fig. 2b).

Eczema

Two RCTs (Tan et al. [14] and Palmer et al. [13]) evaluated the association between eczema and the early versus no early introduction of egg. Neither study (a total of 1,001 participants) showed any significant difference in the development of eczema by the timing of egg introduction (RR 0.90, 95% CI 0.70–1.16, $p = 0.42$, no heterogeneity, $I^2 = 0\%$).

Other Secondary Outcomes

Only 1 RCT (Palmer et al. [13]) investigated asthma (wheezing) and anaphylaxis as an outcome of interest. In this study, there was no significant difference in the development of asthma (wheeze) between the intervention and control groups (RR 1.12, 95% CI 0.87–1.45, $p = 0.39$). Anaphylaxis occurred in 2 participants in the interven-

tion group and 1 participant in the control group, which was not statically significant ($p = 0.62$) [16]. None of the RCTs investigated allergic rhinitis as an outcome of interest.

Subgroup Analysis for High versus Low Dose of Egg Protein

There was heterogeneity among the 6 RCTs. One source of heterogeneity was the dose of egg protein introduced to the infants. A subgroup analysis was applied to assess whether the different doses of egg proteins used in the trials had any effect on egg allergy prevention. As the antigenicity of egg proteins can be reduced by heating, to decrease heterogeneity, we excluded the studies using heated eggs (Natsume et al. [16] and Perkin et al. [10]). A weekly dose of 4,000 mg of egg protein consumption was used as the cutoff to determine a low versus high dose, based on the EAT study by Perkin et al. [10]. This subgroup analysis showed that an early introduction of egg using a lower dose of egg protein (<4,000 mg/week) may be associated with a more successful prevention of egg allergy (RR 0.65, 95% CI 0.43–0.99, $p = 0.04$, vs. RR 0.69, 95% CI 0.41–1.16, $p = 0.16$; Fig. 3a, b).

Discussion

Although there have been recent advances in oral immunotherapy for the management of food allergy [18], there continues to be a lack of curative and sustainable

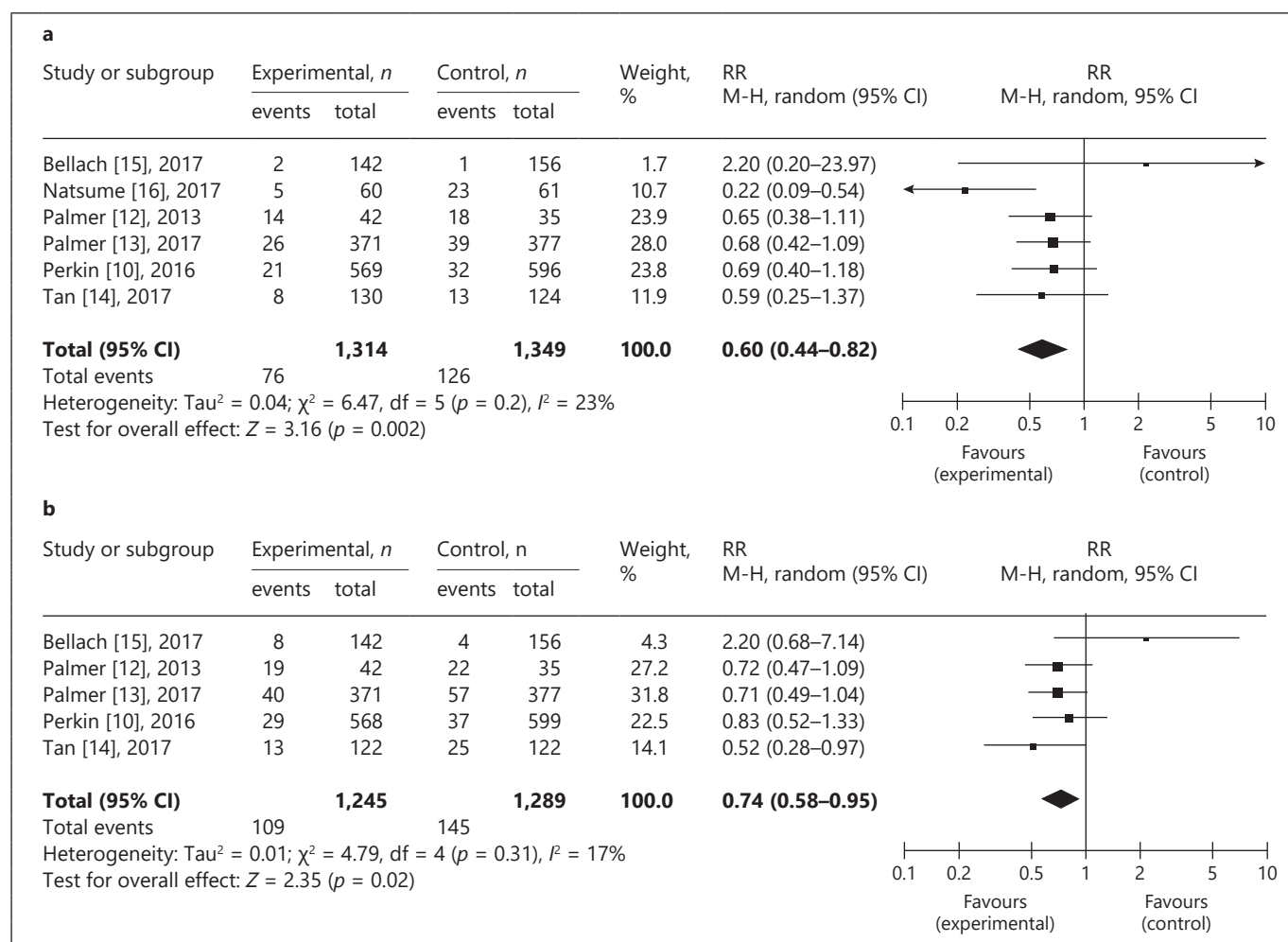


Fig. 2. a A forest plot of the effect of an early introduction (experimental) versus no early introduction (control) of egg protein and the risk of development of egg allergy. **b** A forest plot of the effect of an early introduction (experimental) versus no early introduction (control) of egg to the diet of an infant and the risk of egg sensitization.

treatments. Patients are advised to avoid the offending food and to promptly treat any allergic symptoms or anaphylaxis upon accidental exposure. In the last 10 years, research on primary prevention of food allergy has been an area of great interest. In this systematic review, 6 interventional RCTs evaluating the effectiveness of primary prevention by the early introduction of egg were analyzed. The pooled effect showed evidence that early introduction of egg to an infant's diet may prevent the development of egg allergy compared to no early introduction. However, the quality of evidence was low to moderate due to the significant variation among the study populations and the varying amount and nature of egg protein introduced in each trial (Table 2). One study used sensi-

tization as a surrogate marker for the primary outcome [14], another study used multiple allergenic foods [10], and 2 studies used heated egg [10, 16] while another 4 studies used raw egg [12–15]. Out of the 6 RCTs, 1 was terminated early due to adverse effects [15]. That study showed a nonsignificant increase of sensitization and egg allergy in the group allocated to early egg introduction. However, 5.7% were already sensitized (egg-specific IgE >0.35 kUA/L) prior to randomization, of whom 65% had physician-diagnosed eczema, already indicating that they have a higher risk compared to the 8.5% of nonsensitized children. Most of these children were allergic according to egg challenges and could have reacted in the community in case of nonguided early intervention. Almost half

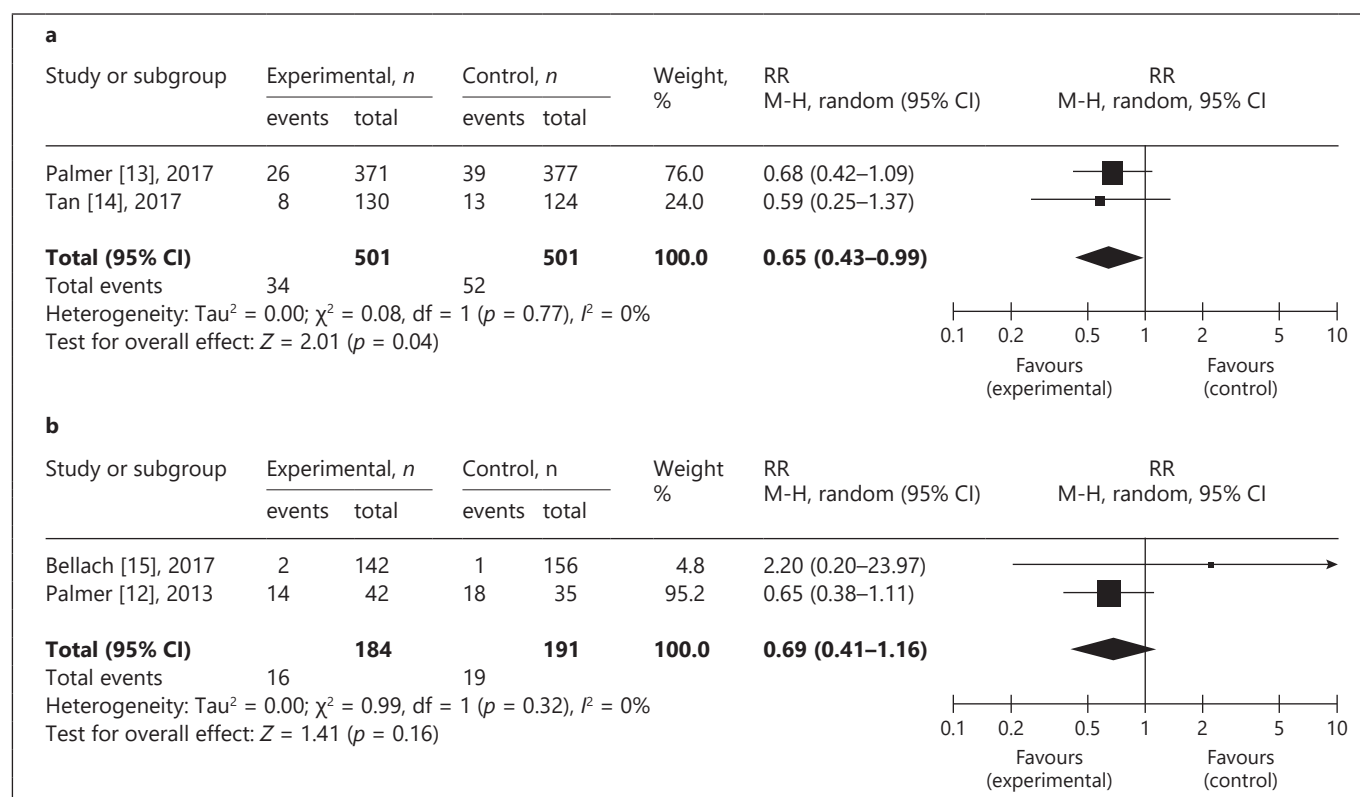


Fig. 3. A forest plot of the effect of early introduction (experimental) versus no early introduction (control) of egg to the diet of an infant. **a** RCTs that used a low dose of egg protein (less than 4,000 mg/week). **b** RCTs that used a high dose of egg protein (greater than or equal to 4,000 mg/week).

of the children reacting to the egg reacted to the first dose, even though they were not sensitized [15]. In the study by Tan et al. [14], 8.5% of the recruited infants reacted to egg within 1 week of introduction despite a negative egg white skin prick test response prior to intervention. In a group of children with moderate to severe eczema, Palmer et al. [12] showed that 36% already had egg IgE >0.35 kUA/L prior to randomization at 4 months of age. In 2017, the same research group published a bigger study in which 5.0% of normal infants of an allergic first-degree relative were sensitized to egg (egg IgE >0.35 kUA/L) before egg was introduced in solid foods [13]. Excluding sensitized infants from randomization may have changed the results of these studies, but the key point is that a significant number of children are already sensitized to eggs at 4 months of age, which suggests a need for caution when infants are fed with eggs for the first time. In 2017, Natsume et al. [16] introduced a much smaller amount of egg (350 mg heated whole egg/week) than the other studies at 6–9 months, which was raised to 1,750 mg/week from 9

to 12 months of age. The study demonstrated a significant protection against egg allergy by early introduction compared to placebo, which led to the termination of the study based on interim analysis. These protective results were supported by IgE, IgG1, IgG4, and IgA analysis, indicating tolerance induction either by primary prevention or hyposensitization.

Despite variation among the studies, the overall findings of this meta-analysis are in support of the recent changes to the guidelines by multiple scientific societies, which recommend against withholding allergenic foods from infants after the age of 4–6 months [5, 19, 20]. However, the data are not strong enough and further studies are needed on the early introduction of egg to the infant diet in order to be considered for adoption into the regulatory guidelines as a means of primary prevention of egg allergy. In contrast, a recent addendum to the guidelines was created for the early introduction of peanut into infant diets to prevent peanut allergy [21]. The induction of oral tolerance to food allergens and its potential immu-

Table 2. Key findings for early versus late introduction of allergenic food using the GRADE approach

Quality assessment				Participants, <i>n</i> (%)		Effect		Quality	Importance	
studies	study design	risk of bias	inconsistency	indirectness	imprecision	early intro- duction of allergenic food	no early introduction	RR (95% CI)	absolute	
Egg allergy (follow up: median 12 months)										
6	Randomized trials	Serious ^a	Not serious; low heterogeneity, <i>I</i> ² 23% (<i>p</i> = 0.26)	Not serious; 1 study used a surrogate marker for the primary outcome, 1 study used multiple allergic foods	Not serious; the 95% CI for the pooled RR is 0.44–0.82	76/1,314 (5.8)	126/1,349 (9.3)	0.60 (0.44–0.82)	37 fewer per 1,000	⊕⊕⊕○ MODERATE CRITICAL
Eczema (follow up: median 12 months)										
2	Randomized trials	Serious ^{a,b,c}	Not serious, low heterogeneity, <i>I</i> ² 0% (<i>p</i> = 0.99)	Not serious	Serious ^d ; the 95% CI for the pooled RR is wide	85/500 (17.0)	93/501 (18.6)	0.9 (0.7–1.16)	19 fewer per 1,000	⊕⊕○ LOW IMPORTANT
Allergy sensitization (follow up: median 12 months)										
5	Randomized trials	Serious ^a	Not serious, low heterogeneity, <i>I</i> ² 17% (<i>p</i> = 0.31)	Not serious; allergy sensitization is a surrogate marker for food allergy	Not serious; the 95% CI for the pooled RR is 0.58–0.95	109/1,245 (8.8)	145/1,289 (11.2)	0.74 (0.58–0.95)	29 fewer per 1,000	⊕⊕⊕○ MODERATE IMPORTANT

Question: Early introduction of allergenic food compared to no early introduction for the development of food allergy in children. CI, Confidence interval; RR, risk ratio. ^a Allocation sequence concealment was unclear in 2 studies and 1 study was not blinded. ^b One study was not blinded. ^c Allocation sequence concealment was unclear in 1 study. ^d Pooled results have no effect or harm.

nological mechanisms have been shown in animal models [22] but are not yet well established in humans. Trials on oral immunotherapy for food allergy have shown that oral tolerance can be achieved; however, it is not definitive and may not be sustained [23]. Allergy sensitization to egg was investigated in some of the studies in the current systematic review and showed that early introduction of egg was associated with a decrease in the rate of egg sensitization. The quality of evidence was rated as moderate, as allergy sensitization is a surrogate marker for food allergy and does not directly indicate the presence of a food allergy (Table 3). This is consistent with recent results from a large prospective Canadian birth cohort study, which found that egg avoidance in the first year of life was significantly associated with increased odds of egg sensitization [24]. In the current review, the secondary outcome of the development of eczema did not differ significantly between the groups; however, it was evaluated in only 2 of the interventional RCTs (Table 2).

The study by Bellach et al. [15], showing a trend of increased allergic sensitization in children who had early egg introduction, used by far the highest dose of raw egg white protein (7,500 mg/week). The study by Natsume et al. [16] used a much lower dose than any of the other studies (only 350 mg/week of heated whole egg protein [233 mg/week of egg white protein] to high-risk infants from 6 to 9 months, and 1,750 mg/week [1,166 mg/week egg white protein] to subjects 9–12 months of age) with a significant protection against egg allergy according to the intention to treat analysis. The study by Natsume et al. [16] was the only one demonstrating unequivocal egg allergy protection by early feeding. The low dose may have worked as an immunotherapy rather than a primary protection, albeit with the desired results. The exact timing of the introduction and amount of protein may play a role in the tolerance induction by early feeding. In an additional subgroup analysis, the weekly dose of egg protein was divided into low versus high dose, using 4,000 mg as the threshold. A low dose of egg protein (<4,000 mg/week) was associated with a more successful primary prevention of egg allergy compared to a high dose (>4,000 mg/week). This low dose is much higher than the threshold of 1.5 mg shown to cause an allergic reaction in children [25]. The difference in effect between a low versus high egg protein dose is likely to have important implications for clinical practice and future research. Finally, among 1,349 control participants in the 6 studies, the overall prevalence of egg allergy was high at 9.3%. This may be explained by the fact that 4 out of the 6 studies included high-risk infants, 2 with a first-degree family

history of allergic disease and 2 studies of infants with atopic dermatitis. However, prevalence of this magnitude was shown in a study by Osborne et al. [26] in Australia, reporting a prevalence of egg allergy at 8.9%.

Limitations

There was a limited number of interventional RCTs (6 studies) that evaluated the association of the early introduction of egg and the development of egg allergy. These studies included populations with different risks and used variable doses of raw or heated egg protein. A few studies also presented methodological concerns, such as allocation sequence concealment and blinding. Publication bias was not addressed because of the small number of studies.

Conclusion

This systematic review and meta-analysis showed that there is only a moderate quality of evidence for an association between the early introduction of egg to the diet of an infant and a lower risk of developing an egg allergy. However, it should be noted that the studies favored atopic individuals as 4 out of 6 studies recruited infants at high risk, of whom a significant number were sensitized at an early stage. Also, caution is needed because of the considerable clinical heterogeneity between the studies and only 1 study [16] out of the 6 showed unequivocal benefit from early feeding, which may have been due to hyposensitization with a low dosage of egg white protein rather than primary prevention. Further studies are still required in a larger population. The dose and nature of egg protein may be a determining factor for successful primary prevention of egg allergy. These findings should be addressed in the context of primary studies.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Supplementary materials

Appendix 1

Construct search strategy example:

MEDLINE Search Strategy

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE (R) Daily and
Ovid MEDLINE (R) <1948 to Present>

1. Children.ti.
2. Children.ab.
3. Infants.ti.
4. Infants.ab.
5. Breast fed children.ti.
6. Breast fed children.ab.
7. Atopic children.ti.
8. Atopic children.ab.
9. High risk atopic infants.ti.
10. High risk atopic infants.ab.
11. Severe eczema infants.ti.
12. severe eczema infants.ab.
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. Food allergy.ti.
15. Food allergy.ab.
16. allergy.ti.
17. allergy.ab.
18. Allergenic food.ti.
19. Allergenic food.ab.
20. Food Hypersensitivity.ti.
21. Food Hypersensitivity.ab.
22. Food tolerance.ti.
23. Food tolerance.ab.
24. Food intolerance.ti.
25. Food intolerance.ab.
26. Primary prevention of food allergy.ti.
27. Primary prevention of food allergy.ab.
28. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. 13 and 28
30. Randomized controlled trial.ti.
31. Randomized controlled trial.ab.
32. Controlled clinical trial.ti.
33. Controlled clinical trial.ab.
34. Double blind method.ti.

- 35. Double blind method.ab.
- 36. Single blind method.ti.
- 37. Single blind method.ab.
- 38. Clinical trial.ti.
- 39. Clinical trial.ab.
- 40. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
- 41. 29 and 40

Appendix 2

Title & Abstract Screening Form

Population

1. Is the article about humans?
 - *If no, EXCLUDE*
 - *If yes or unclear, go to the next question*
 -
2. Is the article about atopic high risk infants or normal risk infants or breast fed infants assist for food allergy?
 - *If no, EXCLUDE*
 - *If yes or unclear, go to the next question*

Intervention and comparison

3. Does the article compare early introduction of allergenic food to exclusive breast feeding till 4 to 6 month of age?

Note: Allergenic foods are; formula milk, egg, peanut, nuts, wheat, soy, sesame, fish and shellfish.

 - *If no, EXCLUDE*
 - *If yes or unclear, go to the next question*

Outcomes

4. Does the article report any of the following outcomes: food allergy, allergy sensitization, asthma, allergic rhinitis, eczema, and/or anaphylaxis?
 - *If no, EXCLUDE*
 - *If yes or unclear, go to the next question*

Study design

5. Is the article a randomized controlled trial?
 - *If no, EXCLUDE*
 - *If yes or unclear, INCLUDE*

Appendix 3

Full text screening form

Early introduction of allergenic foods and the development of food allergy in children							
Article		Limits		Population	Intervention and comparison	Outcome	Decision (include, exclude or uncertain)
ID	Author/ date	Study in human	RCT	On atopic high risk infants or normal risk infants or breast fed infants	Does the article compare early introduction of allergenic food to exclusive breastfeeding till 6 month of age	Does the article report any of the following outcomes: food allergy, allergy sensitization, asthma, allergic rhinitis, eczema, and/or anaphylaxis	

Appendix 4

Data extraction form

A. Source:

1	Reviewer:	BKA STS				
2	Ref ID:	— — — —				
3	Journal name:					
4	Frist author last name:					
5	Year of publication:	<table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>				
6	Language of Publication:	English Non- English ,specify: -----				
7	Country where study took place:	USA Australia UK Japan Other				
8	Number of centers	<table border="1"><tr><td></td><td></td></tr></table>				

9	Funding:	Public	Private	Both	Unclear
10	Are eligibility criteria reported?	Explicit reported	Not explicit	Not reported	
11	Inclusion criteria				
12	Exclusion criteria				

B. Methods

13	Study design	parallel group	cross over	factorial	other
14	Study follow up duration		Weeks	Months	years
15	Number of patients screened		Not Reported		
16	Number of patients eligible		Not Reported		
17	Number of patients randomized		Not Reported		

18	Sequence generation (Randomization) Risk of bias: High Low Unclear	Random number table Computer random-number generator Coin tossing Rolling die Picking allocation from a hat/box Minimization/dynamic allocation Other methods: _____ Methods not described
19	Allocation sequence concealment Risk of bias: High Low Unclear	Central randomization Numbered, opaque, sealed envelopes Envelopes, with at least one of the following not specified: opaque, sealed, and numbered Clearly not concealed Unclear if rigorous concealment method was used
20	Blinding Risk of bias: High Low Unclear	Yes No unclear
21	Who was blinded	
	Patients	Clearly stated that patient is blind Not reported Stated that patients not blinded
	Health care provider	Clearly stated that health care provider is blind

		Not reported Stated that health care provider not blinded
	Data collectors	Clearly stated that data collector is blind Not reported Stated that data collectors not blinded
	Assessors of outcomes	Clearly stated that assessors of outcomes is blind Not reported Stated that assessors of outcomes not blinded
	Data analysts	Clearly stated that data analysts is blind Not reported Stated that data analysts not blinded

C. Participants

		Control	Intervention
22	Age of patients: Mean/median (SD, range)		
23	Female		
24	Number randomized		
25	Number of females randomized		
26	Number lost to followed at all		
27	Number followed; not included		
28	Number first-degree relative history of allergic disease		
29	Number of participants with eczema		
30	Number of breast-fed infants		
31	How was loss to F/U dealt with?	Analysis of only the available data (i.e. ignoring the missing data)	

		Imputing the missing data with replacement values ___ last observation carried forward ___ best/worst case scenario ___ imputing the mean ___ using predicted values from a regression analysis Multiple imputation Statistical models Uncertain/not reported	
32	Intention-to-treat analysis or modified intention to treat	Reported	Not reported
33	Per protocol analysis	Reported	Not reported

D. Interventions

	Control group	Intervention group
34	Exclusive breastfeeding Rice powder Placebo avoidance Not specified Other _____	Cow milk Egg Peanut Sesame Fish Wheat All (Check all that apply)
35	Amount	Gram of protein Not Reported
36	Frequency	Day Week Not Reported

37	Duration	Months Not Reported
38	Authors' affiliated with commercial industry?	Yes No Uncertain/not reported
39	Participant compliance assessed?	Yes: ___ High; ___ Moderate; ___ Low No Uncertain
40	Was trial stopped early?	Yes No Uncertain

E. Outcome:

41	Age at Outcome Assessment	years
42	Food allergy (a reproducible hypersensitivity reaction to a food) (Check all that apply)	Oral food challenge Specific IgE to egg ≥ 0.35 kU/L Allergy skin test ≥ 3 mm of negative control
43	Allergic sensitization (the presence of specific IgE to an allergen) (Check all that apply)	Specific IgE to egg ≥ 0.35 kU/L Allergy skin test ≥ 3 mm of negative control
44	Secondary outcome	Eczema

	(Check all that apply)	Asthma Allergic rhinitis Anaphylaxis
--	------------------------	---

Results

Food allergy to egg		Control	Intervention group
45	Number of randomized		
46	Number of participants with the outcome of interest (%)		
47	Relative risk		
48	95 % confidence interval		
49	Absolut risk reduction		
50	Number need to treat		

Allergic sensitization to egg		Control	Intervention group
51	Number of randomized		
52	Number of participants with the		

	outcome of interest (%)		
53	Relative risk		
54	95 % confidence interval		
55	Absolut risk reduction		
56	Number need to treat		

Eczema		Control	Intervention group
57	Number of randomized		
58	Number of participants with the outcome of interest (%)		
59	Relative risk		
60	95 % confidence interval		
61	Absolut risk reduction		
62	Number need to treat		

Allergic rhinitis		Control	Intervention group
63	Number of randomized		
64	Number of participants with the		

	outcome of interest (%)		
65	Relative risk		
66	95 % confidence interval		
67	Absolut risk reduction		
68	Number need to treat		

Anaphylaxis		Control	Intervention group
75	Number of randomized		
76	Number of participants with the outcome of interest (%)		
77	Relative risk		
78	95 % confidence interval		
79	Absolut risk reduction		
80	Number need to treat		

NOTES:

Appendix 5

PRISMA Flowchart

