Early regular egg exposure in infants with eczema: A randomized controlled trial

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Background: Observational studies suggest that early regular ingestion of allergenic foods might reduce the risk of food allergy.

Objective: We sought to determine whether early regular oral egg exposure will reduce subsequent IgE-mediated egg allergy in infants with moderate-to-severe eczema.

Methods: In a double-blind, randomized controlled trial infants were allocated to 1 teaspoon of pasteurized raw whole egg powder (n = 49) or rice powder (n = 37) daily from 4 to 8 months of age. Cooked egg was introduced to both groups after an observed feed at 8 months. The primary outcome was IgE-mediated egg allergy at 12 months, as defined based on the results of an observed pasteurized raw egg challenge and skin prick tests.

Results: A high proportion (31% [15/49]) of infants randomized to receive egg had an allergic reaction to the egg powder and did not continue powder ingestion. At 4 months of age, before any known egg ingestion, 36% (24/67) of infants already had egg-specific IgE levels of greater than 0.35 kilounits of antibody (kU_A)/L. At 12 months, a lower (but not significant) proportion of infants in the egg group (33%) were given a diagnosis of IgE-mediated egg allergy compared with the control group (51%; relative risk, 0.65; 95% CI, 0.38-1.11; $P = .11$). Egg-specific IgG_4 levels were significantly ($P < .001$) greater in the egg group at both 8 and 12 months.

Conclusion: Induction of immune tolerance pathways and reduction in egg allergy incidence can be achieved by early regular oral egg exposure in infants with eczema. Caution needs to be taken when these high-risk infants are first exposed to egg because many have sensitization already by 4 months of age. (J Allergy Clin Immunol 2013;132:387-92.)

Key words: *Allergy prevention, complementary feeding, eczema, egg, food allergy, oral tolerance, randomized controlled trial*

Egg allergy is the most common food allergy, now affecting 8.9% of children at 1 year of age in Australia.[1] With increasing rates of food allergy,[2] there is ongoing confusion and controversy over the role of allergenic foods in the development of food allergy. Until recently, it has been common practice to avoid egg and other allergenic foods for the primary prevention of food allergy.[3] Although guidelines have been revised to indicate that there is insufficient evidence to support this,[4-7] it is recognized that the level of evidence in this area is generally weak and largely based on observational studies with methodological limitations and that randomized controlled trials are needed to address this more conclusively.

Animal studies have shown that the development of oral tolerance is driven by regular allergen exposure and that avoidance strategies might increase the risk of adverse immune responses to allergens.[8] The potential role of regular food allergen exposure to induce tolerance in human subjects is also illustrated by studies of specific oral tolerance induction in children with food allergy.[9,10] Animal studies have also shown that early exposure to repeated doses of food proteins (allergens) can induce oral tolerance during a critical early window of development.[8] Although the timing of this potential window is not clear in human subjects, delayed introduction of specific foods (egg, cow's milk, fish, and oats) beyond 6 to 9 months of age has been associated with increased risk of allergic disease in nonintervention cohort studies.[11-17] The Australian HealthNuts study[18] found that delaying introduction of egg until 10 to 12 months of age (adjusted odds ratio, 1.6; 95% CI, 1.0-2.6) or after 12 months of age (adjusted odds ratio, 3.4; 95% CI, 1.8-6.5) was associated with significantly higher risk of egg allergy compared with earlier introduction at 4 to 6 months of age. Thus early oral exposure to egg might be an important strategy to prevent or reduce the risk of egg allergy.

Here we report the first randomized controlled trial to investigate whether early introduction of egg reduces the risk of egg allergy in infants with a history of eczema. Infantile eczema is an important risk factor for food allergies,[19] and we targeted this population based on their greater burden of disease and because they are most likely to benefit from the prevention of food allergy.

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Abbreviations used
IQR: Interquartile range
kU_A/L: Kilounits of antibody per liter
RR: Relative risk
SPT: Skin prick test

METHODS

Study design

Singleton term infants with symptoms of moderate-to-severe eczema (determined by using a standardized SCORAD[20] score of ≥15) were recruited at 4 months of age from 2 Australian centers (Adelaide and Perth). Infants who had commenced solids before 4 months of age or who had any previous known direct ingestion of egg were excluded. Written informed consent was obtained before trial participation. Approval was granted by the local institutional review boards (Human Research Ethics Committees) of each center and the Women's and Children's Health Network, Adelaide and Princess Margaret Hospital, Perth. The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12609000415202).

The study was conducted by using a double-blind, randomized, controlled trial design. Baseline characteristics, including maternal age at birth, maternal race, cesarean delivery, smoking in the household, family (first-degree relative) history of allergic disease, infant sex, infant dietary information on breast-feeding and/or formula feeding, and infant history of and treatments used for eczema, were recorded at randomization at 4 months of age. A blood sample was collected before the first exposure to the study powder. Baseline egg-specific IgE and IgG_4 levels were analyzed at the completion of the trial and did not influence eligibility.

Randomization and blinding

Each participating infant was assigned a unique study number and randomly allocated to one of 2 intervention groups. A computer-generated randomization schedule was produced by an independent consultant. The schedule was stratified by infant sex and feeding mode (breast-fed or formula fed if receiving >200 mL of infant formula per day) at 4 months of age. Independent research assistants coded the identically packaged dietary intervention powders, and these research assistants were not involved in the dietary group allocation or assessment process, thus keeping the outcome assessments blinded.

Dietary intervention

The trial compared the effects of 2 food powders (egg and rice) in infants' diets given daily from randomization at 4 months of age until 8 months of age. For both groups, the study powder was administered orally by mixing the powder with infant rice cereal. The intervention group was allocated to 1 teaspoon (= 0.9 g of egg protein, which is equivalent to one sixth of an egg) per day of pasteurized raw whole egg powder manufactured by Farm Pride Foods (Keysborough, Australia). The control group received 1 teaspoon (= 0.25 g of rice protein) per day of rice flour powder (ingredients: white rice only) manufactured by Ward McKenzie Pty Ltd (Altona, Australia). Rice was chosen as the placebo (control group) because rice cereal is commonly the first food introduced and IgE-mediated allergic reactions to rice are uncommon. A medical assessment, including an observed ingestion of the allocated study powder dose (where appropriate), was conducted to confirm any possible allergic reactions to the study powder before a decision was made to cease the powder use. Any infant whose powder use was ceased was still included in all follow-up assessments. Infants in both groups were advised to follow an egg-free diet (with avoidance of egg protein in any food, including foods cooked with egg as an ingredient) from 4 to 8 months of age by an experienced pediatric dietitian and to introduce other solid foods based on family diet preferences and the infant's individual feeding skill development.

Infant allergic disease outcome assessments

The families were contacted by telephone when the infants were 5, 6, 7, and 10 months of age, and at 8 and 12 months of age, the infants attended a hospital appointment. At each contact time point with the families, questions were asked relating to compliance with the dietary intervention, infant feeding, egg intake, symptoms of allergic disease, doctor's visits for eczema, and use of any treatment medications for eczema. At the 8- and 12-month appointments, the infant's eczema was assessed by using SCORAD scores,[20] and a blood sample was collected to measure whole egg–specific IgE and egg white–specific IgG_4 serum antibody concentrations. See the Methods section in this article's Online Repository at www.jacionline.org for more information.

Throughout this trial, an allergic reaction was defined as at least 3 cases of concurrent noncontact urticaria persisting for at least 5 minutes and/or generalized skin erythema (but not an exacerbation of eczema alone) and/or vomiting (forceful/projectile) and/or anaphylaxis (evidence of circulatory or respiratory involvement). A serious adverse event was defined as any death, admission to the intensive care unit, or anaphylactic reaction. Serious adverse events were reviewed by a serious adverse event committee, and any such events were reported to the human research ethics committees.

At 8 months of age, all participating infants had a medically supervised cooked egg exposure, in which the infant was given 2 teaspoons of mashed hard-boiled whole egg (equivalent to one sixth of an egg) to eat and observed for at least 2 hours afterward. Unless the infant experienced an allergic reaction, the families were advised to commence the inclusion of cooked egg (examples given included hard boiled or fried egg, omelet, quiche, egg in baked goods, egg in meatballs, or egg used for crumbing foods) in the infant's diet from 8 to 12 months of age.

At 12 months of age, all infants had a medically supervised pasteurized raw egg challenge in which the infant was given half of a whole egg (see the Methods section in this article's Online Repository for more details) and observed for at least 2 hours afterward. Unless the infant experienced an allergic reaction, the families were advised to include all forms of egg-containing foods in the infant's diet. Infants were excluded from the challenge process if they had previous anaphylaxis to egg or if an independent medical decision not to proceed with the egg challenge was made due to a previous allergic reaction to egg. On the same day but before the egg challenge, the infants had skin prick tests (SPTs; see the Methods section in this article's Online Repository for details).

The primary outcome was the diagnosis of IgE-mediated egg allergy at 12 months of age, which was defined as an allergic reaction to the pasteurized raw egg challenge and associated evidence of sensitization to egg or when an independent medical decision not to proceed with the egg challenge was made due to a previous allergic reaction to egg and associated evidence of sensitization to egg.

Statistical analysis

A sample size estimate was calculated based on the assumption that the expected prevalence of IgE-mediated egg allergy at 12 months of age in a population of infants with eczema would be 40%,[21] and therefore to detect an absolute reduction of 20% (relative reduction of 50%), from 40% to 20% (with 85% power, $\alpha = .05$), we would have required 103 infants per group. Allowing for 10% loss to follow-up, the aim was to recruit a total of 226 infants into the trial. However, the study recruitment was paused in September 2011 at the request of the Human Research Ethics Committee at Princess Margaret Hospital, Perth, Australia, to examine the rate of allergic reactions to the study powder and cases of anaphylaxis. An independent, unblinded data safety monitoring committee review was undertaken, and the recommendation from this Committee was that the trial should continue. The decision was made by the ethics committee to reopen the trial for recruitment in May 2012; however, by this time, insufficient funds remained to recommence recruitment, and the chief investigators decided the trial should be terminated early without reaching the sample size originally estimated.

Analyses were performed according to the intention-to-treat principle. The proportion of infants with diagnosed IgE-mediated egg allergy at 12 months of age was compared between groups. Secondary comparisons between groups included the proportion of children with cooked egg allergy, eczema severity

(objective SCORAD score), and sensitization to egg. Independent-samples *t* tests, Mann-Whitney *U* tests, Pearson χ^2 tests, and Fisher exact tests were used to test differences between the groups. Statistical significance was assessed at the .05 level. Analyses were performed with SPSS statistical software, version 20 (SPSS, Chicago, Ill).

RESULTS

Enrollment for the trial began on July 15, 2009, and ended on September 7, 2011. Eighty-six infants were randomized into the trial, with 49 randomized to the egg group and 37 randomized to the rice group. There were no significant differences in baseline characteristics between the 2 groups (Table I). Data collection was completed on May 25, 2012. Ninety percent (77/86) of infants attended their final appointment, with 77 (90%) of 86 infants having SPTs and 67 (78%) of 86 infants undertaking an egg challenge. Nine (2 in the rice group) parents withdrew their infant's consent to participate during the study for the following reasons: became too busy to attend hospital appointments (n = 4, 1 in the rice group), did not like the study powder (n = 2, 1 in the rice group), infant had repeated illnesses (n = 1), family moved overseas (n = 1), and parents did not want the raw egg challenge (n = 1).

TABLE I. Baseline characteristics

Characteristic	Egg group (n = 49)	Control group (n = 37)	*P* value
Maternal age at birth (y)*	32.8 (5.5)	32.1 (3.4)	.48
Maternal white race†	36 (73%)	32 (86%)	.14
Cesarean section birth†	17 (35%)	11 (30%)	.63
Maternal history of allergic disease†	37 (76%)	25 (68%)	.42
First-degree relative history of allergic disease†	44 (90%)	35 (95%)	.69
Infant male sex†	31 (63%)	26 (70%)	.50
Age of onset of eczema (mo)*	1.8 (1.1)	1.8 (0.9)	.75
Eczema severity (objective SCORAD score)‡	33.8 (29.2-37.5)	32.7 (25.0-39.5)	.46
Use of prescription steroid cream†	40 (82%)	28 (76%)	.50
Ever breast-fed†	48 (98%)	37 (100%)	1.00
Breast-fed at randomization†	40 (82%)	31 (84%)	.96
Smoking in the household†	8 (16%)	3 (8%)	.34

Values are presented as follows: *means (SDs), †numbers (percentages), or ‡medians (IQRs).

Intervention, compliance, and safety

A high proportion (21% [18/86]) of infants randomized had an allergic reaction to their allocated study powder. The proportion of reactors was higher (31% [15/49]) in those allocated to receive egg. Most of these (10/15) had a reaction on first exposure to the egg powder, including 1 case of anaphylaxis. Three infants in the rice group had allergic reactions (all had generalized skin erythema and vomiting) to the rice powder, and these infants were advised to avoid rice in their diet and followed up for their suspected rice allergy outside the study by an independent allergist. No participating infants had a positive SPT response to rice at 12 months of age. The trial outcomes of the 18 infants who had allergic reactions to their allocated study powder are detailed in Table II.

For the infants without an allergic reaction to the study powder, compliance with powder use was high. In the egg group 31 (94%) of 33 infants ingested the study powder at least 4 days per week on average during the intervention period, as did 31 (97%) of 32 infants in the control group. Compliance with the egg-free diet intervention from 4 to 8 months of age did not differ between the groups: 78% in the egg group compared with 64% in the control group ($P = .15$). Of the 23 infants (10 in the egg group and 13 in the control group) who accidentally ingested an egg-containing food during the intervention period, only 1 infant (in the egg group) did so on more than 1 occasion. During the intervention period, only 1 allergic reaction after ingestion of cake mix containing raw egg (by an infant in the rice group) was reported. The most common egg-containing foods that were accidentally eaten were baked goods (biscuits/cake, n = 12) and ice cream/custard (n = 3). Compliance with the inclusion of cooked egg in the diets of infants who did not react to the cooked egg exposure from 8 to 12 months of age was high, with all of these infants (n = 63) consuming egg as an ingredient in foods, and 59 (94%) of 63 of the infants consuming whole egg in the form of quiche, omelet, hard-boiled egg, or scrambled egg.

Four infants experienced a serious adverse event. In the egg group 1 infant had a hospital intensive care unit admission with food protein–induced enterocolitis syndrome after a rechallenge with the study powder to confirm a previous reaction, and another had anaphylaxis on first exposure to the study powder. In the rice group 2 infants had anaphylaxis, 1 after the cooked egg exposure and 1 after the pasteurized raw egg challenge.

Clinical outcomes

For the primary outcome, a lower proportion of infants in the egg group (33% [14/42]) were given a diagnosis of IgE-mediated egg allergy at 12 months of age compared with the control group (51% [18/35]); however, the difference did not reach statistical significance (relative risk [RR], 0.65; 95% CI, 0.38-1.11; $P = .11$; Fig 1). Overall, 22 (33%) of 67 of the infants who underwent the pasteurized raw egg challenge had an allergic reaction. Ten infants did not have a pasteurized raw egg challenge because of an independent medical decision not to proceed based on a previous documented allergic reaction to egg and associated evidence of sensitization (positive SPT response) to egg. Secondary outcome analyses found a lower proportion of infants in the egg group (45% [19/42]) were sensitized to egg (positive SPT response) at 12 months of age compared with the control group (63% [22/35]); however, the difference did not reach statistical significance (RR, 0.72; 95% CI, 0.47-1.09; $P = .12$; Fig 1). There were no differences in the severity and extent of eczema (objective SCORAD score) at 8 months of age (median in the egg group of 7.6, with an interquartile range [IQR] of 3.6-14.5 [n = 42] and median in the control group of 7.8, with an IQR of 3.6-14.1 [n = 35], $P = .80$) or at 12 months of age (median in the egg group of 7.2, with an IQR of 0.0-12.2 [n = 42] and median in the control group of 8.2, with an IQR of 0.0-14.4 [n = 35], $P = .35$). There was also no difference in the proportion of infants using prescription steroid cream between 4 and 12 months of age (90% vs 97% in the egg and control groups, respectively; $P = .37$) or in the number of visits to a doctor for eczema (1 visit on average in each group, $P = .75$).

At 8 months of age, the rate of allergic reactions to cooked egg was 16% (12/75): 6 (15%) of 40 in the egg group and 6 (17%) of 35 in the control group (RR, 0.88; 95% CI, 0.31-2.47; $P = .80$).

TABLE II. Clinical outcomes of infants (n = 18) who had an allergic reaction to the study powder

Allocated study powder	Doses of study powder before powder use ceased	Cooked egg exposure	Pasteurized raw egg challenge	IgE-mediated egg allergy at 12 mo of age
Egg	6	Allergic reaction	No challenge	Yes
Egg	3	Tolerated	Allergic reaction	Yes
Egg	1	Tolerated	Allergic reaction	Yes
Egg	1	No exposure	No challenge	Yes
Egg	1	No exposure	No challenge	Yes
Egg	5	Allergic reaction	No challenge	Yes
Egg	3	Allergic reaction	No challenge	Yes
Egg	1	No exposure	Withdrawn	Unknown (withdrawn)
Egg	1	Tolerated	Allergic reaction	Yes
Egg	43	Tolerated	Tolerated	No
Egg	1	Tolerated	Allergic reaction	Yes
Egg	1	Allergic reaction	No challenge	Yes
Egg	1	Tolerated	Allergic reaction	Yes
Egg	1	No exposure (anaphylaxis to study powder)	No challenge (anaphylaxis to study powder)	Yes
Egg	1	Tolerated	Allergic reaction	Yes
Rice	3	Tolerated	Allergic reaction	Yes
Rice	7	Allergic reaction (anaphylaxis)	No challenge (anaphylaxis to cooked egg exposure)	Yes
Rice	3	Allergic reaction	No challenge	Yes

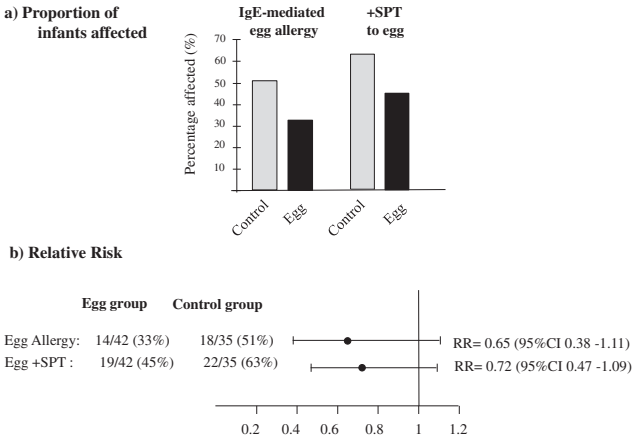

FIG 1. IgE-mediated egg allergy and positive SPT response *(+SPT)* to egg at 12 months of age. **A,** Proportion of infants. **B,** RR between the egg and control groups.

Eleven infants did not have cooked egg exposure: 4 because of independent medical advice after an allergic reaction to the study powder, 1 because of repeated illnesses, and 6 because they were withdrawn. Twenty-one (95%) of 22 infants (6 in the egg group and 15 in the control group) who reacted to the pasteurized raw egg challenge were able to tolerate cooked egg previously.

IgE and IgG_4 antibody measurements

There were no differences in baseline egg-specific IgE levels between the groups or at any other time point (Table III). At 4 months of age, before any known ingestion of egg, 36% (24/67) of the infants already had egg-specific IgE levels of greater than 0.35 kU_A/L. Within the egg group at 4 months of age, the egg-specific IgE concentrations were significantly greater (P = .001) for those infants who had an allergic reaction to the egg powder (median, 0.78 kU_A/L; IQR, 0.55-2.07 kU_A/L; n = 11) compared with those who tolerated the powder (median, 0.05 kU_A/L; IQR, 0.05-0.39 kU_A/L; n = 24).

Early ingestion of egg (egg group) was associated with significantly (P < .001) and persistently higher egg-specific IgG_4 levels (Fig 2 and Table III). The median IgE/IgG_4 ratio at 12 months of age in the egg group (0.39; IQR, 0.05-4.15) was significantly lower (P = .001) than in the control group (5.14; IQR, 1.43-25.28). In infants with IgE-mediated egg allergy, the median IgE/IgG_4 ratio at 12 months of age (median, 15.83; IQR, 5.13-65.07) was significantly higher (P < .001) than for infants who tolerated the raw egg challenge (median, 0.35; IQR, 0.05-1.43; Fig 3). The egg-specific IgE concentrations at 12 months of age in infants with IgE-mediated egg allergy (median, 2.37; IQR, 1.23-9.72) were also significantly higher (P < .001) than for infants who tolerated the raw egg challenge (median, 0.13; IQR, 0.05-0.76; Fig 4).

DISCUSSION

This is the first reported randomized controlled trial to investigate the hypothesis that early regular oral exposure to an allergenic food can induce oral tolerance and reduce the risk of subsequent food allergy. We specifically targeted children with moderate-to-severe eczema in this study because of their particularly high risk of food allergy. Recognizing that neither the rate of sensitization nor the rate of clinical reaction has been previously described in this population at this very young age, we adopted a "community scenario" approach in this study and elected not to pretest or exclude children on the basis of an egg-specific IgE levels at randomization. As a result, we observed a high proportion (36%) of infants already sensitized to egg before randomization at 4 months of age, and 31% who were allocated to receive egg powder had a clinical reaction, including 1 case of anaphylaxis. This clearly indicates that a high proportion of young infants with moderate-to-severe eczema are already

TABLE III. Egg-specific IgE and IgG_4 antibody concentrations

	Egg group	Control group	P value
Egg-specific IgE level (kU_A/L) at 4 mo of age	0.23 (0.05-0.78), n = 35	0.05 (0.05-0.31), n = 31	.40
Egg-specific IgE level (kU_A/L) at 8 mo of age	0.34 (0.05-0.86), n = 36	0.52 (0.05-3.92), n = 23	.22
Egg-specific IgE level (kU_A/L) at 12 mo of age	0.54 (0.05-2.55), n = 40	0.40 (0.05-2.32), n = 29	.88
Egg-specific IgG_4 level (mg_A/L) at 4 mo of age	0.04 (0.04-0.04), n = 35	0.04 (0.04-0.07), n = 30	.23
Egg-specific IgG_4 level (mg_A/L) at 8 mo of age	1.00 (0.06-3.00), n = 36	0.04 (0.04-0.04), n = 23	<.001
Egg-specific IgG_4 level (mg_A/L) at 12 mo of age	1.76 (0.16-9.00), n = 40	0.04 (0.04-0.74), n = 29	<.001

Values are presented as medians (IQRs).
mg_A/L, Milligrams of antibody per liter.

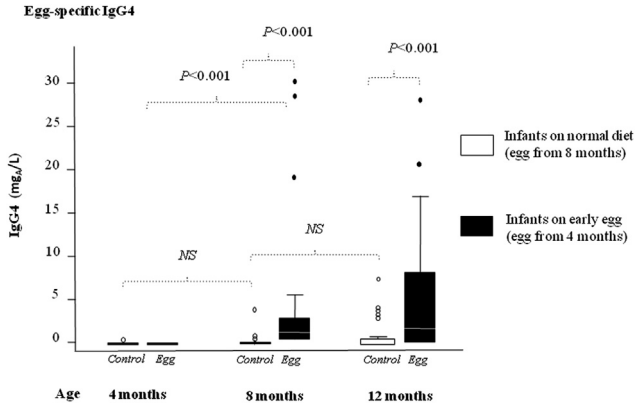

FIG 2. Egg-specific IgG_4 (in milligrams of antibody per liter) concentrations at 4, 8, and 12 months of age. *NS*, Not significant.

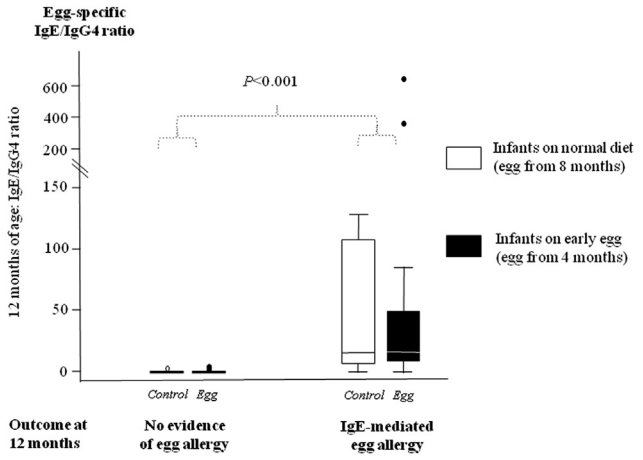

FIG 3. IgE/IgG_4 ratios at 12 months of age in infants with IgE-mediated egg allergy compared with those seen in infants who tolerated the egg challenge. For infants with IgE-mediated egg allergy, the median IgE/IgG_4 ratio in the egg group was 15.90 (IQR, 4.03-56.86), and that in the control group was 15.75 (IQR, 6.42-110.63). For infants who tolerated the egg challenge, the median IgE/IgG_4 ratio in the egg group was 0.09 (IQR, 0.02-0.43), and that in the control group was 1.43 (IQR, 0.48-1.43).

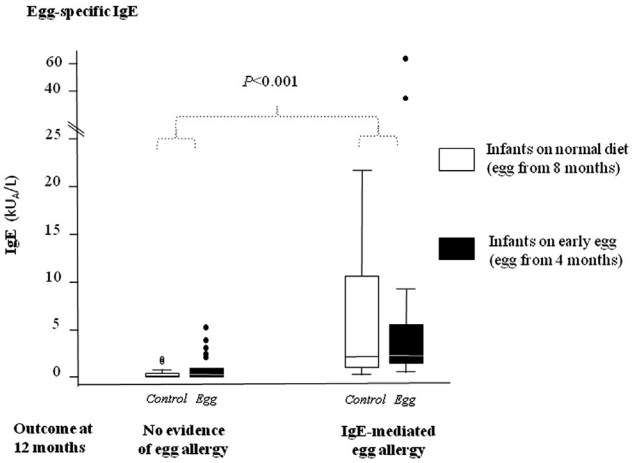

FIG 4. Egg-specific IgE concentrations at 12 months of age in infants with IgE-mediated egg allergy compared with those seen in infants who tolerated the egg challenge. For infants with IgE-mediated egg allergy, the median IgE concentration in the egg group was 2.42 (IQR, 1.56-7.50), and that in the control group was 2.32 (IQR, 1.01-11.40). For infants who tolerated the egg challenge, the median IgE concentration in the egg group was 0.13 (IQR, 0.05-0.84), and that in the control group was 0.05 (IQR, 0.05-0.60).

sensitized to egg before commencing solid foods (in all cases there was no previous history of known direct ingestion of egg) through other routes, potentially *in utero* across the placenta, through the defective skin barrier, or through breast milk, much earlier than 4 months of age and emphasizes the need for caution when first introducing allergenic foods to this high-risk group. Importantly, it is also increasingly clear that the processes leading to food sensitization are already strongly established by 4 months of age, indicating that much earlier preventive interventions will ultimately be needed. Differences in neonatal immune function of children with subsequent food allergy[22,23] suggest that these events are initiated *in utero* and consolidated during the very early postnatal period. With such a dramatic increase in food allergy, there is a pressing need to define events around much earlier allergen encounter.

This study was terminated early for logistic reasons (see the Methods section), and we acknowledge that this is a major limitation because of the resulting insufficient power to show statistically significant definitive results. Even so, the trend for lower incidence of egg allergy in the egg group (33%) compared with the control group (51%) reduces previous concerns that early introduction of this allergenic food would be associated with increased egg allergy risk. In fact, the data point to the contrary and deserve further study. There are now at least 3 other randomized controlled trials (Trial Registry details: ACTRN 12610000388011, ACTRN 12611000535976, and JPRN-UMIN000008673) investigating early regular egg exposure to reduce the risk of egg allergy development. However, each of these trials is targeting infants at lower risk of egg allergy than those in the present study. Our present findings in this very high-risk population will therefore contribute a valuable dimension to the composite picture that will emerge as the results of each of these trials come to light.

We chose a particularly allergenic form of egg for the intervention group study powder, namely pasteurized raw egg, which has equivalent allergenic properties to those of raw egg.[24] The rationale was to induce tolerance to the range of epitopes encountered in the most allergenic forms of egg by using a powder form that could be easily mixed with the infant's solid foods. However, this form of egg is also more likely to induce reactions in infants who are already sensitized. It is possible that early intervention with cooked or baked egg might achieve tolerance with less risk of reactivity, although the observational Australian HealthNuts study[18] suggested that first exposure to more allergenic (unbaked) egg was more likely to reduce the egg allergy risk. More intervention studies are needed to determine how best to deliver the allergen, although ideally, this should be in natural foods.

In conclusion, induction of immune tolerance pathways and reduction in the egg allergy rate can be achieved by early regular oral exposure to egg from 4 months of age in infants with moderate-to-severe eczema. The earlier introduction of egg in solid foods does not appear to increase the risk of egg allergy in this high-risk group. However, caution needs to be taken when these high-risk infants are first exposed to egg because many have sensitization already and clinical reactivity by 4 months of age. This points to much earlier events in the initiation of food sensitization, well before the introduction of complementary feeding.

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Clinical implications: Caution needs to be taken when infants with moderate-to-severe eczema are first exposed to egg because many have sensitization already and clinical reactivity by 4 months of age.

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METHODS

SPTs

At 12 months of age, on the same day but before the egg challenge, the infants had SPTs performed by one of 6 experienced nurses. The allergens tested were rice (Stallergenes, Antony, France), whole egg (Stallergenes), egg white (Stallergenes), pasteurized raw whole egg (actual food and not an extract), cow's milk (ALK-Abelló, Hørsholm, Denmark), wheat (Stallergenes), fish (tuna; Stallergenes), peanut (Stallergenes), cashew nut (Stallergenes), grass pollen perennial ryegrass (Stallergenes), cat hair (ALK-Abelló), and the house dust mite *Dermatophagoides pteronyssinus* (Stallergenes). Glycerin and histamine (Stallergenes) were used as negative and positive controls, respectively. A response was considered positive if there was a mean of the horizontal and perpendicular wheal diameters of 3 mm or greater in size than the mean wheal of the negative control site at 15 minutes. Sensitization was defined as a positive SPT response to at least 1 of the allergens assessed.

Pasteurized raw egg challenges

At 12 months of age, the pasteurized raw egg challenge was performed according to a low-risk or high-risk protocol. Infants who were already eating egg as part of their regular diets followed the low-risk protocol, which entailed a single dose of 30 mL of pasteurized raw egg (equivalent to half an egg). The half an egg challenge dose was 3 times more than the one sixth of an egg dose that the egg group infants had ingested per day during the intervention phase and was determined to be a realistic amount for all 12-month-old infants to consume. The high-risk protocol was reserved for infants who had previously had a suspected allergic reaction to egg, had never eaten any egg, or had a positive SPT response to 1 or more of the egg allergens tested. This high-risk protocol entailed 6 doses of increasing amounts of pasteurized raw egg (drop inside lip, 1, 2, 5, 10, and 20 mL), with the doses at 15-minute intervals. The challenge was ceased if the infant had an allergic reaction.

Antibody measurements

Whole egg–specific IgE and egg white–specific IgG_4 serum antibody concentrations were measured with the ImmunoCAP 250 system (Phadia AB, Uppsala, Sweden). For specific IgE, the lower limit of detection was 0.1 kU_A/L, and for specific IgG_4, the lower limit of detection was 0.07 mg of antibody/L. For analysis, values of less than the lower limit of detection were replaced by half the lower limit of detection.[E1] All researchers remained blind to the blood sample results throughout the trial to avoid any study bias.

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