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

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Abstract

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

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

Methods: In a double-blinded randomized controlled trial, infants were allocated to one teaspoon of pasteurized raw whole egg powder (n=49) or rice powder (n=37) daily from 4-8-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 defined by an observed pasteurized raw egg challenge and skin prick tests.

Results: A high proportion (31%) of infants randomized to receive egg (15/49) had an allergic reaction to the egg powder and did not continue powder ingestion. At 4-months of age, prior to any known egg ingestion, 36% (24/67) infants already had egg-specific IgE >0.35 kU_A/L. At 12-months, a lower (but not significant) proportion of infants in the egg group (33%) were diagnosed with IgE-mediated egg allergy compared to the control group (51%; relative risk 0.65; 95% confidence intervals 0.38 to 1.11; P=0.11). Egg-specific IgG4 levels were significantly (P<0.001) higher in the egg group at both 8 and 12-months.

Conclusion: Induction of immune tolerance pathways and reduction in egg allergy incidence may 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 as many have already developed sensitization by 4-months of age.

Clinical Implications

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

Capsule Summary

Induction of immune tolerance pathways and reduction in egg allergy incidence may be achieved by early regular oral egg exposure in infants with eczema provided the infant tolerates their first few exposures to egg.

Key words

Allergy prevention, complementary feeding, eczema, egg, food allergy, oral tolerance, randomized controlled trial.

Abbreviations

CI - confidence intervals

IgE - immunoglobulin E

IgG4 - immunoglobulin G4

ITT - intention to treat

RCT - randomized controlled trial

RR - relative risk

SCORAD - scoring system for atopic dermatitis/eczema

SOTI - specific oral tolerance induction

SPT - skin prick test

Introduction

Egg allergy is the most common food allergy now affecting 8.9% of children at 1 year of age in Australia [1]. With rising 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, based largely on observational studies with methodological limitations and that randomized control 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 may increase the risk of adverse immune responses to allergens [8]. The potential role of regular food allergen exposure to induce tolerance in humans is also illustrated by studies of specific oral tolerance induction (SOTI) in food allergic children [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]. While the timing of this potential 'window' is not clear in humans, delayed introduction of specific foods (egg, cow's milk, fish, oats) beyond 6-9 months of age has been associated with increased risk of allergic disease in non-intervention cohort studies [11-17]. The Australian Healthnuts study [18] found that delaying introduction of egg until 10-12-months (adjusted OR, 1.6, 95% CI, 1.0-2.6) or after 12-months (adjusted OR 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. Thus early oral exposure to egg may be an important strategy to prevent or reduce the risk of developing an 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 as those most likely to benefit from the prevention of food allergy.

Methods

Study design

Singleton, term infants with symptoms of moderate to severe eczema (determined using a standardized scoring system for atopic dermatitis/eczema [SCORAD] [20] score of ≥15) were recruited at 4 months of age from two Australian centers (Adelaide and Perth). Infants who had commenced solids prior to 4-months of age or who had any previous known direct ingestion of egg were excluded. Written informed consent was obtained prior to trial participation. Approval was granted by the local Institutional Review Boards (Human Research Ethics Committees) of each centre, 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 using a double-blinded randomized controlled trial design. Baseline characteristics including maternal age at birth, maternal race, Caesarean delivery, smoking in the household, family (first degree relative) history of allergic disease, infant sex, infant dietary information on breastfeeding and/or formula feeding, infant history of and treatments used for eczema were recorded at randomization at 4-months of age. A blood sample was collected prior to the first exposure to the study powder. Baseline egg-specific IgE and IgG4 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 into one of two intervention groups. A computer-generated randomization schedule was produced by an independent consultant. The schedule was stratified by infant sex and feeding mode (breastfed or formula fed if receiving >200ml 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 two 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 given orally by mixing the powder with infant rice cereal. The intervention group was allocated to 1 teaspoon (=0.9g egg protein equivalent to 1/6 of an egg) per day of pasteurized raw whole egg powder manufactured by Farm Pride Foods, Keysborough, Australia. The control group received 1 teaspoon (=0.25g 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) as 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 (were appropriate), was conducted to confirm any possible allergic reactions to the study powder prior to a decision being 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 infant was 5, 6, 7 and 10 months of age, and at 8 and 12-months of age the infant 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 visits for eczema and the use of any treatment medications for eczema. At the 8 and 12 month appointments, the infant's eczema was assessed using SCORAD [20] and a blood sample was collected to measure whole egg-specific IgE and egg white-specific IgG4 serum antibody concentrations (see the on-line repository for more details).

Throughout this trial an allergic reaction was defined as at least 3 concurrent non-contact urticaria persisting for at least 5 minutes and/or generalised 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, admissions to Intensive Care 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, where the infant was given 2 teaspoons of mashed hard-boiled whole egg (equivalent to 1/6 of an egg) to eat and observed for at least 2 hours afterwards. 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, omelette, quiche, egg in baked goods, egg in meatballs or egg used for crumbing foods) in the infant's diet from 8-12-months of age.

At 12-months of age, all infants had a medically supervised pasteurized raw egg challenge where the infant was given ½ whole egg (see the on-line repository for more details) and observed for at least 2 hours afterwards. 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 for whom 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 prior to the egg challenge, the infants had skin prick tests (SPT) (see the on-line repository for details).

The primary outcome was the diagnosis of IgE-mediated egg allergy at 12-months of age defined as an allergic reaction to the pasteurized raw egg challenge and associated evidence of sensitization to egg or where 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], so to detect an absolute reduction of 20% (relative reduction of 50%) from 40% to 20% (with 85% power, alpha-value 0.05), 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, 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 re-open the trial for recruitment in May 2012, however by this time insufficient funds remained to re-commence 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 sensitized to egg. Independent Samples T-Test, Mann-Whitney U, Pearson Chi-Square and Fisher's Exact Tests were used to test differences between the groups. Statistical significance was assessed at the 0.05 level. Analyses were performed using SPSS Statistics Software version 20. (IBM, USA).

Results

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

Intervention, compliance and safety

A high proportion (21%) of infants randomized (18/86) had an allergic reaction to their allocated study powder. The proportion of reactors was higher (31%) in those allocated to receive egg (15/49). Most of these (10/15) had a reaction on the *first* exposure to the egg powder, including one 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 were followed up for their suspected rice allergy outside the study by an independent allergist. No participating infants had a positive SPT 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 2.

For the infants without an allergic reaction to the study powder, compliance with the powder use was high. In the egg group 31/33 (94%) infants ingested the study powder at least 4 days

per week on average during the intervention period, as did 31/32 (97%) infants in the control group. Compliance with the egg-free diet intervention from 4-8-months of age did not differ between the groups; 78% in the egg group compared to 64% in the control group (*P*=0.15). 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 one infant (in the egg group) did so on more than one occasion and only one 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 into the diet of the infants, who did not react to the cooked egg exposure, from 8-12 months of age was high with all of these infants (n=63) consuming egg as an ingredient in foods, and 59/63 (94%) infants consuming whole egg as either quiche, omelette, hard-boiled or scrambled egg.

Four infants experienced a serious adverse event. In the egg group, one infant had a hospital Intensive Care admission with food protein-induced enterocolitis syndrome (FPIES) after a re-challenge with the study powder to confirm a previous reaction and another had anaphylaxis on first exposure to the study powder. In the rice group, two infants had anaphylaxis, one after the cooked egg exposure and one after the pasteurized raw egg challenge.

Clinical outcomes

For the primary outcome, a lower proportion of infants in the egg group (14/42=33%) were diagnosed with IgE-mediated egg allergy at 12-months of age compared to the control group (18/35=51%), however the difference did not reach statistical significance (relative risk (RR) 0.65; 95% confidence intervals (CI) 0.38 to 1.11; *P*=0.11). Overall 22/67 (33%) of infants

who had 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) to egg. Secondary outcome analyses found a lower proportion of infants in the egg group (19/42=45%) were sensitized to egg (positive SPT) at 12-months of age compared to the control group (22/35=63%), however the difference did not reach statistical significance (RR 0.72; 95% CI 0.47 to 1.09; *P*=0.12). There were no differences in the severity and extent of eczema (objective SCORAD score) at 8-months of age (median in egg group =7.6, IQR 3.6-14.5; n=42 and median in the control group =7.8, IQR 3.6-14.1, n=35, *P*=0.80) or at 12-months of age (median in egg group =7.2, IQR 0.0-12.2; n=42 and median in the control group =8.2, IQR 0.0-14.4, n=35, *P*=0.35). There was also no difference in the proportion of infants using prescription steroid cream between 4 to 12-months of age (90% vs 97% in the egg and control groups respectively *P*=0.37), nor in number of visits to a doctor for eczema (one visit on average in each group, *P*=0.75).

At 8-months of age, the rate of allergic reaction to cooked egg was 16% (12/75); 6/40 (15%) in the egg group and 6/35 (17%) in the control group (RR 0.88; 95% CI 0.31 to 2.47; *P*=0.80). Eleven infants did not have a cooked egg exposure; 4 due to independent medical advice after an allergic reaction to the study powder, 1 due to repeated illnesses and 6 withdrawn. 21/22 (95%) infants (6 in egg group and 15 in control group) who reacted to the pasteurized raw egg challenge were able to tolerate cooked egg prior.

IgE and IgG4 antibody measurements

There were no differences in baseline egg-specific IgE levels between the groups or at any other time point (Table 3). At 4-months of age, prior to any known ingestion of egg, 36%

296 (24/67) infants already had egg-specific IgE >0.35 kU_A/L. Within the egg group at 4-months
297 of age, the egg-specific IgE concentrations were significantly higher (P=0.001) for those
298 infants who had an allergic reaction to the egg powder (median = 0.78 kU_A/L, IQR 0.55-2.07,
299 n=11) compared to those who tolerated the powder (median = 0.05 kU_A/L, IQR 0.05-0.39,
300 n=24).
301
302 Early ingestion of egg (egg group) was associated with significantly (P<0.001) and
303 persistently higher egg-specific IgG4 levels (Table 3 and Figure 1). The median IgE/IgG4
304 ratio at 12-months of age in the egg group (0.39; IQR 0.05-4.15) was significantly lower
305 (P=0.001) than the control group (5.14; IQR 1.43-25.28). In infants with IgE-mediated egg
306 allergy, the median IgE/IgG4 ratio at 12-months of age (median 15.83; IQR 5.13-65.07) was
307 significantly higher (P<0.001) than for infants who tolerated the raw egg challenge (median
308 0.35; IQR 0.05-1.43) (Figure 2). The egg-specific IgE concentrations at 12-months of age in
309 infants with IgE-mediated egg allergy (median 2.37; IQR 1.23-9.72) were also significantly
310 higher (P<0.001) than for infants who tolerated the raw egg challenge (median 0.13; IQR
311 0.05-0.76) (Figure 3).
312

Discussion

This is the first reported RCT 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. Recognising 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 pre-test or exclude children on the basis of an egg-specific IgE level at randomisation. As a result we observed a high proportion (36%) of infants already sensitized to egg *prior* to randomization at 4-months of age and 31% who were allocated to receive egg powder had a clinical reaction, including one case of anaphylaxis. This clearly indicates that a high proportion of young infants with moderate to severe eczema are *already* sensitized to egg prior to 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 subsequently food allergic children [22, 23] suggest that these events are initiated *in utero* and consolidated during the very early postnatal period. With such a dramatic rise 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 methods) and we acknowledge that this is a major limitation due to 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 to the control group (51%) reduces previous concerns that early introduction of this allergenic food would be associated with increased egg allergy risk, and that the data points to the contrary and deserves further study. There are now at least three other RCTs (Trial Registry details ACTRN 12610000388011, ACTRN 12611000535976, 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 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 that of raw egg [24]. The rationale was to induce tolerance to the range of epitopes encountered in the most allergenic forms of egg, using a powder form that could be easily mixed in with the infant's solid foods. However, this form of egg is also more likely to induce reactions in infants that 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 egg allergy risk. More intervention studies are needed to determine the best form to deliver the allergen, although ideally this should be in natural foods.

Conclusion

Induction of immune tolerance pathways and reduction in the egg allergy rate may be achieved by early regular oral exposure to egg from 4-months of age in infants with moderate

to severe eczema. Caution needs to be taken when these high-risk infants are first exposed to egg as many have already developed sensitization 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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452 ***Table 1: Baseline Characteristics.*** *Values are *mean (standard deviation), . ^ numbers (percentages) or [&] median (Inter Quartile Range).*

Characteristic	*Egg (n=49)*	*Control (n=37)*	*P value*
Maternal age at birth (years) *	32.8 (5.5)	32.1 (3.4)	0.48
Maternal Caucasian race ^	36 (73%)	32 (86%)	0.14
Caesarian-section birth ^	17 (35%)	11 (30%)	0.63
Maternal history of allergic disease ^	37 (76%)	25 (68%)	0.42
1st degree relative history of allergic disease ^	44 (90%)	35 (95%)	0.69
Infant male sex ^	31 (63%)	26 (70%)	0.50
Age of onset of eczema (months) *	1.8 (1.1)	1.8 (0.9)	0.75
Eczema severity (objective SCORAD score) &	33.8 (29.2,37.5)	32.7 (25.0,39.5)	0.46
Use of prescription steroid cream ^	40 (82%)	28 (76%)	0.50
Ever breastfed ^	48 (98%)	37 (100%)	1.00
Breastfed at randomisation ^	40 (82%)	31 (84%)	0.96
Smoking in the household ^	8 (16%)	3 (8%)	0.34

456 ***Table 2: Clinical outcomes of infants (n=18) who had an allergic reaction to the study powder.***

Allocated study powder	***Doses of study powder prior to powder use ceased***	***Cooked Egg Exposure***	***Pasteurised Raw Egg Challenge***	***IgE- mediated Egg Allergy at 12 months 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

457

458

459 ***Table 3: Egg-specific IgE (kU_A/L) and IgG4 (mg_A/L) antibody concentrations (median, IQR).***

	Egg	*Control*	*P value*
Egg-specific IgE at 4 months of age	0.23 (0.05, 0.78) *(n=35)*	0.05 (0.05, 0.31) *(n=31)*	0.40
Egg-specific IgE at 8 months of age	0.34 (0.05, 0.86) *(n=36)*	0.52 (0.05, 3.92) *(n=23)*	0.22
Egg-specific IgE at 12 months of age	0.54 (0.05, 2.55) *(n=40)*	0.40 (0.05, 2.32) *(n=29)*	0.88
Egg-specific IgG4 at 4 months of age	0.04 (0.04, 0.04) *(n=35)*	0.04 (0.04, 0.07) *(n=30)*	0.23
Egg-specific IgG4 at 8 months of age	1.00 (0.06, 3.00) *(n=36)*	0.04 (0.04, 0.04) *(n=23)*	<0.001
Egg-specific IgG4 at 12 months of age	1.76 (0.16, 9.00) *(n=40)*	0.04 (0.04, 0.74) *(n=29)*	<0.001

460 Abbreviation: IQR, Inter quartile range.

461

462 **Figure Legends**

463

464 **Figure 1 : Egg-specific IgG4 (mg_A/L) concentrations at 4, 8 and 12-months of age.**

465

466 **Figure 2**: **IgE/IgG4 ratio at 12-months of age in infants with IgE-mediated egg allergy**
467 **compared to those infants who tolerated the egg challenge**. For infants with IgE-mediated
468 egg allergy, median IgE/IgG4 ratio in the egg group was 15.90 (IQR 4.03-56.86) and in the
469 control group was 15.75 (IQR 6.42-110.63). For infants who tolerated the egg challenge, the
470 median IgE/IgG4 ratio in the egg group was 0.09 (IQR 0.02-0.43) and in the control group
471 was 1.43 (IQR 0.48-1.43).

472

473 **Figure 3**: **Egg-specific IgE concentrations at 12-months of age in infants with IgE-**
474 **mediated egg allergy compared to those infants who tolerated the egg challenge**. For
475 infants with IgE-mediated egg allergy, the median IgE concentration in the egg group was
476 2.42 (IQR 1.56-7.50) and in the control group was 2.32 (IQR 1.01-11.40). For infants who
477 tolerated the egg challenge, the median IgE concentration in the egg group was 0.13 (IQR
478 0.05-0.84) and in the control group was 0.05 (IQR 0.05-0.60).

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