



Safety and feasibility of heated egg yolk challenge for children with egg allergies

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Keywords

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Abstract

Background: Hen's egg allergy is a frequent cause of childhood food allergy. Egg yolk is used in various commonly consumed foods; if children with allergy to hen's egg could eat heated egg yolk, their quality of life (QOL) would improve. No reports exist regarding oral food challenges (OFCs) for heated egg yolk. We aimed to clarify whether pediatric patients allergic to hen's egg could consume heated egg yolk.

Methods: Data from pediatric patients who had undergone OFCs for heated egg yolk were evaluated retrospectively.

Results: Among 919 patients, positive OFC results were obtained in 17.0% of patients; seven presented with severe symptoms. Older age, high specific IgE value for ovomucoid, low total IgE levels, and history of anaphylaxis related to food other than hen's egg were risk factors for positive OFC results. Specific IgE values for egg white, ovomucoid, and egg yolk, indicative of a negative predictive value >95%, were 0.71, 0.41, and 0.17 kU_A/l, respectively. A specific IgE to ovomucoid levels of 100 kU_A/l predicted heated egg yolk-positive OFCs for 38.3% of patients. Among 763 patients with a negative OFC, seven (0.9%) reacted to heated egg yolk at home, and 756 (99.1%) consumed hen's egg yolk safely.

Conclusions: Most pediatric patients allergic to heated hen's egg safely consumed heated egg yolk. Heated egg yolk OFCs rarely provoked severe symptoms and may be recommended for improving the QOL of children with allergy to hen's egg.

Hen's egg is among the most frequent causes of IgE-mediated food allergy in childhood (1–3). The estimated prevalence of egg allergy is approximately 2% among infants in Western countries (4–6), although most patients naturally acquire tolerance to eggs (1, 2, 7).

Egg yolk is a binder used to make many foods (8). Although most patients allergic to raw eggs can consume heated whole eggs (9), patients reactive to heated whole egg, including various threshold doses (10), are generally instructed to completely eliminate eggs from their diets (6). Egg white is the major allergen in hen's egg (8); egg yolks are less allergenic than egg whites (11). Egg whites and yolks have shown cross-reactivity *in vitro* (12); nevertheless, clinical cross-reactivity is unknown.

The oral food challenge (OFC) test is the gold standard for diagnosing and confirming acquired tolerance to food allergies (5, 13, 14). Although there are some reports about hen's egg OFCs (15–17), there is limited knowledge about egg yolk OFCs (18), and no reports regarding heated egg yolk OFC.

The quality of life (QOL) of patients with egg allergies and their guardians is poor regarding meal selection, risk of reaction, and prognosis (19, 20). If small amounts of egg (e.g., in breads, cookies, and seasonings) could be ingested, QOL may improve (21). Moreover, if accidental exposure to small amounts of egg products caused no symptoms, fear of severe symptoms upon accidental ingestion would decrease. The aim of this study was to clarify whether pediatric patients who reacted to heated whole egg could safely consume heated egg yolk.

Methods

Study participants

This study retrospectively evaluated data from patients who had conclusive OFC results for heated egg yolk, documented in clinical records at the Department of Pediatrics at the National Hospital Organization Sagamihara National Hospital between

March 2008 and March 2013. Data were analyzed between 2014 and 2015.

Inclusion/exclusion criteria

Patients with a history of immediate reaction to heated hen's egg were enrolled (Fig. 1). The following specific IgE (sIgE) titers (Immuno CAP™; Thermo Fisher Scientific/Phadia, Uppsala, Sweden) were measured within 6 months of OFC: sIgE to egg white, ovomucoid, and egg yolk. OFCs were not performed for patients with comorbid symptoms, such as severe eczema or respiratory symptoms, which would affect the determination of OFC results (3). We excluded patients whose laboratory or clinical data were missing. Moreover, we excluded patients with a previous positive heated egg yolk OFC to avoid bias from a second positive result in these patients. Histories of anaphylaxis were not established as an exclusion criterion, nor were any exclusion criteria established considering the sIgE antibody titers to the above antigens. Anaphylaxis, defined as decreased blood pressure or severe multi-organ symptoms, is described in the World Allergy Organization's Anaphylaxis Guidelines (22). Patients without a clinical history of allergic reaction to whole hen's egg were excluded because we could not assess how they would actually react to whole hen's egg.

Materials for OFC

Challenge foods were uniformly prepared in the Nutrition Management Department of Sagami National Hospital under pre-established conditions (Table S1). For heated egg yolk OFC, cooked pumpkin cakes were provided; they were prepared using raw egg yolks that had been manually separated from whole eggs, and trace amounts of egg white were included with the egg yolks. The pumpkin cake was heated in a microwave oven (1000 W for 90 s; core temperature: 90°C). The pumpkin cake was evaluated for egg protein content (whole-egg protein including ovalbumin, ovotransferrin, and

ovomucoid) using the FASTKIT ELISA Version III Egg (NH Foods Ltd., Osaka, Japan). The measured egg protein totaled 213.2 mg (equal to 1/29 of one whole egg) (Table 1).

OFC testing method

Drugs that could potentially affect OFC results (3), such as antihistamines and leukotriene receptor antagonists, were discontinued 72 h before OFC. Three doses of pumpkin cake were administered using the 30-min interval method (23), starting from 1/8 of the total load, followed by 3/8 at 30 min, and 1/2 at 60 min. We observed the patients for at least 3 h after the final administration.

Positive criteria

Positive OFCs were determined based on the presence of induced symptoms (3). We assessed symptoms using the Anaphylaxis Guidelines of Japan (Table S2) (24). Objective symptoms were considered positive criteria. If mild subjective symptoms appeared, the patient was carefully observed to confirm that symptoms did not worsen, and the challenge was continued.

Treatment for induced symptoms

We administered appropriate treatment corresponding with symptom severity, including fluid resuscitation, oxygenation, antihistamines, steroids, β_2 stimulant inhalation, and adrenaline injections. We used intramuscular adrenaline injections for strong gastrointestinal symptoms, severe respiratory symptoms, hypotension, loss of consciousness, and cases where respiratory symptoms persisted after β_2 stimulant inhalation.

Instructions to patients with negative OFC results

Patients with negative heated egg yolk OFC results were instructed to eat foods containing a small amount of whole egg,

Figure 1 Patient eligibility criteria. This study excluded 1244 patients without a clinical history of allergic reaction to whole egg, 121 patients with a previous positive egg yolk oral food challenge (OFC), 70 patients with missing laboratory data, and 15 patients with missing clinical information regarding egg yolk OFC. Data from 919 patients with a clinical history of allergic reaction to heated whole egg were analyzed.

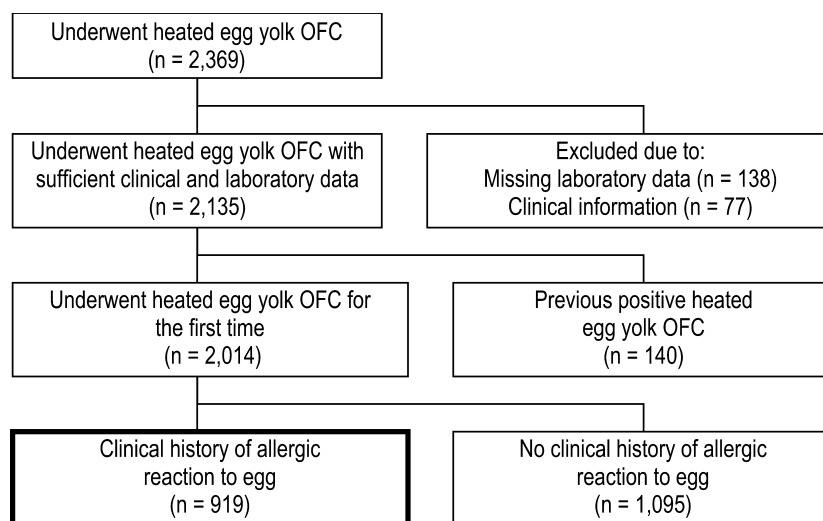


Table 1 Egg protein amounts

Form of challenge food	Egg protein
Raw egg (52.1 g)	6322.2 mg
Boiled whole egg (54.2 g)	6749.2 mg
Boiled one egg yolk (14 g)	7 mg
Pumpkin cake containing half of a whole egg (48.4 g)	3314.1 mg
Pumpkin cake containing one egg yolk (70 g) (in this study)	213.2 mg

The amount of egg protein was measured using the FASTKIT ver. III enzyme-linked immunosorbent assay egg kit from NH Foods Ltd (Osaka, Japan).

such as bread or hamburger, at home to confirm the negative OFC results. We allowed them to use one cooked egg yolk that had been manually separated from whole eggs; trace amounts of egg white were included with the yolk. We also provided the same recipe for pumpkin cake with egg yolk used in the OFC. Additionally, we allowed patients with negative OFC results to consume heated egg yolk or a trace amount of heated whole egg (equal to 1/60 whole egg, e.g., a seasoned powder for sprinkling over rice) with written instructions. Patients' reports on the amount of daily egg intake after OFC and whether they could safely consume heated egg yolk at home were collected by a doctor at first hospital visit within 1 month after negative OFC.

Statistical analyses

For statistical comparisons between two groups, we used the Mann-Whitney *U*-test or Fisher's exact test. Univariate and multivariate analyses were analyzed by logistic regression, and *p*-values <0.05 were considered statistically significant. Multivariate logistic regression analyses were performed with stepwise selection using the statistically significant variables from univariate analyses to obtain adjusted odd ratios. For variables to predict the probability of positive OFC, *p*-values <0.05 were considered statistically significant. We calculated probabilities for the outcome of OFC using the sIgE value in relation to egg white, ovomucoid, and egg yolk with logistic regression (25), and created fitted probability curves for positive OFCs. We also calculated receiver operating characteristic (ROC) curves for positive challenge and analyzed the area under the curve (AUC). In addition, we determined subdivided fitted probability curves for age. We calculated the 95% negative predictive sIgE value, at which approximately 95% of patients would be predicted to have a clinical reaction and the 95% negative predictive sIgE value, at which 95% of patients would be predicted to have no clinical reaction. SPSS 20.0 (IBM Corporation, Armonk, NY, USA) was used for all statistical analyses.

Ethical considerations

This study was approved by the Ethics Committee of Sagamihara National Hospital. Written informed consent for

OFC was obtained from all participants and parents prior to OFC. We used illustrated documents in explaining the procedure to children. Written informed consent for this study was obtained in the outpatient clinic after OFC. Details on this study were posted in the outpatient clinic and on the website of Sagamihara National Hospital.

Results

Study participants

We analyzed the records of 2369 patients who underwent heated egg yolk OFC (Fig. 1). We excluded 138 patients with missing laboratory data and 77 patients with missing clinical information. We excluded 140 patients with previous positive heated egg yolk OFC. We also excluded 1095 patients without a clinical history of allergic reaction to whole egg. Data from 919 patients with a clinical history of allergic reaction to heated whole egg were analyzed.

Baseline clinical characteristics

Median age was 3.2 years (Table 2). Past history of anaphylaxis to hen's egg was observed in 186 patients (20.2%). Atopic dermatitis was the most common allergic complication (47.8%). Table S3 displays the clinical characteristics of excluded participants with no clinical history of allergic reaction to egg (positive rate: 10.2%) or with a previous heated egg yolk OFC (positive rate: 31.4%).

Comparison of patient profiles and immunologic parameters for OFC

Oral food challenge results were positive for 17.0% of patients. Clinical backgrounds of patients in the positive and negative groups were compared (Table S4). In the OFC-positive group, patients were older and had a past history of anaphylactic

Table 2 Baseline clinical characteristics of study participants who received heated egg yolk oral food challenge

Characteristic	(n = 919)
Sex (male)	598 (65.1%)
Age (years)	3.2 (1.8–5.4)
History of anaphylaxis related to egg	186 (20.2%)
History of anaphylaxis related to other foods	308 (33.5%)
Atopic dermatitis, current	439 (47.8%)
Bronchial asthma, current	221 (24.0%)
Allergic rhinitis, current	84 (9.1%)
Total IgE (IU/ml)	334 (106–1040)
Specific IgE value for egg white (kU _A /l)	13.0 (4.9–31.2)
Specific IgE value for egg yolk (kU _A /l)	2.7 (0.9–6.8)
Specific IgE value for ovomucoid (kU _A /l)	6.9 (2.0–20.1)

IgE, immunoglobulin E.

Data are expressed as median (25th–75th percentile) or n (%), as appropriate.

reaction to hen's egg or other foods. Additionally, current asthma and allergic rhinitis were significantly more frequent in the OFC-positive group than in the OFC-negative group. Moreover, total IgE and sIgE levels related to egg white, ovomucoid, and egg yolk were significantly higher in the OFC-positive group than in the OFC-negative group.

Multivariate logistic regression analyses and probability curve

Results from multivariate logistic regression analyses are shown in Table 3. Among all significant variables in Table S4, multivariate analyses were adjusted by the statistically significant five predictors of positive OFCs: a history of anaphylaxis related to hen's egg, a history of anaphylaxis related to food other than hen's egg, bronchial asthma, allergic rhinitis, and age. Specific IgE values for ovomucoid, egg white, and egg yolk were significant factors in predicting positive OFC. Multivariate analyses found that total IgE values were not significant factors. ROC curves for positive challenges are shown in Fig. S1. AUC analysis indicated that sIgE value for ovomucoid was the most predictive variable (AUC: 0.702) (Fig. S1). When probabilities of the outcome were examined, the percentage of positive OFCs increased as sIgE values for egg white, ovomucoid, and egg yolk increased (Fig. 2). Subdivided fitted probability curves for age are presented in Fig. S2. Older age was associated with a higher probability of OFC failure in all probability curves (Fig. S2a–c). We also plotted fitted probability curves for excluded participants with no clinical history of allergic reaction to egg or with previous heated egg yolk OFC (Figs S3 and S4).

Table 3 Multivariate analysis for factors related to positive reaction to heated egg yolk

(n = 919)	Crude OR (95% CI)	p value	Adjusted OR (95% CI)	p value
History of anaphylaxis related to hen's egg	1.861 (1.260–2.748)	0.002		
History of anaphylaxis related to food other than hen's egg	1.795 (1.264–2.550)	0.001		
Bronchial asthma, current	1.822 (1.255–2.646)	0.002		
Allergic rhinitis, current	1.990 (1.190–3.326)	0.009		
Age (1-y increments)	1.143 (1.081–1.207)	<0.001		
Total IgE (10-fold increments)	1.771 (1.344–2.335)	<0.001	1.383 (0.996–1.921)	0.053
Specific IgE value for ovomucoid (10-fold increments)	2.812 (2.116–3.738)	<0.001	2.542 (1.902–3.398)	<0.001
Specific IgE value for egg white (10-fold increments)	2.889 (2.351–3.551)	<0.001	2.597 (1.847–3.652)	<0.001
Specific IgE value for egg yolk (10-fold increments)	2.940 (1.966–4.396)	<0.001	2.466 (1.612–3.773)	<0.001

IgE, immunoglobulin E; OR, odds ratio; CI, confidence interval.

All statistically significant variables from Table 1 are shown in Table 2. OR was adjusted by five statistically significant predictors of positive oral food challenges: History of anaphylaxis related to hen's egg, history of anaphylaxis related to food other than hen's egg, bronchial asthma, allergic rhinitis, and age.

Positive or negative results for OFC

We could not calculate the sIgE values for egg white, ovomucoid, and egg yolk at which approximately 95% of patients would be predicted to have a clinical reaction (26). The sIgE values predicting negative OFC results for 95% of patients were 0.71, 0.41, and 0.17 kU_A/l for egg white, ovomucoid, and egg yolk, respectively (Fig 2, Table S5). If the sIgE value for ovomucoid was 100 kU_A/l, the predicted rate of positive OFC was 38.3% (Fig 2). Fig S2b shows that a predicted 17% of patients aged ≤3 years would have a positive OFC if they had an ovomucoid sIgE value of 100 kU_A/l.

Symptoms and treatment during OFC

We analyzed induced symptoms and symptom severity during the OFC. Gastrointestinal symptoms were the most frequently reported, followed by skin, respiratory, and cardiovascular or neurologic symptoms (Table 4). Anaphylactic symptoms were observed in 33 patients, with 26 having limited, moderate symptoms. Severe symptoms were observed in seven patients, and no patients developed decreased blood pressure, including shock. Among the seven patients with severe symptoms, one had continuous cramps and emesis, one had a barking cough, one had throat tightness, and four had a persistent cough. A moderate cardiovascular symptom observed during OFC was facial pallor with normal blood pressure and heart rate. Multivariate analysis for factors related to anaphylactic reaction during OFC is shown in Table S6. Specific IgE values

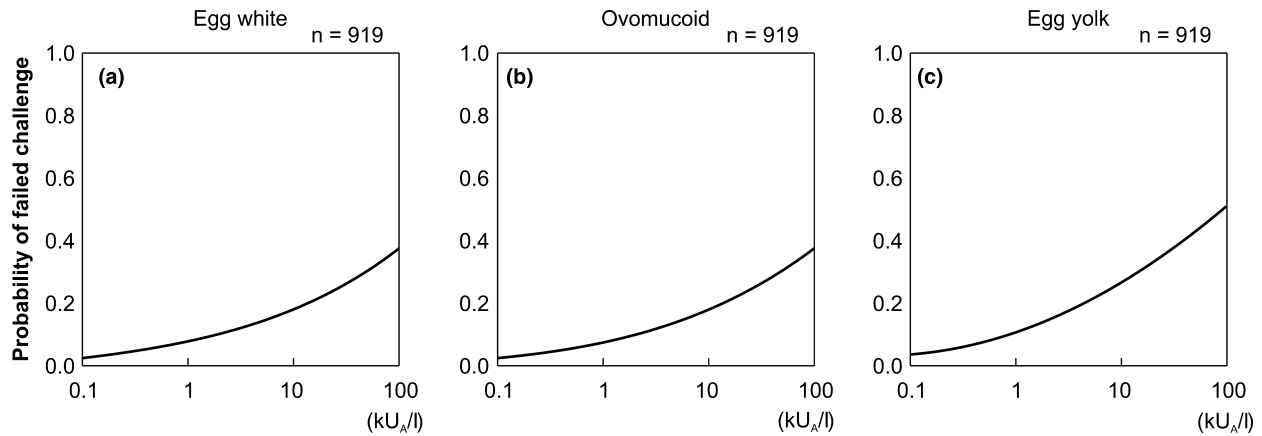


Figure 2 Fitted predicted probability curves for the positive outcome to an oral food challenge (OFC) at a given ovomucoid-specific IgE value (a), egg white-specific IgE value (b), and egg yolk-specific IgE value (c) for heated egg yolk. Probabilities for the outcome of OFC for egg white, ovomucoid, and egg yolk serum IgE levels were calculated using logistic regression. The percentage of positive OFC increased as egg white-, ovomucoid-, and egg yolk-specific serum IgE levels increased. The specific IgE (sIgE) values predicting negative OFC results for 95% of patients were 1.2, 0.34, and 0.17 kU_A/l for egg white, ovomucoid, and egg yolk, respectively. The median age of participants in this study was 3.2 (interquartile range, 1.8–5.4) years.

Table 4 Clinical reactions and treatment in positive egg yolk oral food challenges (n = 156)

Symptoms	n (%)
Gastrointestinal	94 (60.3%)
Skin	83 (53.2%)
Respiratory	60 (38.5%)
Cardiovascular	1 (0.6%)
Neurologic	1 (0.6%)
Anaphylaxis	33 (21.2%)
Severity	
Grade 1 (mild)	65 (41.7%)
Grade 2 (moderate)	84 (53.8%)
Grade 3 (severe)	7 (4.5%)
Treatment	
Antihistamine	61 (39.1%)
β ₂ stimulant inhalation	35 (22.4%)
Steroid	27 (17.3%)
Adrenaline	7 (4.5%)
Any treatment	74 (47.4%)

Data are expressed as n (%). Severity was defined by grading the symptoms as described in Table S2. Both oral and parenteral treatments with antihistamines and steroids have been included.

for ovomucoid and egg white were risk factors related to anaphylactic reaction during OFC.

Drugs were administered to 82 (52.6%) of the OFC-positive patients; treatments administered were antihistamines (39.1%), β₂ stimulant inhalation (22.4%), steroids (17.3%), and intramuscular adrenaline injection (4.5%).

Symptoms at home after negative OFC

Among 763 patients with negative heated egg yolk OFC, seven (0.9%) reacted to heated egg yolk at home, including mild skin

symptoms (n = 4), vomiting (n = 2), and diarrhea (n = 2); no moderate-to-severe symptoms were observed. Among the others, one continued to avoid egg yolk and was lost to follow-up due to moving, and six continued to ingest egg yolk and tolerated whole egg 0.8–4.5 years (median 2.2 years) after OFC. In total, 756 (99.1%) patients ingested heated egg yolk safely.

Discussion

To our knowledge, our study is the first to reveal a clinical outcome of high safety and feasibility for heated egg yolk OFC in patients who reacted to whole hen’s egg. In contrast with whole-egg OFCs, most patients tend to pass the challenge of heated egg yolk OFCs. Compared with the 17% positive OFCs in our study’s heated egg yolk, Lemon-Mule et al. (13) reported 23% for heated whole-egg OFC, with a median sIgE level for egg white of 5.1 kU_A/l, lower than the 13.0 kU_A/l we found. In our study, only seven (4.5%) patients presented with severe symptoms. Perry et al. (27) and Järvinen et al. (28) both reported administration of intramuscular adrenaline in approximately 11% of positive OFC cases, a higher rate of administration than the 4.5% in our study. Our results indicate that heated egg yolk OFC may be safer than heated whole-egg OFC and may offer an alternative to the traditional heated egg challenge in managing children allergic to eggs. Furthermore, the heated egg yolk OFC could be implemented more safely in patients with a suspected egg allergy who have no clinical history of allergic reaction to egg than in those with a clinical history of allergic reaction to egg.

In a univariate analysis, many significant factors were noted. While only a history of anaphylaxis to food other than hen’s egg, age, specific IgE levels for ovomucoid, and total IgE levels were significant predictors of positive OFCs to heated egg yolk in a multivariate analysis. A previous study which included

subjects with and without past immediate reaction to egg found that the risk of induced symptoms in younger children was higher than in older children (29), which differs from the findings in our study. This inconsistency may originate from selection bias in OFC; patients with past severe reaction tend to receive OFC at an older age. Therefore, we cannot generalize our finding that age is risk factor for a positive OFC. After our multivariate analyses were adjusted by statistically significant patient factors, total IgE was no longer significant. Low total IgE levels were reported as a risk factor for positive OFC in milk and whole-egg OFC (30), in contrast with our findings for heated egg yolk OFC.

The sIgE levels for egg white, ovomucoid, and egg yolk indicating a negative predictive value >95% were 0.71, 0.41, and 0.17 kU_A/l, respectively. Thus, patients with low levels of sIgE antibodies may be able to safely consume heated egg yolk without OFCs. If sIgE values for ovomucoid were ≥100 kU_A/l, the predicted rate of positivity for heated egg yolk OFC was only 38.3%. Moreover, only 17.0% of patients aged ≤3 years were predicted to have a positive OFC if their sIgE value to ovomucoid was ≥100 kU_A/l. These numbers indicate that heated egg yolk OFC can be safely recommended for younger children.

In this study, a small amount of egg white was included with each egg yolk during the heated egg yolk OFC. Children with negative OFC results could therefore eat foods containing a small amount of egg white in addition to egg yolk (e.g., cookies, salad dressing, and bread); fear of severe symptoms

upon accidental ingestion may be reduced, and overall QOL considering food may be improved.

This study had several limitations. First, it was not a double-blind, placebo-controlled OFC. Second, all included patients had a past history of immediate reaction to egg; hence, additional studies are needed to confirm our findings in other patient populations.

We conclude that heated egg yolk OFCs can help patients to consume heated egg yolk or trace amounts of whole hen's egg safely and effectively. Most whole hen's egg-allergic pediatric patients could consume heated hen's egg yolk, and severe symptoms were rare. Documenting a negative heated yolk OFC in children with allergy to whole hen's egg may improve quality of life.

Acknowledgments

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Conflict of interests

MPB is employed as Medical Director at Thermo Fisher Scientific, Uppsala, Sweden. All other authors have no conflict of interests.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Receiver operating characteristic (ROC) curves for positive challenge.

Figure S2. Fitted predicted probability curves for a positive challenge outcome at a given ovomucoid-specific IgE value (a), egg white-specific IgE value (b), and egg yolk-specific IgE value for heated egg yolk (c), subdivided by age.

Figure S3. Fitted predicted probability curves for the challenge outcome at a given ovomucoid-specific IgE value (a), egg white-specific IgE value (b), and egg yolk-specific IgE value for heated egg yolk (c) among patients who did not have a previous reaction to eggs.

Figure S4. Fitted predicted probability curves for the challenge outcome at a given ovomucoid-specific IgE value (a), egg white-specific IgE value (b), and

egg yolk-specific IgE value for heated egg yolk (c) among patients who had a previous positive result in a heated egg yolk challenge.

Table S1. Challenge food in the egg yolk oral food challenge.

Table S2. Symptom grading.

Table S3. Clinical characteristics of excluded participants who received heated egg yolk oral food challenge (OFC).

Table S4. Comparison of patients according to oral food challenge results (positive vs. negative).

Table S5. Clinical efficacy of specific immunoglobulin E to egg white, ovomucoid, and egg yolk for predicting positive oral food challenge results.

Table S6. Multivariate analysis for factors related to anaphylactic reaction during oral food challenge (OFC).