

ORIGINAL ARTICLE

ANAPHYLAXIS

Outcome of oral food challenges in children in relation to symptom-eliciting allergen dose and allergen-specific IgE

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Abstract

Background: Oral food challenge (FC) protocols are discussed with reference to starting doses, dose increments, safety, and predictability of results. The aim of this study was to evaluate the relation of eliciting allergen doses, specific IgE levels and predictive factors to the outcome of FCs in children.

Methods: In 869 children (median age 1.2 years), FCs were performed with cow's milk ($n = 633$), hen's egg ($n = 456$), wheat ($n = 265$) and/or soy ($n = 317$) starting at 3–5 mg of protein. Each of the seven doses was administered every 30 min using semi-log increases. Severity of symptoms was graded from I to V. IgE was determined prior to challenges.

Results: Of the children allergic to egg or milk, 9% and 10%, respectively, experienced reactions already at the first dose. Of these, 14% (egg) and 4% (milk) experienced grade IV reactions. In contrast, few children reacted to the first doses of wheat or soy, and most reactions occurred after the maximum dose. For all allergens, grade V reactions did not occur. However, grade IV reactions were seen at all eliciting doses. Elevated specific IgE level, young age and a history of atopic dermatitis were associated with a positive challenge outcome for milk or egg, and also IgE levels were associated with lower eliciting allergen doses and more severe symptoms.

Conclusion: Oral FCs bear a risk of severe reactions at all dose levels. Doses of 3–5 mg protein induced symptoms in up to 10% of children allergic to milk or egg. However, food-specific IgE levels are of limited clinical value for the estimation of FC reactions.

Oral food challenges (FC) are the gold standard in the diagnostic workup of food-related symptoms. Although standardization of FC tests has been attempted for many years (1, 2), various protocols are still used throughout the world, with a wide range of time intervals, incrementing steps and allergen amounts as the starting dose (3–5). Several investigators have correlated food-specific serum immunoglobulin E (IgE) or skin prick test results with the outcome of FC tests to generate probability curves depicting the likelihood of patients reacting to a specific food (6–11). However, as the established

diagnostic decision points differ considerably, it seems that they apply only to the specific patient population under investigation and rarely allow omission of oral FCs.

Limited data exist on the relation of the level of sensitization to the severity of FC reactions (12–18). To our knowledge, only two small studies on peanut-allergic patients analyzed the impact of the allergen amount on the severity of reactions during the challenge (19, 20). Moreover, few data exist on the minimal eliciting dose of food-allergic reactions, which are important to define threshold levels for the food industry. The aim of this study was to evaluate the relation of symptom-eliciting allergen doses and specific IgE levels to severity of symptoms during FCs with cow's milk, hen's egg, wheat, or soy in children and of possible predictors of the challenge outcome.

Abbreviations

DBPCFC double-blind, placebo-controlled food challenge; FC food challenge; GI gastrointestinal; IgE immunoglobulin E; vs versus.

Methods

Patients

The study population consists of children referred consecutively to the Department of Pediatric Pneumology and Immunology at Children's Hospital Charité, Berlin, Germany, for the evaluation of suspected food allergy to cow's milk, hen's egg, wheat, or soy. Indication to perform FCs was based on patients' history (e.g. worsening of atopic dermatitis (21), urticaria, vomiting in conjunction with consumption of the respective food or atopic dermatitis in conjunction with food-specific IgE without prior consumption of the relevant food). The study was approved by the local institutional review board.

Oral food challenges

Oral FCs were performed according to a protocol published earlier (1). Briefly, seven increasing doses were administered at 30-min intervals using a semi-log scale, for example 0.1, 0.3, 1, 3, 10, 30, and 100 ml of fresh pasteurized cow's milk (3.5% fat; 3 mg to 3.3 g protein). Further, we used 0.1–100.0 ml Alpro soy milk (4 mg to 3.6 g protein); wheat/gluten powder (Kroener, Ibbenbueren, Germany, 3 mg to 2.8 g protein); and pasteurized hen's egg (5 mg to 4.6 g protein).

The severity of clinical symptoms was graded following a five-level grading system of food-induced anaphylaxis (22, 23). However, we rated diarrhea as comparable in severity to repetitive vomiting (severity grade III, not IV).

Grade I: skin symptoms: localized pruritus, flushing, urticaria, angioedema; *gastrointestinal (GI) tract symptoms:* oral pruritus, oral 'tingling,' mild lip swelling; no respiratory, cardiovascular or neurological symptoms.

Grade II: skin symptoms: generalized pruritus, flushing, urticaria, angioedema; *GI tract symptoms:* any of the above and/or nausea or a single episode of emesis; *respiratory symptoms:* nasal congestion and/or sneezing; no cardiovascular symptoms.

Grade III: skin symptoms: any of the above; *GI tract symptoms:* any of the above plus repetitive vomiting or diarrhea; *respiratory symptoms:* rhinorrhea, marked congestion, sensation of throat pruritus or tightness; *cardiovascular symptoms:* tachycardia (increase: 15 beats/min).

Grade IV: skin symptoms: any of the above; *GI tract:* any of the above; *respiratory symptoms:* any of the above plus hoarseness, 'barky' cough, difficulty swallowing, dyspnea, wheezing, cyanosis; *cardiovascular symptoms:* any of the above plus dysrhythmia and/or mild hypotension.

Grade V: skin symptoms: any of the above; *GI tract symptoms:* any of the above, loss of bowel control; *respiratory symptoms:* any of the above, respiratory arrest; *cardiovascular symptoms:* severe bradycardia and/or hypotension or cardiac arrest, loss of consciousness.

Determination of specific IgE antibodies

Blood was drawn prior to the FC. Patient serum was analyzed for specific IgE to cow's milk, hen's egg, wheat, and

soy, using the Immuno-CAP-System FEIA® (Phadia, Uppsala, Sweden; lower detection limit <0.35 kU/l). For levels >100 kU/l, the serum was diluted to acquire exact levels.

Statistics

For the statistical analysis, we used SAS 9.2 (SAS Institute Inc, Cary, NC, USA). Only children with complete data for symptom severity and the last dose step were included. Logistic regression models were used for the prediction of challenge positivity, symptom severity ($\geq$ grade II), and dose step (reaction before last dose). The models included adjustment for age (<1 vs $\geq$ 1 year), specific IgE (<0.35 vs $\geq$ 0.35 kU/l and <0.7 vs $\geq$ 0.7 kU/l), history of atopic dermatitis or wheeze, family history of allergic diseases, and dose step/symptom severity during the FC.

Results

We performed 1671 oral FCs with cow's milk, hen's egg, wheat, or soy in 869 children (Table 1). For all allergens, objective symptoms occurred at all dose steps (Fig. 1A). With milk and egg, 10% and 9% of patients, respectively, showed an objective clinical reaction already at 3–5 mg given as the first dose. In FCs with wheat or soy, the majority of patients had objective symptoms only after the final dose.

Allergen amount and symptom severity

In FCs with milk or egg, the whole spectrum of clinical reactions, with the exception of fatal or near-fatal symptoms (grade V), was seen at every given allergen amount (Fig. 1B, Table 2). Importantly, in milk- and egg-allergic children reacting to the first dose, grade IV reactions (most often dyspnea or wheezing) were seen in 4% and 14% of these children, respectively. Also for wheat, a large proportion (67%) experienced grade III reactions at the first dose. Only children with FC with soy had few more severe reactions at larger doses.

Food-specific IgE

Patients undergoing FCs had allergen-specific IgE levels of <0.35 to 872 kU/l (Table 1). We found increasing specific IgE levels with increasing severity of reactions to FC with milk, egg, and wheat (Fig. 2). In contrast, there was no relation of specific IgE levels to the eliciting allergen doses for milk and egg (Fig. 3).

Prediction of challenge outcomes

Elevated specific IgE levels (above 0.35 kU/l) were associated with a positive outcome of FCs to milk and egg (OR 4.6 [3.5–8.9] and 14.9 [7.4–30.2]), but only moderately to wheat and soy (Fig. 4A). In FC with milk and egg, an elevated IgE level had a weak association with more severe symptoms ($\geq$ grade II; Fig. 4B) and with reactions before the final dose step (OR 3.4 [1.5–7.6] and 9.7 [2.7–34.6] (Fig. 4C).

Table 1 Patient characteristics, type, and result of food challenges

		Cow's milk		Hen's egg		Wheat		Soy	
Number of oral food challenges		<i>n</i> = 633		<i>n</i> = 456		<i>n</i> = 265		<i>n</i> = 317	
Age (years)	median (min–max)	1.0	(0.2–16.2)	1.6	(0.3–14.9)	1.4	(0.1–16.0)	1.1	(0.3–16.1)
Specific IgE (kU/l)	% sIgE <0.35 kU/l	31.3		17.2		27.4		41.7	
	% sIgE 0.35–0.69 kU/l	11.6		8.0		7.5		8.3	
	% sIgE 0.70–3.49 kU/l	22.8		27.0		23.9		24.6	
	% sIgE 3.5–17.49 kU/l	18.4		33.7		21.7		15.5	
	% sIgE 17.5–49.99 kU/l	9.0		9.8		10.6		6.1	
	% sIgE 50–100 kU/l	4.2		3.3		7.5		2.3	
	% sIgE >100 kU/l	2.6		1.0		1.3		1.5	
History of atopic dermatitis	<i>n</i> (%)	557	(88)	410	(91)	229	(87)	296	(94)
History of wheeze	<i>n</i> (%)	94	(15)	91	(20)	48	(18)	58	(18)
History of allergic rhino-conjunctivitis	<i>n</i> (%)	48	(8)	47	(10)	18	(7)	24	(8)
DBPCFC	<i>n</i> (%)	458	(73)	310	(68)	212	(80)	213	(68)
Positive food challenge	<i>n</i> (%)	305	(48)	313	(69)	88	(33)	51	(16)

DBPCFC, double-blind placebo-controlled food challenge.

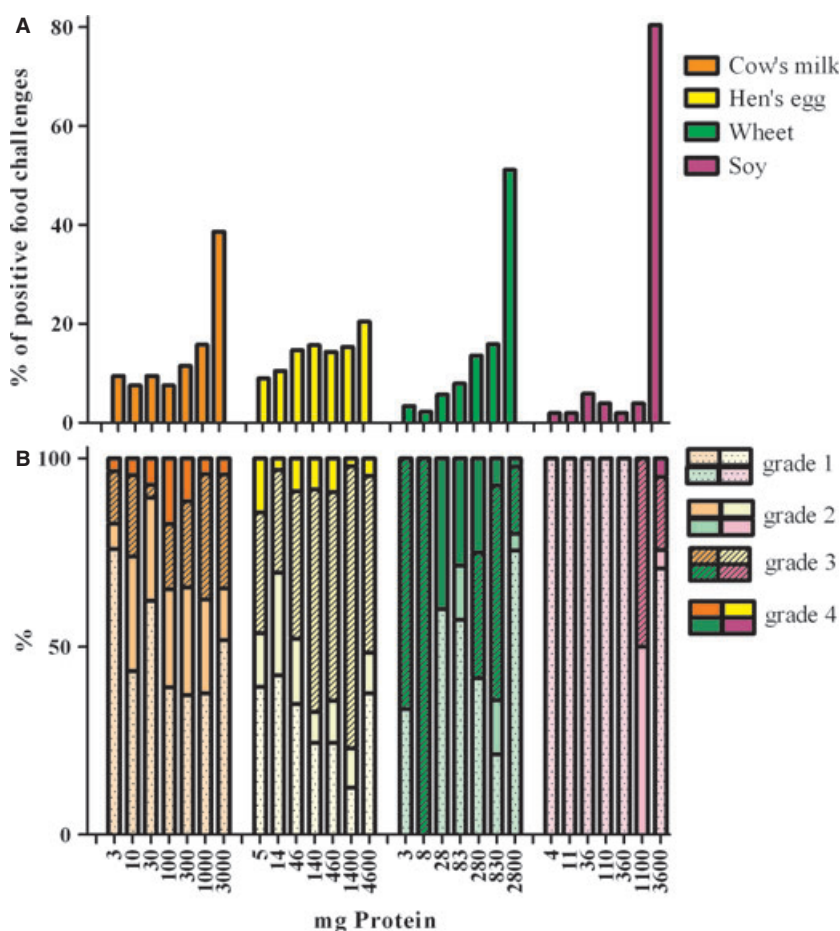
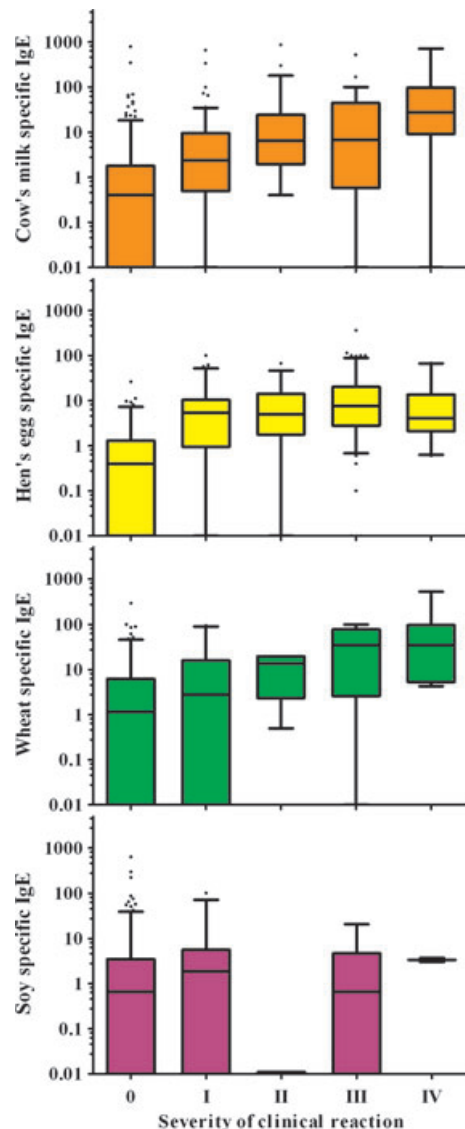
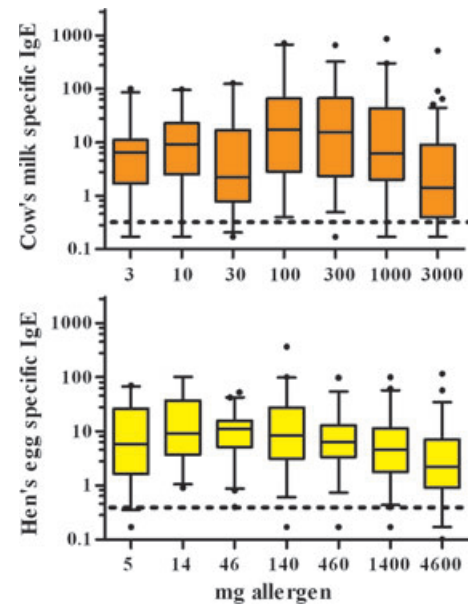

Figure 1 (A) Distribution of positive food challenges to seven allergen dose steps (approximately 3 mg to 5 g protein). (B) Distribution of severity of clinical reactions by dose steps.

Table 2 Severity of clinical reactions

	Cow's milk		Hen's egg		Wheat		Soy	
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)
Grade I	150	(49)	94	(30)	50	(57)	37	(73)
Grade II	61	(20)	42	(13)	5	(6)	3	(6)
Grade III	75	(25)	156	(50)	24	(27)	9	(18)
Grade IV	19	(6)	21	(7)	9	(10)	2	(4)

**Figure 2** Serum-specific immunoglobulin E levels by severity of clinical reactions to oral food challenges. Grade 0: no reaction, I mild skin symptoms; II general skin symptoms; III gastrointestinal symptoms; IV respiratory symptoms; and V not seen: anaphylactic shock (median: —, 5–95th percentile ⊥).

Young age (<1 year) was a predictor for a positive outcome of FCs only with milk or egg, but was less common with more severe symptoms (Fig. 4A,B). Patient's age and

**Figure 3** Serum-specific immunoglobulin E levels by dose step at first symptom (approximately 3 mg to 5 g protein, median: —, 5–95th percentile ⊥).

the eliciting allergen doses were not related (Fig. 4C). Atopic dermatitis was recorded more often in children with a positive FC with milk or egg, but in milk challenges, these children usually had milder symptoms. A history of wheezing or a positive family history for atopic dermatitis, asthma, or allergic rhino-conjunctivitis was not related to any outcome assessed.

Discussion

Analyzing 1671 oral FCs with cow's milk, hen's egg, wheat, or soy, severe reactions were observed at every dose step. Elevated food-specific serum IgE levels were associated with a positive outcome of FCs. In children allergic to milk or egg, elevated specific IgE levels were further indicative for reactions to lower allergen amounts and, weakly, also for more severe symptoms. Furthermore, in these children, a history of atopic dermatitis was indicative of a positive challenge outcome, however associated with milder symptoms.

At every dose step during FCs for all applied allergens, we found children with clinical reactions. In our protocol, starting with 3–5 mg of food protein, almost every tenth patient reacted already to the first allergen dose of milk or egg. The percentage of patients reacting to the first dose in other studies vary according to the allergen used and the applied amount of protein. In the literature, protocols for oral FCs differ with respect to the starting dose (12, 24). For example, in milk and egg challenges, protein doses of 0.2–200 mg have been used (3). Based on a review of published FC studies, 1% of patients with milk allergy were estimated to react at 8.6 mg of protein (egg: 3.4 mg, soy 2.2 mg) (24). In our study, 10% of patients reacted to a dose of 3 mg milk

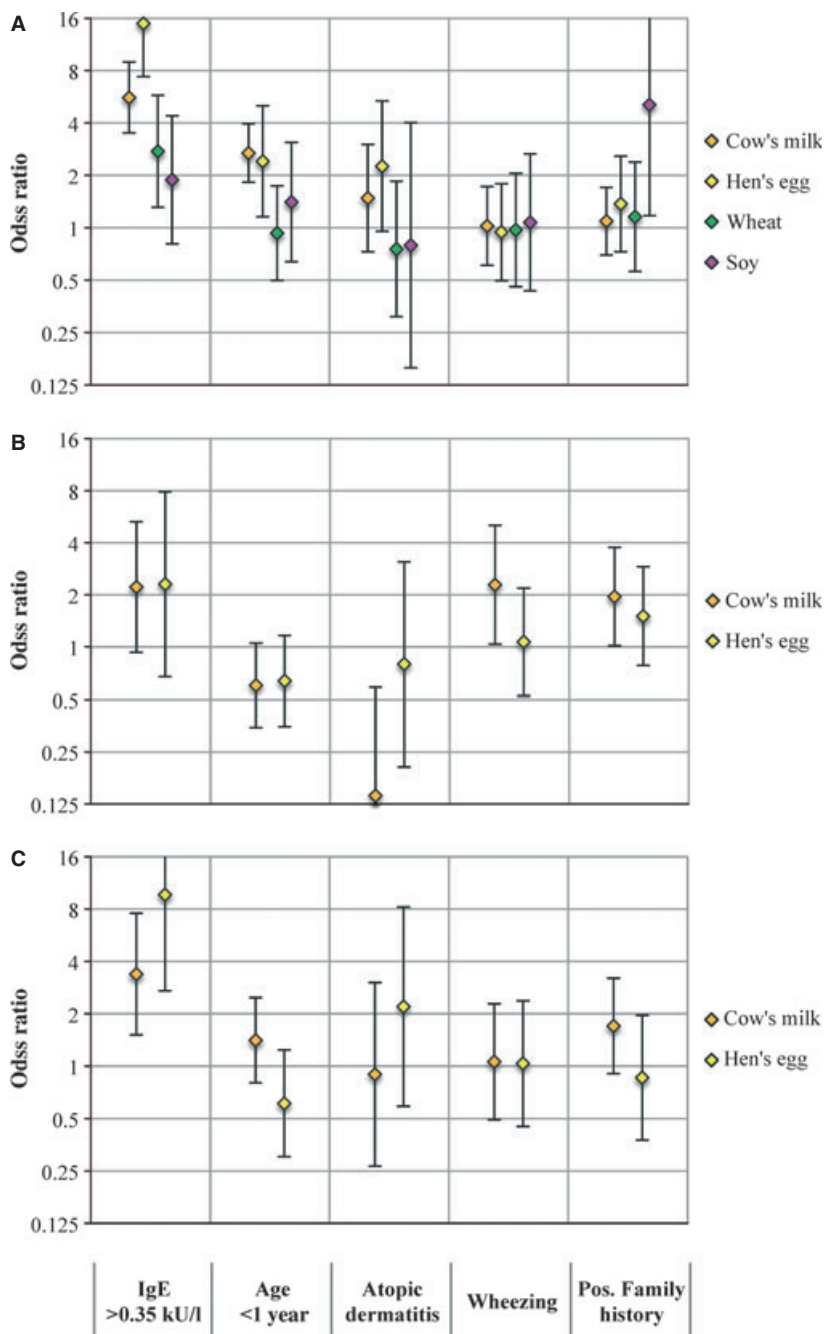


Figure 4 Association between anamnestic parameters and challenge outcomes. Odds ratio and 95% confidence intervals based on logistic regression model including mutual adjustment for all shown factors, stratified by food item. (A) Prediction of food challenge posi-

tivity. (B) Prediction of symptom severity (grades II–IV) in positive food challenges. (C) Prediction of early reaction (dose steps 1–6 of 7) in positive food challenges. Models B and C could not be applied to wheat or soy food challenge results owing to lower patient numbers.

protein and 9% to 5 mg of egg. This discrepancy might be explained by different allergen preparations applied (3) or by incomparable age. In keeping with the above-mentioned review (24), 2% of our patients reacted to 4 mg of soy.

We observed severe reactions during FC with milk, egg, and wheat already at the first allergen doses given, and further,

more severe reactions to FCs with these allergens were not related to higher allergen doses. The literature on peanut-allergic patients is contradictory to this point (19, 20). Proposed starting doses in the position paper of the European Academy of Allergology and Clinical Immunology were 3 mg protein for milk, 1 mg for egg, 100 mg for wheat, and 1 mg for soy

(2). From our data, we conclude that with starting doses of 3–5 mg for milk or egg, 0.5–1% of patients are still at risk of severe reactions at the first dose. For wheat, 100 mg protein (2) seems too high, and with regard to the high proportion of severe symptoms in our protocol, we propose the same dose as above. For soy, 100 mg would have been safe enough to make the diagnosis without inducing severe reactions.

Several authors have reported on the association between food-specific IgE levels and the outcome of FCs and have tried to establish cutoff values that have a predictive value for a positive FC outcome (6, 7, 9–11). However, the cutoffs differ for the allergens used and for different populations. We also found an association between elevated food-specific serum IgE levels and FC positivity for all four allergens, confirming that clinical food allergy is much more likely in children with documented sensitization.

Only few conflicting data exist on the relation of food-specific IgE levels to the severity of clinical reactions during FC or to the dose relation during FCs. In our statistical model, elevated IgE levels for milk or egg were indicative for reactions to lower allergen amounts. Sicherer reported that food-specific IgE did not correlate well with the dose causing a reaction or with severity; however, a large number of patients (49%) had responded to a rather large amount of allergen at the first dose, so that this might affect the correlation. Further, different allergens were used, and we saw this effect only in milk and egg allergy (12). Concerning specific IgE and the FC threshold level in egg-allergic children, one study did not find a significant relation, although specific IgE correlated with a positive outcome (10). In line with our data, in peanut-allergic children, an inverse relation of specific IgE levels to the eliciting allergen dose was found (17). The different information on this association may result from differing FC protocols and varying statistical approaches.

The multivariate analysis of our data further showed a weak association of specific IgE levels with more severe symptoms during the FCs with milk or egg. In one study on milk-allergic children, no differences between specific IgE values of those with skin, respiratory, or gastrointestinal symptoms were found; however, the symptoms were not categorized to allow the assessment of severity (13). In line with our findings in peanut-allergic patients, specific IgE levels correlated with an outcome score combining symptom severity and allergen doses (14). With respect to the clinical relevance, however, we regard IgE levels of limited help because the associations are weak; the overlap between the values in the subgroups is wide, and therefore, individual prognostic evaluations are difficult.

A positive challenge outcome with milk or egg was related to a younger age. To our knowledge, there is only one recent study investigating the association between age and eliciting doses in peanut-allergic children, showing an inverse association between age and allergen doses (17). However, in our study, young age was rather related to less severe symptoms. Therefore, we do not consider a risk-adapted FC protocol necessary for this group.

A clinical history of atopic dermatitis, but not of wheezing, was related to a positive outcome in FC with milk or egg, however not with wheat or soy. Children with a history of

atopic dermatitis had a higher risk to react to low-allergen-dose steps in FC with egg, but not with milk. More severe symptoms during the FC were associated also with a history of wheezing in milk-allergic children. Reasons for these associations might be that food-related symptoms during the FC occur earlier or more obviously in the affected skin, or more severely in children with bronchial hyperreactivity; however, this would also be the case for the other allergens. These findings should be further studied separately.

Our study comprises a large number of FCs and a broad range of allergen dose steps. Therefore, we were able to perform a multivariate analysis of the relation between key parameters of the FC outcome and between several confounders. A protocol testing seven allergen doses and increasing the dose every 30 min in a semi-logarithmic way in our opinion comprises a wide range of doses necessary to have good sensitivity but minimizes the risk of severe reactions all in a reasonable length of time. However, even with rather low allergen doses, we saw a relevant proportion of early reactions so these starting doses do not allow the analysis of *no observed adverse effect levels* (NOAELs), defined as the amount of the offending food that would not elicit any symptoms (2, 3, 25), which is important regarding the declaration of allergens by the food industry (26).

The retrospective analysis of our data set is limited by the fact that the population is not completely homogenous. Different indications were accepted: Most patients with milk challenges had been tested because of positive reactions in the history, whereas regarding other allergens, the patients were often tested for the exclusion of allergy (e.g. soy challenges in case of milk allergy). No data on the severity or time point of prior food reactions had been collected, so that some patients might have already lost some of the clinical relevance of their allergy but still have elevated IgE levels, which might affect the statistical results.

In conclusion, oral FCs bear a risk of severe reactions at all dose levels including initial reactions at low doses. Adding to threshold-level discussions, doses of 3–5 mg protein induced symptoms in up to 10% of children allergic to either milk or egg; therefore, lower starting doses should be used to establish NOAELs or minimize anaphylactic reactions during FCs. Food-specific IgE levels and other predictors such as age and clinical history, although associated with some outcome parameters, are of limited value for the estimation of the individual outcome of FCs and seem to have little clinical relevance for the design of FC protocols.

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Author contributions

Claudia Rolinck-Werninghaus substantially contributed to the acquisition of data, analysis, and interpretation of data

and involved in drafting the article. Bodo Niggemann substantially contributed to the conception/design of the study and interpretation of data and involved in the critical revision of the article for important intellectual content. Linus Grabenhenrich substantially contributed to the analysis and interpretation of data and involved in the critical revision of the article for important intellectual content. Ulrich Wahn substantially contributed to the conception and design of the study and involved in the critical revision of the article for important intellectual content. Kirsten Beyer substantially contributed to the conception and design of the study, and acquisition and interpretation of data and involved in the

critical revision of the article for important intellectual content. All authors involved in the final approval of the version to be published.

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Conflict of interest

These statements are indicated separately on the ICMJE form.

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