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Frequent baked egg ingestion was not associated with change in rate of decline in egg skin prick test in children with challenge confirmed egg allergy

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Summary

Background It is controversial whether egg-allergic children should strictly avoid all forms of egg, or if regular ingestion of baked egg will either delay or hasten the resolution of egg allergy.

Objective This is the first study to examine the relationship between frequency of baked egg ingestion and rate of decline in egg skin prick test size in egg-allergic children.

Methodology This was a retrospective clinical cohort study. All children with challenge-proven egg allergy who attended the Royal Children's Hospital Allergy Department 1996–2005 and had at least two egg skin prick tests performed in this period were included ($n = 125$). Frequency of baked egg ingestion was assessed by telephone questionnaire as follows: (a) *frequent* ($>$ once per week), (b) *regular* ($>$ once every 3 months, up to $\leq$ once per week) or (c) *strict avoidance* ($\leq$ once every 3 months). The relationship between frequency of baked egg ingestion and rate of decline in egg skin prick test size was examined by multiple linear regression, adjusting for potential confounders.

Results Mean rate of decline in egg skin prick test size in all children was 0.7 mm/year (95% CI 0.5–1.0 mm/year). There was no evidence ($P = 0.57$) that the rate of decline in egg skin prick test size differed between children who undertook *frequent ingestion* ($n = 21$, mean 0.4 mm/year, 95% CI -0.3 –1.2 mm/year), *regular ingestion* ($n = 37$, mean 0.9 mm/year, 95% CI 0.4–1.4 mm/year) or *strict avoidance* ($n = 67$, mean 0.7 mm/year, 95% CI 0.4–1.1 mm/year) of baked egg.

Conclusions Compared with strict dietary avoidance, frequent consumption of baked egg was not associated with a different rate of decline in egg skin prick test size in egg-allergic children.

Clinical Relevance Given that dietary restrictions can adversely impact on the family, it is reasonable to consider liberalizing baked egg in the diet of egg-allergic children.

Keywords baked egg, egg allergy, natural history, skin prick test, tolerance

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Introduction

Egg allergy is the commonest food allergy in children, with a cumulative prevalence in childhood of 0.5–2.5% [1, 2]. Our recent large population-based cross-sectional study of 12-month-old Australian infants found a prevalence of egg allergy of 8.9% [3].

The cornerstone of management of egg allergy is dietary avoidance, and current expert recommendations

advise strict avoidance of all egg in the diet [4, 5]. This is based in part on the widespread belief that strict avoidance may hasten or increase the likelihood of tolerance, despite limited evidence to support this [6, 7]. Strict avoidance of all egg is difficult to achieve as egg is ubiquitous in manufactured food products [8], and up to 47% of children have an accidental exposure within 5 years [9, 10]. Moreover, the majority of children with egg allergy are able to safely tolerate egg in baked

goods [11–14], presumably due to the reduced allergenicity of heated ovalbumin [15, 16] and low allergen dose (one slice of a baked two-egg cake will deliver one-sixth of an egg). Strict elimination reduces the potential for allergic reaction including life-threatening anaphylaxis; however, major disadvantages are a significantly reduced quality-of-life for patients and their families due to the discipline and vigilance required to maintain such a stringent diet and the impact of limited dietary choices on nutritional adequacy [17].

Allen et al. [10] recently reported that there was no difference in the degree of adherence to a strict egg-avoidance diet amongst egg-allergic children who achieved oral tolerance over a 5-year period ($n = 84$); however, the specific relationship between degree of egg ingestion and development of tolerance was not assessed. Moreover, recent studies suggest that regular intake of small quantities of egg can lead to immunomodulatory changes typically associated with development of tolerance, and hence may be beneficial for resolution of egg allergy [14, 18].

Our study aimed to determine if frequent ingestion of baked egg by egg-allergic children would alter the natural history of egg allergy. Although oral food challenge is established as the gold standard of determining tolerance [19], its outcome is categorical and does not allow for tracking over time in a quantitative manner. We hence utilized the rate of change in egg skin prick test (SPT) weal size as a surrogate measure of tolerance acquisition over time, acknowledging that a negative SPT may lag behind clinical tolerance.

Methods

Study setting

The Department of Allergy and Immunology, Royal Children's Hospital, is the only academic tertiary paediatric allergy service performing oral food challenges in Victoria, Australia, for a population of approximately 5.2 million. The Department maintains a database that records the results of all SPT and oral food challenges performed. The study sample was identified by searching this database.

Study design and sample

This is a retrospective clinical cohort study. All children identified from the Department database that had a positive oral food challenge to raw egg white, and hence egg allergy, over a 10-year period (1996–2005) were eligible for the study. Study participants beyond 2005 were not included as the Department changed its SPT device from Prick Lancets (Stallergenes SA, Antony, France) to Greer Pick (Greer Labs, Lenoir, NC,

USA), which may have affected SPT weal sizes. A positive challenge was defined as the presence of clearly demonstrable symptoms of IgE-mediated allergy occurring within 2 h of raw egg-white ingestion: urticaria, angioedema, rhinoconjunctivitis, gastrointestinal, respiratory and/or cardiovascular symptoms; detected in hospital on day 1 of the challenge, or captured via a follow-up phone call 1 week post challenge following continued daily ingestion of raw egg white at home.

Inclusion criteria

Study participants with egg allergy were included in this study if they had a positive egg-white SPT (≥ 3 mm above saline control) performed within 12 months prior to the oral food challenge followed by at least one further egg-white SPT performed after the oral food challenge which is at least 6 months after the initial SPT. SPT was performed with Prick Lancets (Stallergenes SA) using egg-white extract (Hollister-Stier Laboratories, Spokane, WA, USA) on the participant's back (for infants and younger children) or forearm (for older children and adolescents).

Data collection

One-hundred and sixty-five participants fulfilled the inclusion criteria. Of these, 140 (85%) were contactable, and all agreed to a structured telephone questionnaire administered by a clinician (either MR or DT) over two time periods (Fig. 1): August 2008 (pilot study) and May 2009. Of these, seven (5%) were excluded as their approach to dietary avoidance of egg was inconsistent during the period under study, and a further eight (6%) were excluded due to the parents' inability to recall frequency of baked egg ingestion during the study period. Telephone questionnaire sought to determine whether parents were initially advised by their physician to avoid all forms of egg, or if small amounts of baked egg in cakes or biscuits were allowed, and whether families adhered to this advice. Parents were also asked about the frequency of baked egg ingestion during the study period; whether these were mostly accidental or intentional exposures; and what, if any, allergic reactions their child developed when baked egg was ingested. Additional clinical data were collected (from a combination of the telephone questionnaire, medical records and database) including the study participant's date of birth, gender, presence of other allergic disease (eczema, asthma, allergic rhinitis), other food allergy or sensitization, past anaphylaxis, past prescription of an adrenaline autoinjector, past administration of adrenaline and family history of allergic disease. We defined 'significant allergic disease' as follows: eczema – use of topical corticosteroid for 10

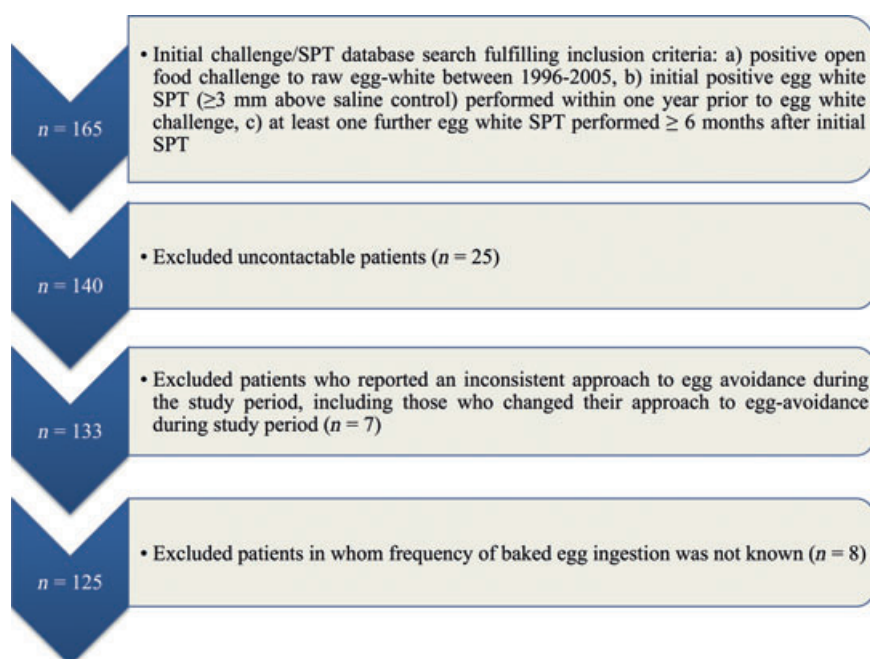


Fig. 1. Patient selection.

consecutive days at any stage; allergic rhinitis – use of intranasal corticosteroid for three consecutive months at any stage; and asthma – use of inhaled corticosteroid preventer for three consecutive months at any stage.

Definition of baked egg ingestion

Parents were asked the following question during the telephone-administered questionnaire: 'During the study period, how often did your child have small amounts of well-cooked egg in foods, such as cakes or biscuits?'. Based on this information, study participants were categorized into three groups for frequency of baked egg ingestion: (a) *frequent ingestion* ($>$ once per week), (b) *regular ingestion* ($>$ once every 3 months, up to $\leq$ once per week) or (c) *strict avoidance* ($\leq$ once every 3 months). For example, if a parent reported their child consumed baked egg at a rate of approximately once every 2 weeks, the child is categorized into the *regular ingestion* group. In addition, the frequency of baked egg ingestion reported by parents was then converted to a common unit, 'times per year', such that this can be visualized on a graph showing the relationship between egg ingestion and rate of decline in egg-white SPT (see below). For example, if a participant reported baked egg ingestion every 2 weeks, this was converted to baked egg ingestion 26 times per year.

Statistical analysis

For each participant, the rate of decline in egg-white SPT was calculated as the ratio of the change in SPT

weal size to the length of time elapsed between the first and final SPT. SPT measurements of 0 mm were taken to be the final SPT and any subsequent SPT results were not used in the calculation of the rate of decline.

Depending on the covariate distribution of data, Pearson's chi-square test in contingency tables, the analysis of variance (ANOVA) or the Kruskal–Wallis test (a non-parametric ANOVA) were used to investigate the association between the baseline characteristics and the categories of frequency of baked egg ingestion. Multiple linear regression was used to generate the average rate of decline in SPT for each category of frequency of baked egg ingestion, adjusted for potential confounders. All analyses were performed with StataSE 9.0 (StataCorp, College Station, TX, USA).

Ethics

The study was approved by the Royal Children's Hospital Human Research Ethics Committee.

Results

Baseline characteristics including frequency of ingestion of baked egg

The baseline clinical characteristics of 125 study participants are outlined in Table 1. Fifty-four per cent of the study cohort undertook *strict avoidance* ($\leq$ once every 3 months), 30% *regular ingestion* ($>$ once every 3 months, up to $\leq$ once per week) and 17% *frequent ingestion* ($>$ once per week) of baked

Table 1. Baseline clinical characteristics

Clinical characteristics	All children	Strict avoidance of baked egg	Ingested baked egg regularly	Ingested baked egg frequently	P-value
No. patients	125	67 (54%)	37 (30%)	21 (17%)	
Age at challenge, median, years (IQR)	5.1 (3.2–6.0)	5.0 (3.0–6.5)	5.3 (3.6–5.8)	4.8 (3.1–5.6)	0.58
Duration of follow-up, median, years (IQR)	3.0 (2.0–4.9)	3.3 (2.2–5.1)	3.1 (2.1–4.9)	2.7 (1.5–3.8)	0.35
Interval between initial SPT and oral food challenge, median, months (IQR)	1.0 (0.0–3.0)	0.7 (0.0–2.1)	1.5 (0.0–3.7)	1.9 (0.3–3.6)	0.10
Male, n (%)	78 (62%)	40 (60%)	24 (65%)	14 (67%)	0.79
Past anaphylaxis (%)	69 (55%)	38 (57%)	18 (49%)	13 (62%)	0.58
Egg anaphylaxis	40 (32%)	24 (36%)	9 (24%)	7 (33%)	0.48
Ever been administered adrenaline	30 (24%)	16 (24%)	11 (30%)	3 (14%)	0.42
Ever been prescribed adrenaline auto-injector	105 (84%)	58 (87%)	29 (78%)	18 (86%)	0.54
Other food allergy/sensitization	115 (92%)	60 (90%)	34 (92%)	21 (100%)	0.31
Peanut	104 (83%)	54 (81%)	30 (81%)	20 (95%)	0.27
Tree nuts	84 (67%)	39 (58%)	29 (78%)	16 (76%)	0.07
Cow's milk	50 (40%)	34 (51%)	11 (30%)	5 (24%)	0.03
Shellfish	18 (14%)	8 (12%)	6 (16%)	4 (19%)	0.67
Fish	15 (12%)	6 (9%)	5 (14%)	4 (19%)	0.44
Wheat	15 (12%)	9 (13%)	4 (11%)	2 (10%)	0.86
Soy	7 (6%)	4 (6%)	1 (3%)	2 (10%)	0.54
Other atopic disease, n (%)	117 (94%)	63 (94%)	34 (92%)	20 (95%)	0.19
Eczema	105 (84%)	59 (88%)	31 (84%)	15 (71%)	1.00
Significant eczema	54 (43%)	29 (43%)	16 (43%)	9 (43%)	0.61
Asthma	94 (75%)	49 (73%)	30 (81%)	15 (71%)	0.13
Significant asthma	47 (38%)	22 (33%)	13 (35%)	12 (57%)	0.62
Allergic rhinitis	82 (66%)	46 (69%)	24 (65%)	12 (57%)	0.53
Significant allergic rhinitis	20 (16%)	9 (13%)	6 (16%)	5 (24%)	
Family history of allergic disease	114 (91%)	59 (88%)	36 (97%)	19 (90%)	0.28
Father	55 (44%)	29 (43%)	21 (57%)	5 (24%)	0.05
Mother	71 (57%)	38 (57%)	18 (49%)	15 (71%)	0.24
Sibling(s)	87 (70%)	42 (63%)	29 (78%)	16 (76%)	0.42

egg. The *strict-avoidance* group had a higher rate of cow's milk allergy or sensitization (51%, $p = 0.03$), and the *frequent ingestion* group had a lower rate of father having any allergic disease (24%, $p = 0.05$). The baseline clinical characteristics were otherwise similar between the three groups. The study cohort's median age at initial raw egg-white challenge was 5.1 years (IQR 3.2–6.0 years) and the median follow-up duration was 3.0 years (IQR 2.0–4.9 years). Median interval between initial SPT and initial raw egg-white challenge was 1.0 month (IQR 0.0–3.0 months).

Physician's advice regarding egg avoidance

Fifty-seven participants (46%) were initially advised by their physician to avoid egg strictly while 52 (42%) were advised to liberalize baked egg in the diet (Table 2). Sixteen (13%) did not recall the initial advice by their physician and excluded from Table 2. Physicians were more likely to advise strict dietary avoidance of all egg if the child had coexisting eczema or cow's milk allergy/sensitization ($P = 0.04$ and $P < 0.01$, respectively). The rates of past anaphylaxis amongst

those instructed to undertake strict egg avoidance vs. partial egg avoidance were not different (63% and 50%, respectively, for any anaphylaxis; and for egg anaphylaxis 37% and 27%, respectively). Moreover, the likelihood of a physician recommending strict egg avoidance was not different in those with past egg anaphylaxis (53%, 21 of 40 participants) as compared with those without past egg anaphylaxis (52%, 36 of 69 study participants).

Adherence to initial advice regarding egg avoidance amongst study participants was high. Adherence to the physician's advice to strictly avoid egg was 86%, and 14% of participants advised to strictly avoid egg intentionally consumed baked egg during the study period. Conversely, 17% of those advised by their physician that baked egg could be consumed chose to maintain strict dietary avoidance of all egg including baked egg.

Reaction upon exposure to baked egg

For the majority of children in the *regular* and *frequent ingestion* group, consumption of baked egg was

Table 2. Physician's dietary advice

	All children whose parent could recall physician advice	Advised to strictly avoid all egg	Advised to ingest baked egg	P-value
No. patients	109	57 (46%)	52 (42%)	
Eczema				
No eczema	16 (15%)	5 (9%)	11 (21%)	0.04
Mild eczema	49 (45%)	25 (44%)	24 (46%)	
Significant eczema	44 (40%)	27 (47%)	17 (33%)	
Asthma				
No asthma	28 (26%)	17 (30%)	11 (21%)	0.30
Mild asthma	39 (36%)	20 (35%)	19 (37%)	
Significant asthma	42 (39%)	20 (35%)	22 (42%)	
Allergic rhinitis				
No allergic rhinitis	39 (36%)	19 (33%)	20 (38%)	0.80
Mild allergic rhinitis	51 (47%)	29 (51%)	22 (42%)	
Significant allergic rhinitis	19 (17%)	9 (6%)	10 (19%)	
Other food allergy/sensitization	114 (91%)	50 (88%)	48 (92%)	0.43
Cow's milk	50 (40%)	29 (51%)	11 (21%)	< 0.01
Soy	7 (6%)	3 (5%)	2 (4%)	
Wheat	15 (12%)	6 (11%)	5 (10%)	
Peanut	104 (83%)	44 (77%)	45 (87%)	0.21
Tree nut	66 (53%)	27 (47%)	31 (60%)	0.20
Fish	15 (12%)	6 (11%)	8 (15%)	0.45
Shellfish	18 (14%)	8 (14%)	9 (17%)	0.64
Family history of allergic disease	114 (91%)	50 (88%)	48 (92%)	0.43
Past anaphylaxis				
Past anaphylaxis to any allergen	72 (58%)	36 (63%)	26 (50%)	0.28
Past anaphylaxis to egg	40 (32%)	21 (37%)	14 (27%)	0.27
Adrenaline				
Past adrenaline injection	36 (29%)	16 (28%)	15 (29%)	0.75
Adrenaline autoinjector prescription	107 (86%)	51 (89%)	42 (81%)	0.20

intentional (86% and 100%, respectively), in comparison to only 38% in the *strict-avoidance* group (Table 3). IgE-mediated allergic reactions to egg occurred in 14% of the clinical cohort, more commonly in the *strict-avoidance* group (38%), compared

with participants who undertook *regular* (8%) and *frequent ingestion* (0%) ($P < 0.01$). The rate of IgE-mediated allergic reactions was not associated with either allergy or sensitization to cow's milk ($P = 0.10$) or peanut ($P = 0.70$). Two study participants developed

Table 3. Reaction upon exposure to baked egg and rate of decline in egg-white SPT

	All children	Strict avoidance of baked egg	Ingested baked egg regularly	Ingested baked egg frequently	P-value
No. patients	125	67 (54%)	37 (30%)	21 (17%)	
Occurrence of exposure(s) to baked egg	79 (63%)	21 (31%)	37 (100%)	21 (100%)	
Exposures mostly intentional	61 (77%)	8 (38%)	32 (86%)	21 (100%)	< 0.01
Outcome following exposure					
No reaction	58 (73%)	8 (38%)	31 (84%)	19 (90%)	< 0.01
IgE-mediated reaction	11 (14%)	8 (38%)	3 (8%)	0 (0%)	
Anaphylaxis	2 (3%)	2 (10%)	0 (0%)	0 (0%)	
Eczema/delayed GIT symptoms	4 (5%)	1 (5%)	2 (5%)	1 (5%)	
Unable to recall/not determined	6 (8%)	4 (19%)	1 (3%)	1 (5%)	
Mean egg SPT					
Initial, mm (95% CI)*	5.9 (5.5–6.2)	6.1 (5.6–6.6)	5.7 (5.0–6.4)	5.6 (4.7–6.5)	0.94
Final, mm (95% CI)**	4.5 (3.9–5.2)	4.6 (3.7–5.4)	4.2 (3.1–5.4)	4.9 (2.9–6.9)	0.25
Rate of SPT decline, mean, mm/year (95% CI)	0.7 (0.5–1.0)	0.7 (0.4–1.1)	0.9 (0.4–1.4)	0.4 (–0.3–1.2)	0.57

anaphylaxis upon ingestion of baked egg in egg-containing foods, and both were from the *frequent ingestion* group. A small proportion of patients (6%) developed eczema or delayed gastrointestinal reactions upon baked egg ingestion.

Rate of decline in egg SPT weal size

The mean rate of decline in egg SPT weal size for all children was 0.7 mm/year (95% CI 0.5–1.0 mm/year). Mean weal sizes for the initial and final SPT were 5.9 mm (95% CI 5.5–6.2 mm) and 4.5 mm (95% CI 3.9–5.2 mm), respectively. The relationship between frequency of baked egg ingestion and rate of decline in egg SPT was examined (Fig. 2). There was no evidence ($P = 0.57$) that the average rate of decline in egg SPT differed between participants taking *frequent ingestion* (mean 0.4 mm/year, 95% CI –0.3–1.2 mm/year), *regular ingestion* (mean 0.9 mm/year, 95% CI 0.4–1.4 mm/year) or *strict avoidance* (mean 0.7 mm/year, 95% CI 0.4–1.1 mm/year) of baked egg. This finding remained unchanged after investigating for potential confounding effects of age, gender, past anaphylaxis to any food, past egg anaphylaxis, past administration of adrenaline, past prescription of an adrenaline autoinjector, other food allergy/sensitization (peanut, tree nuts, milk, shellfish, fish, wheat, soy), other atopic disease (eczema, significant eczema, asthma, significant asthma, allergic rhinitis, significant allergic rhinitis), family history of allergic disease (father, mother, sibling) and physician's dietary advice.

Discussion

This is the first study to investigate the relationship between frequency of baked egg ingestion and rate of decline in egg SPT weal size in a homogeneous group of children with food-challenge confirmed egg allergy. We did not find that frequent baked egg ingestion was associated with change in the rate of decline in egg-white SPT compared with strict avoidance in egg-allergic children. Our findings suggest that children with egg allergy who are tolerant to baked egg can continue to incorporate such foods into their diet, allowing improved quality-of-life without detrimentally influencing the rate of resolution of egg sensitization, and by inference egg tolerance. In contrast to recent studies [14, 18], we did not find that frequent baked egg ingestion was associated with an increased rate of resolution of egg sensitization.

The strength of our study lies in the homogeneity of study participants at study entry, as only children with the strictest definition of IgE-mediated egg-white allergy, i.e. those with a positive immediate allergic reaction during a hospital-based open raw egg-white challenge along with a recently positive egg SPT, were selected. We were stringent in not including children who only had a positive SPT without a history of reaction to egg to avoid including children who may not have egg allergy – this was especially important given that we were using SPT as a surrogate marker for acquisition of tolerance. Furthermore, frequency of egg ingestion was carefully determined via a clinician-administered telephone

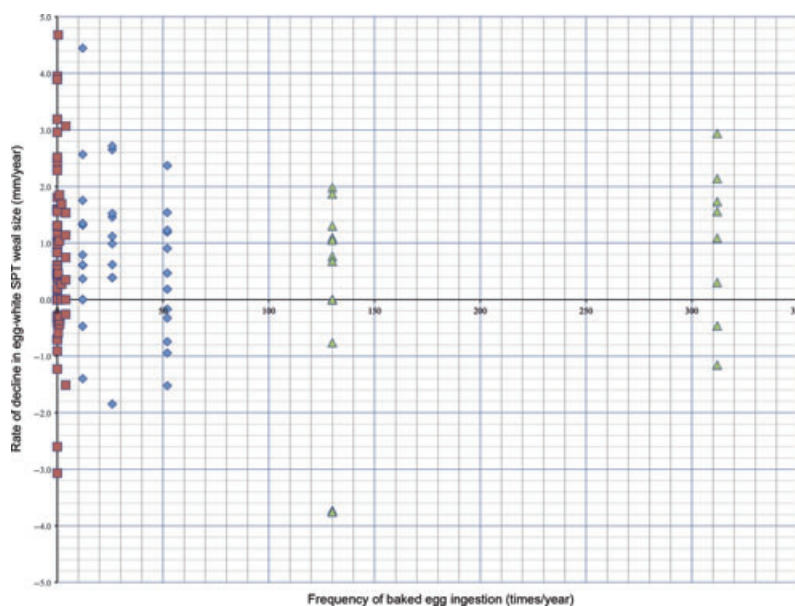


Fig. 2. Frequency of baked egg ingestion and rate of decline in egg-white SPT weal size. ■ Strict avoidance of baked egg. ◆ Regular ingestion of baked egg. ▲ Frequent ingestion of baked egg.

questionnaire with the parent. The study design enabled us to directly compare participants who strictly avoided all forms of egg, to those who frequently ingested baked egg in their diet.

A number of caveats can be considered. This study did not establish, and hence was not able to adjust for the potential confounder of, whether study participants were already ingesting baked egg at study baseline. However, physician or parent/patient self selection to ingest baked egg due to a previous ability to tolerate such foods would be expected to result in a faster rate of resolution of egg SPT size in those participants frequently ingesting baked egg, which was not observed. Although the frequency of ingestion of 'egg within cake and biscuits' was determined, the volume of baked egg ingested on each occasion was not precisely quantified. It is important to note that the retrospective nature of our study, including the administration of a questionnaire many years after the period of egg avoidance (mean 8.4 years, standard deviation 3.0 years), may have potentially resulted in non-differential misclassification of frequency of egg ingestion due to parental recall error. This non-differential misclassification may have contributed to the null results that we observed in the study. However, we consider that parents of children with food allergy are, in fact, highly observant of their child's diet and hence likely to be relatively precise in their recollection of degree of baked egg avoidance. Further, participants with an inconsistent approach to dietary avoidance were excluded, thus minimizing the potential for non-differential misclassification.

Like previous investigators, our study utilized the rate of change in egg SPT weal size as a surrogate biomarker for tolerance [20]. Although an oral food challenge represents the definitive approach to demonstrate persistent allergy or tolerance acquisition [19], it cannot be performed repeatedly over time to monitor for acquisition of tolerance; moreover, it does not allow quantitative tracking of allergy status or acquisition of tolerance. Further, although SPT does not always accurately predict allergy or tolerance when performed for the purpose of making a diagnosis of food allergy, in subjects with challenge-proven allergy (as in this study), SPT size can be used as a surrogate biomarker for acquisition of tolerance, with decline in SPT weal size indicating reduced allergen-specific Th2 responses and presumed increase in allergen-specific Th1 and Treg responses. Indeed, SPT weal size is commonly used by practitioners in the clinical setting to track the progress of tolerance acquisition [20–22].

In the study by Allen *et al.* [10], food challenges were not conducted routinely for all egg-allergic children by defined selection criteria, and there is likely to have been significant selection bias for performing a food

challenge, with physicians being more likely to request an oral food challenge in study participants who were considered likely to have outgrown their egg allergy. This may have contributed towards the null results reported [10]. To address this, we directly assessed the relationship between frequency of baked egg ingestion and change in SPT size in children with egg allergy confirmed by food challenge and found no adverse or beneficial effects. Recent observations have suggested that ingestion of baked egg may hasten the development of tolerance to egg: Lemon-Mule *et al.* [14] noted immunological changes in children who regularly consumed baked egg which paralleled changes associated with acquisition of clinical tolerance, and Konstantinou *et al.* [18] reported that the majority of children placed on an egg oral immunotherapy programme passed an oral food challenge to egg. In these studies, the relationship between frequency of egg ingestion and change in immune parameters or development of tolerance was not directly assessed. Furthermore, both studies did not include a control group of children not ingesting egg, so it is not possible to determine if the observations from these studies were a result of the natural history of egg allergy or due to regular baked egg consumption. The heterogeneity of study populations, with egg allergy variably defined by positive oral food challenge, positive egg SPT or serum-specific IgE, may also have led to inclusion of participants who were egg sensitized but not allergic, which would exaggerate the observation that egg-allergic patients who regularly ingested baked egg achieved more rapid immune tolerance. Our finding that regular or frequent ingestion of baked egg was not associated with more rapid resolution of egg SPT size may relate to a lower dose or inconsistent timing of egg protein intake (as compared to the dosing applied in oral immunotherapy protocols) that fails to induce significant immunomodulatory effects, or may indicate that frequent ingestion of baked egg is in fact not associated with more rapid acquisition of tolerance.

While intuitively one might have expected a physician's recommendation for strict egg avoidance to be influenced by the presence of past egg anaphylaxis, this was not observed in our study or in the study by Allen *et al.* [10]. Instead, physicians were more likely to recommend strict egg avoidance if there was a history of eczema, or co-existing allergy or sensitization to cow's milk. Cow's milk allergy usually presents in infancy when other complementary foods (including baked egg) have not yet been introduced, which may have influenced the decision by physicians to recommend strict avoidance. The frequent association of egg sensitization/allergy and eczema, and the common assumption that ingestion of even small amounts of egg in this setting can exacerbate eczema [23], may have contributed to physicians recommending strict

avoidance in children with eczema. Nevertheless, adjustment for both of these factors did not modify our findings regarding the relationship between frequency of egg ingestion and the rate of decline in egg SPT weal size. Furthermore, rates of IgE-mediated allergic reactions were not higher amongst children with either allergy or sensitization to cow's milk or eczema.

Adherence to specialist recommendation for either strict egg avoidance or inclusion of baked egg was high in our study (84%), suggesting that a change in clinical practice would be followed by the majority of patients. Interestingly, adherence to specialist advice was slightly lower in the study by Allen *et al.* (68%) [10], which may have been related to the heterogeneity of egg-allergic participants in their study, as asymptomatic egg-sensitized children may be more likely to go against a recommendation to avoid egg strictly.

An interesting observation in our study was that the rate of allergic reactions resulting from accidental exposure was higher amongst those study participants strictly avoiding egg (38%) as compared with those regularly or frequently ingesting egg (8% and 0%, $p = 0.001$). Given that the proportion of participants with past egg anaphylaxis was similar across the three groups, this suggests that regular or frequent ingestion of egg may induce desensitization to egg and hence protect against allergic reactions associated with accidental ingestion [14, 24], although we note that such intake was insufficient to modify SPT size, and by inference, egg-specific IgE levels. One caveat to this hypothesis is that we were not able to adjust for reverse causation, study participants who have had an IgE-mediated allergic reaction to baked egg prior to study entry would have potentially self-selected themselves into the strict-avoidance group. Importantly two patients (3%) developed anaphylaxis when baked egg was consumed, highlighting that introduction of baked egg into the diet of egg-allergic children who have not previously ingested small amounts of egg in baked goods should be undertaken under supervision of an allergy specialist.

In conclusion, we did not find that frequent baked egg ingestion was associated with a different rate of decline in egg SPT weal size, when compared with strict dietary avoidance. Given these findings, and the understanding that dietary restrictions can adversely

impact on the family, it is reasonable to consider liberalizing baked egg in the diet of egg-allergic children as this would improve the quality-of-life for both the child and their family. There are two important caveats to this suggested approach: first, that liberalization of baked egg can only be applied to egg within baked goods (not to whole egg foods such as quiche or foods containing less well-cooked egg) and second, that the ability to tolerate baked egg should firstly be established via history or food challenge under specialist supervision. Randomized controlled trials are required to confirm our findings.

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Author Contributions

MT conceived and designed the study, designed data collection tools, monitored data collection, drafted and revised the manuscript. She is the guarantor. DT contributed to study design, designed data collection tools, collected data, cleaned and analysed the data, and drafted and revised the manuscript. SD contributed to study design, analysed the data, and contributed to drafting and revision of the manuscript. MR contributed to study design, contributed to design of data collection tools, collected data and contributed to manuscript revision. KA contributed to study design and to revision of the manuscript. LG contributed to data analysis and to revision of the manuscript.

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