

DR TAKAO FUJISAWA (Orcid ID : 0000-0002-9196-9436)

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Factors associated with outcome of egg allergy 1 year after oral food challenge: A good baseline quality of life may be beneficial

Kana Hamada¹, Mizuho Nagao¹, Ryo Imakiire^{1,2}, Kanae Furuya^{1,3}, Yumi Mizuno¹, Yasunori Sato⁴, Mayumi Matsunaga¹, Shingo Yamada¹, Kazutaka Nogami¹, Miyuki Hoshi¹, Taiga Kobori¹, Keigo Kainuma¹, Kazumoto Iijima⁵ & Takao Fujisawa¹

¹Allergy Center, National Hospital Organization Mie National Hospital, Tsu, Japan

²Department of Pediatrics, Kagoshima University School of Medicine, Kagoshima, Japan

³Aichi Konan College, Konan, Japan

⁴Department of Preventive Medicine and Public Health, Keio University School of Medicine, Tokyo, Japan

⁵Department of Pediatrics, Kobe University of Graduate School of Medicine, Kobe, Japan

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Correspondence: Takao Fujisawa, M.D., Ph.D.

Allergy Center, National Hospital Organization Mie National Hospital

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ABSTRACT

Background: Safely liberalizing the diet to include an allergenic food may accelerate resolution of food allergy. The outcome of liberalization, however, varies among patients.

Methods: We conducted a prospective observational study to identify factors associated with outcome for egg allergy 1 year after oral food challenge (OFC). We enrolled children <72 months-old who had egg allergy and underwent OFC for determination of the safe intake quantity of egg allergen. Each child's baseline clinical background was recorded. Caregivers used the Food Allergy Quality of Life Questionnaire–Parent Form (FAQLQ–PF) to assess their children's QoL. Dietary advice based on the OFC result was provided to support safe egg consumption. At 1 year after OFC, the quantity of egg each child safely consumed in daily life was surveyed. We classified the outcome as Successful (Group S) if the quantity increased during the 1 year, or as Unsuccessful (Group U) if it did not. Factors associated with the outcome were investigated by multivariate logistic regression analysis.

Results: A total of 93 children were enrolled, and after 1 year 57 finished in Group S and 36 in Group U. The mean FAQLQ–PF score at baseline was significantly lower (i.e., a better QoL) in Group S than in Group U. Multivariate logistic regression analysis identified a good QoL and absence of comorbid asthma or atopic dermatitis as factors predicting a favorable outcome.

Conclusion: QoL may affect food allergy outcome. Intervention focusing on the QoL may promote outgrowing of food allergies. (246 words)

KEYWORDS

food hypersensitivity, egg hypersensitivity, quality of life

KEY MESSAGE

Factors associated with natural outgrowing of food allergies are still to be clarified. In this study we investigated factors associated with the outcome of egg allergy 1 year after oral food challenge, focusing on the quality of life (QoL). The children's baseline QoL was evaluated using the Food Allergy QoL Questionnaire–Parent Form. Multivariate logistic regression analysis identified a good baseline QoL as a factor predicting increased intake of egg in daily life. Intervention focusing on children's baseline QoL may promote their outgrowing of food allergies.

INTRODUCTION

Food allergies pose a significant public health concern due to their increasing incidence in infants and children in the last few decades worldwide, and particularly in industrialized countries.^{1,2}

Conventional management of patients with food allergies generally consists of avoidance of the allergenic food and being prepared for any adverse reactions from unintended food ingestion.³

Since many children with a food allergy outgrow the disease,⁴ it is common for parents to follow the above strategy and wait for “the day of resolution”.

Recently, however, observations that dietary inclusion of baked hen’s egg or cow’s milk accelerated resolution of egg or milk allergy have attracted attention.⁵⁻¹⁰ Although evidence for the potential of baked products to promote outgrowing the disease still awaits well-designed randomized controlled studies,¹¹ partial liberalization of a child’s diet may be beneficial due to the improved quality of life (QoL) and nutritional status.¹² Japanese guidelines¹³ provide dietary guidance on how to consume a small, safe amount of an allergenic food based on the results of OFC using a low dose of allergen.

The natural course of food allergy, however, varies widely from complete resolution to persistence,⁴ and it may affect the results of management. Reported predictors of persistence of a food allergy in the natural course include a history of anaphylaxis, the presence of another food allergy, comorbid allergic diseases such as asthma, reaction to even a low allergen dose, elevated allergen-specific IgE (sIgE) levels, etc.^{4,14,15} In addition, mothers with a high level of anxiety, even after a negative OFC for their child, were reluctant to reintroduce the offending food.¹⁶

We therefore designed and conducted an IQ-FA (Impact of QoL on Food Allergy) study to identify factors that are associated with the natural course of food allergies in children, with special focus on the QoL. In our current follow-on study, we aimed to investigate factors related to successful introduction of egg to the diet of egg-allergic children based on OFC-based dietary

advice.

METHODS

Our earlier IQ-FA study enrolled children aged less than 13 years with food allergy who had undergone OFC at National Hospital Organization Mie National Hospital, a tertiary hospital for pediatric allergies. In our current study, we focused on children younger than 72 months of age who had egg allergy, since that is the most prevalent pediatric food allergy in Japan¹³ and most cases resolve by 72 months.¹⁴

OFCs were performed based on the Japanese Guideline for Food Allergy.¹³ The total challenge dose was decided for each patient by pediatric allergy specialists based on the patient's history of food-induced reactions, sIgE level, age, comorbid allergic diseases, and the caregivers' preference. The low dose was 1/32 of a cooked whole egg, the medium dose 1/8–1/2 of a cooked egg, and the high dose one cooked whole egg. Based on the OFC results, a registered dietitian then provided dietary advice for minimal avoidance of egg. When the OFC was negative, the caregiver was advised to give the child egg at home in an amount not exceeding the total challenge dose. When the OFC was positive, but the induced symptoms were mild, the advice was to consume egg in an amount not exceeding the threshold dose at home. When the OFC was positive, with moderate to severe induced symptoms, complete elimination of egg was advised.¹³ Child patients consumed egg in the instructed amount 2–3 times a week and visited our outpatient clinic once every 1–3 months. At each visit, if patients reported that they safely consumed the amount of egg, they were then allowed to increase the amount by about 20%.

The amount of egg consumed at home was classified into 5 levels: level 0, complete elimination; level 1: cooked egg yolk without egg white (1/32 egg equivalent); level 2: a small roll or stick of bread (1/16–1/8 egg equivalent); level 3: a small donut or small cake (1/4–1/2 egg

equivalent); level 4: 1/2–1 cooked egg; and level 5: >1 cooked egg. At 1 year after OFC, the amount of egg that each patient safely consumed in daily life was surveyed using a web-based questionnaire or by interview at an outpatient clinic and classified into the 6 levels described above. We classified the patient as “Successful” introduction of egg (Group S) if the level was higher than the initial level, or as “Unsuccessful” introduction of egg (Group U) if the level remained the same or had decreased.

The QoL of children was evaluated using the Japanese version¹⁷ of the Food Allergy QoL Questionnaire–Parent Form (FAQLQ–PF).¹⁸ The FAQLQ–PF allows parents to report their child’s health-related QoL from the child’s perspective. It consists of 3 domains: emotional impact (EI), food anxiety (FA) and social dietary limitations (SDL). The parents/caregivers of the patients answered each question on a 7–point Likert scale from “not at all” to “extremely”, in which a higher score indicates a worse QoL. The FAQLQ–PF was administered at OFC (baseline) and 1 year later. The study protocol was reviewed and approved by the Institutional Review Board of Mie National Hospital.

Statistical analysis

The χ^2 or Fisher exact test was used to compare categorical variables, while the Mann–Whitney U test was used to compare continuous variables between the 2 groups. Multivariate logistic regression analysis was performed to evaluate factors related to increasing egg consumption (dependent variable). Independent variables were selected based on their clinical relevance. To dichotomize the FAQLQ-PF total score and specific IgE level, a cutoff value for the 1–year outcome was determined using a receiver operating characteristic (ROC) curve. All reported P values are 2-tailed, with a P value of <.05 considered to be statistically significant. Statistical analyses were performed with GraphPad Prism 8 (GraphPad Software; La Jolla, California) and

SPSS (version 26; SPSS; Chicago, Illinois).

RESULTS

Patient characteristics and outcome

A total of 316 food-allergy patients were enrolled in the IQ-FA study, and 128 met the eligibility criteria of the present study. The OFC indicated that one patient had outgrown the egg allergy and was therefore excluded. The remaining 127 patients were followed up for 1 year after having received dietary advice, and 93 patients (73.2%) participated in the outcome survey (Figure 1).

Fifty-seven patients (61.3%) were classified as “Successful” introduction of egg (Group S) and 36 (38.7%) as “Unsuccessful (Group U). The distributions of the intake levels at entry (OFC) and at 1 year after OFC in Group U and Group S are shown in Figs. 2A and B. There was a significant leftward shift (toward lower levels) in the distribution in Group U (χ^2 test for trend: $P=0.0252$) and a significant rightward (toward higher levels) shift in Group S (χ^2 test for trend: $P<0.0001$). Patients who experienced an egg-induced symptom(s) during the 1-year period numbered 19 (33%) and 17 (47%) in Groups S and U, respectively. There was no statistical difference in the prevalence.

Table 1 summarizes the clinical characteristics at the time of OFC. The subjects had a median age of 24 months and were predominantly boys, with comorbid and parental allergic diseases. One-fourth of the subjects had a history of anaphylaxis to some food, and most of them had multiple food allergies, with a median of 4 avoided foods (Table 1).

Comparing the two groups, the patients in Group U were older and had higher prevalences of atopic dermatitis and asthma. Egg white (EW) and ovomucoid (OM) sIgE levels were also significantly higher in Group U. The groups showed no differences in the proportions of comorbid allergic rhinitis, family history of allergic diseases, history of food-induced anaphylaxis or first–

time OFC. There was no difference in the number of avoided foods (Table 1). None of the patients with asthma experienced exacerbation during the follow-up period. Two patients (1 in each Group) experienced a temporary flare-up of atopic dermatitis during the follow-up, but the symptoms were promptly controlled.

FAQLQ-PF

The total and subscale scores for the FAQLQ-PF at OFC were compared between Groups S and U. All the scores in Group U were significantly higher than those in Group S, indicating a better initial QOL in the Successful patients (Figure 3). At 1 year after OFC, the caregivers of 48 patients (15 in Group U; 33 in Group S) completed the FAQLQ-PF again. The scores remained the same in Group U. In contrast, both the total and SDL subscale scores had decreased significantly in Group S, indicating improvement in the QoL (Table 2). Accordingly, after 1 year, Group U still showed statistically higher scores, i.e., a worse QoL, compared with Group S (Table S1).

Factors associated with increased egg intake after 1 year

Multivariate logistic regression was performed to identify factors associated with a favorable outcome, i.e., an increase in the intake level of egg at 1 year after OFC. The explanatory variables were age, EW-sIgE, OFC results, number of avoided foods, history of anaphylaxis, parental allergic disease, comorbid asthma, comorbid atopic dermatitis, and the FAQLQ-PF total score. Continuous variables were dichotomized based on the optimal cut-off levels (for EW-sIgE and FAQLQ-PF) (Fig. S1) or clinical relevance (age, number of avoided foods). Although age <25 months and EW-sIgE <25 kU_A/L were associated with a favorable outcome in univariate analysis, only absence of comorbid asthma or comorbid atopic dermatitis and an FAQLQ-PF total score <3.8 were found to be independently associated with a favorable outcome, with adjusted ORs of

3.573, 3.311 and 3.614, respectively (Table 3).

DISCUSSION

In this study, we investigated factors associated with the clinical course of egg allergy, with special focus on the disease-specific QoL.¹⁷ The QoL was evaluated at the time of OFC, when a threshold of safe consumption was determined for dietary advice, and analyzed with regard to its relationship with the 1-year outcome. We found that a better QoL at the OFC was an independent predictor of increased consumption of egg at 1 year after OFC, indicating that outgrowing of egg allergy was associated with the baseline QoL.

The mechanisms by which children naturally outgrow food allergy have yet to be elucidated.¹⁹⁻²¹ Identification of clinical factors that accurately predict the prognosis of food allergy may help clarify the involved mechanisms.²² We performed a systematic review of studies of the natural history of food allergy, focusing on predictive factors for outgrowing an allergy. We used “food allergy” and “natural history” as keywords to conduct a Pubmed search of original research articles in English, published from January 1963 through April 2020. This search yielded a total of 358 studies. We excluded 306 studies that dealt with irrelevant topics such as non-food allergy, anaphylaxis and eosinophilic esophagitis. We also excluded 20 studies that did not deal with prognostic factors. Finally, we selected 32 studies that investigated factors involved in the natural history of allergy to food allergens (Figure S2).

Table S2 summarizes the factors that were reported to be negatively associated with outgrowing a food allergy: high specific IgE, large skin-prick-test reactions, systemic food-induced symptoms, a history of anaphylaxis, comorbid asthma and atopic dermatitis, a family history of allergic disease, and multiple sensitizations (Table S2). Our present study found that comorbid asthma and atopic dermatitis were independently associated with unfavorable outcome

of egg allergy, which is in agreement with earlier studies. We also found the disease-specific QoL to be a predictive factor of food allergy outcome. Although Franxman et al. reported that the QoL of patients improved after they underwent OFC, regardless of the OFC result,²³ no studies found an association between the QoL and the future food allergy outcome. We believe that this is the first study to find the disease-specific QoL to be a factor that may influence the natural history of food allergy.

Food allergy is a serious burden for affected patients and their caregivers because it requires strict performance of a variety of tasks, including careful cooking/eating to avoid the offending allergen, causes anxiety over the risk of anaphylaxis, and limits common social activities associated with eating. Thus, the parents of children with food allergy were reported to have a poorer general QoL than the parents of normal children.²⁴ The health-related QoL of children and adolescents with food allergy was shown to be worse than not only that of the general population but also that of type 1 diabetes patients.²⁵ Our present results indicate that a poor QoL is not only a consequence of the child's food allergy but also a factor that possibly influences the future status of the child's disease.

In fact, a prospective study that assessed the nutritional habits of children with food allergy before and after OFC in relation to their mothers' anxiety showed a negative correlation between the mothers' anxiety before OFC and the degree of change in the nutritional habits of their children after OFC.¹⁶ The authors stated that a positive attitude of mothers toward food before OFC promoted subsequent food reintroduction, which increased children's interest in tasting new foods, and led to favorable changes in nutritional habits. A negative initial maternal attitude, on the other hand, led to an unfavorable attitude in the child.¹⁶ Likewise, in our present study, a better QoL—which is partly equivalent to less anxiety—may have led to the child having a positive attitude toward food and an increase in egg intake. This tendency was observed regardless of both

the OFC results and the severity of egg allergy, represented by the specific-IgE level. Since intake of a small amount of an allergenic food after a negative low-dose OFC was reported to increase the intake threshold,^{26,27} a better initial QoL may promote outgrowing the allergy.

We also found that the initial QoL for the "Successful" patients had improved by 1 year after the OFC, whereas the QoL for the "Unsuccessful" patients remained unchanged or became worse. The QoL of food allergy patients was reported to be worse in older children, probably because of a long period of food avoidance and increased social activities involving food.^{28,29} Conversely, a negative OFC³⁰ and oral immunotherapy³¹ were associated with a better QoL. Our results are consistent with those earlier reports.

This study has at least 4 limitations. First, we used a questionnaire to determine the daily amount of egg consumed at 1 year after OFC, rather than repeat the OFC. However, the threshold determined by OFC does not always reflect a patient's actual eating habits. We believe that the caregiver-reported actual intake is more clinically relevant than an "experimental" OFC threshold. Second, the number of subjects was relatively small, and the statistical power to identify prognostic factors was thus not strong. Third, we followed up the patients for only 1 year and evaluated only the trend toward outgrowing egg allergy, not actual achievement of that goal. Further studies are needed to confirm our present findings. Fourth, we did not survey the socioeconomic or education status of the caregivers of the subjects, factors that might affect the outcome.

In conclusion, we found that a better QoL at baseline was associated with a child's outgrowing egg allergy, while vice versa, a poorer QoL was associated with delayed resolution. A caregiver's psychological status, partly expressed as the disease-specific QoL, may have an impact on a child's food allergy outcome. Intervention focusing on the child's baseline QoL may lead to better management and resolution of food allergies.

AUTHOR CONTRIBUTIONS

Mizuho Nagao and Takao Fujisawa conceived the study. Kana Hamada, Mizuho Nagao, Ryo Imakiire, Kanae Furuya, Yumi Mizuno, Mayumi Matsunaga, Shingo Yamada, Kazutaka Nogami, Miyuki Hoshi, Taiga Kobori and Keigo Kainuma recruited the subjects and contributed to data collection. Kana Hamada, Takao Fujisawa and Mizuho Nagao conducted the analyses of the data. Yasunori Sato supervised the statistical analyses. Kana Hamada and Takao Fujisawa wrote the manuscript. Kazumoto Iijima made critical comments on the study design and manuscript. All the listed authors were involved in the review of the manuscript and approved the final content.

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Figure legends

Figure 1

Flow diagram of the subjects

Figure 2

Levels of egg intake at initial OFC (solid bar) and 1 year later (open bar) in Group U (A) and Group S (B).

Egg intake levels were classified as level 0: complete elimination; level 1: cooked egg yolk without egg white (1/32 egg equivalent); level 2: a small roll or stick of bread (1/16–1/8 egg equivalent); level 3: a donut or small cake (1/4–1/2 egg equivalent); level 4: 1/2–1 cooked egg; and level 5: >1 cooked egg.

Figure 3

Comparison of FAQLQ-PF scores between Group U and Group S.

Horizontal bars indicate the median score. The total and subscale scores (emotional impact, food anxiety and social dietary limitations) in Group U were significantly higher, i.e., worse, than in Group S. (P values; Mann–Whitney test)

Legends for supplemental figures

Figure S1 ROC curves of FAQLQ-PF (A) and EW-sIgE (B)

Receiver operating characteristic (ROC) curves were constructed to identify cut-off values for predicting the egg allergy outcome 1 year after OFC. The optimal cut-off values determined from the Youden index were 3.8 and 25 for the FAQLQ-PF total score and EW-sIgE, respectively. AUCs (Area under the ROC curve) for the 2 factors were 0.70 (95%CI; 0.59-0.82) and 0.65 (95%CI; 0.53-0.78), respectively.

Figure S2. Flow diagram of the systematic literature review

Table 1 Clinical characteristics of the subjects at OFC

		All subjects (n=93)	Group U (n=36)	Group S (n=57)	P value
Age in months; median (IQR)		24 (12-44)	42 (22-62)	18 (11-33)	<0.001
Gender; n (boys %)		57 (61%)	22 (61%)	35 (61%)	>0.999
Comorbid allergic diseases n (%)	Atopic dermatitis	55 (59%) ^b	27 (75%)	28 (49%)	0.017
	Asthma	17 (18%)	12 (33%)	5 (9%)	0.005
	Allergic rhinitis	51 (55%)	22 (61%)	29 (51%)	0.395
Family history of allergic diseases n (%)	Father	76 (82%)	32 (89%)	44 (77%)	0.180
	Mother	65 (70%)	29 (81%)	36 (63%)	0.104
History of food-induced anaphylaxis; n (%)		21 (23%)	10 (28%)	11 (19%)	0.446
First OFC; n (%)		53 (57%)	17 (47%) ^c	36 (63%) ^c	0.140
Number of avoided foods; median (IQR)		4 (2-6)	4 (3-5)	3 (2-6)	0.306
EW-sIgE (kU _A /L); median (IQR)		20.5 (6.1-56.2)	44.7 (11.7-99.8)	17.2 (5.5-41.8)	0.013
OM-sIgE (kU _A /L); median (IQR)		8.3 (1.9-34.3)	18.0 (6.8-75.7)	5.1 (0.8-15.8)	0.001

IQR: interquartile range

Table 2 Comparison of FAQLQ-PF scores at OFC and 1 year later

(a) Group U (n=15)

FAQLQ-PF	At OFC	At 1 year	P value
Total score; median (IQR)	4.0 (3.3-4.7)	4.5 (4.1-4.9)	0.252
Subscales; median (IQR)			
Emotional impact	3.5 (3.0-4.8)	4.5 (3.9-4.7)	0.184
Food anxiety	4.3 (3.3-4.5)	4.9 (3.6-5.3)	0.208
Social dietary limitations	4.6 (3.7-5.2)	4.8 (4.4-4.9)	0.359

(b) Group S (n=33)

FAQLQ-PF	At OFC	At 1 year	P value
Total score; median (IQR)	3.6 (2.6-4.4)	3.2 (1.6-3.8)	0.016
Subscales; median (IQR)			
Emotional impact	3.2 (2.3-4.2)	3.0 (1.7-3.8)	0.050
Food anxiety	3.7 (2.3-4.3)	3.0 (1.3-3.8)	0.081
Social dietary limitations	4.2 (3.2-4.6)	3.6 (1.9-4.1)	0.004

IQR: interquartile range

Table 3 Factors associated with a favorable outcome for egg allergy

Variables	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Age <25 months	4.205 (1.746-10.47)	0.002	-	-
EW-sIgE <25 kU _A /L	3.000 (1.268-6.865)	0.017	-	-
Negative OFC	1.354 (0.538-3.522)	0.622	-	-
Number of avoided foods <3	2.029 (0.804-4.774)	0.179	-	-
No history of anaphylaxis	1.608 (0.638-4.300)	0.446	-	-
No history of parental allergic disease	5.714 (0.779-65.05)	0.146	-	-
No comorbid asthma	5.200 (1.753-14.36)	0.005	3.573 (1.037-12.31)	0.044
No comorbid atopic dermatitis	3.107 (1.256-7.251)	0.017	3.311 (1.185-9.252)	0.022
FAQLQ-PF total score <3.8	4.333 (1.803-10.54)	0.001	3.614 (1.373-9.508)	0.009

The chi-square test was used for univariate analysis. Binary logistic regression analysis was used for multivariate analysis, and backward variable selection was performed to identify a prediction model for a favorable outcome, defined as an increase in the intake level of egg after 1 year, from the 9 explanatory variables in the table.

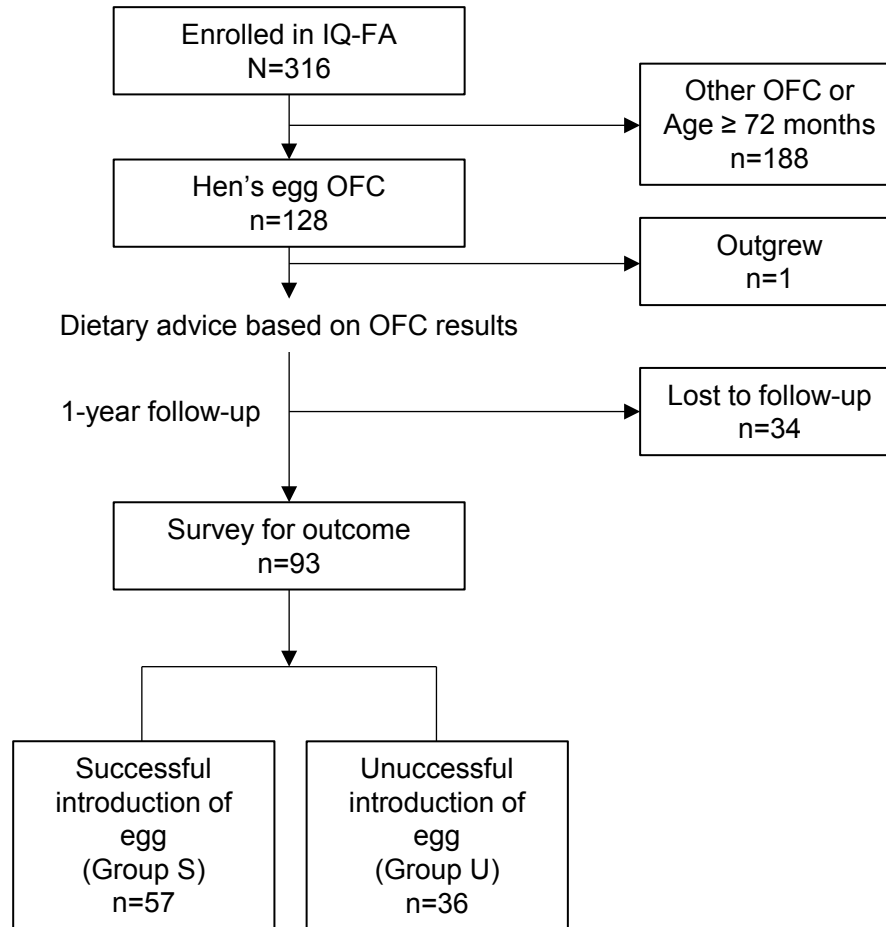


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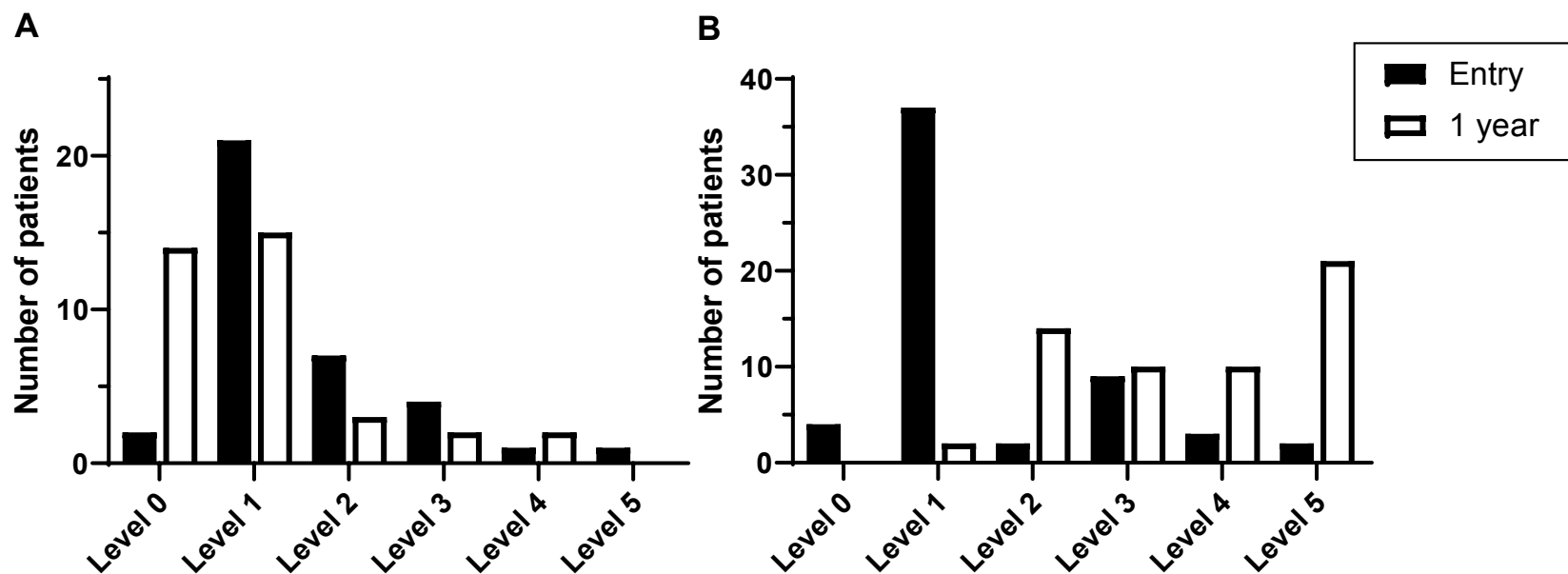


Figure 2

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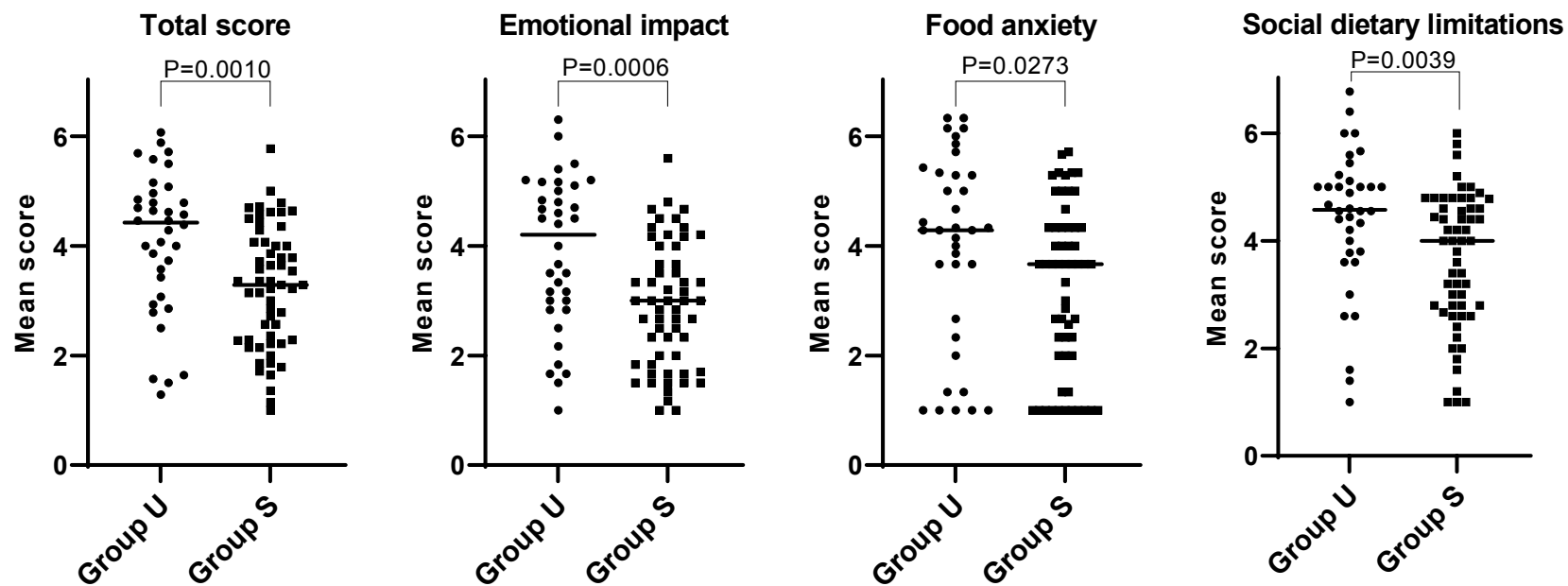


Figure 3

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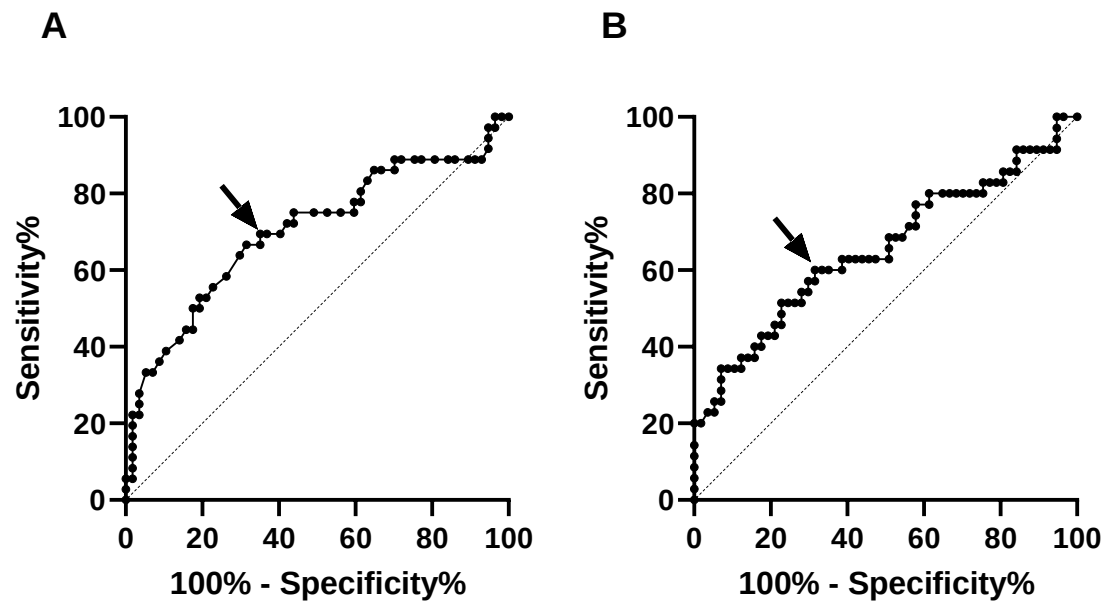


Figure S1

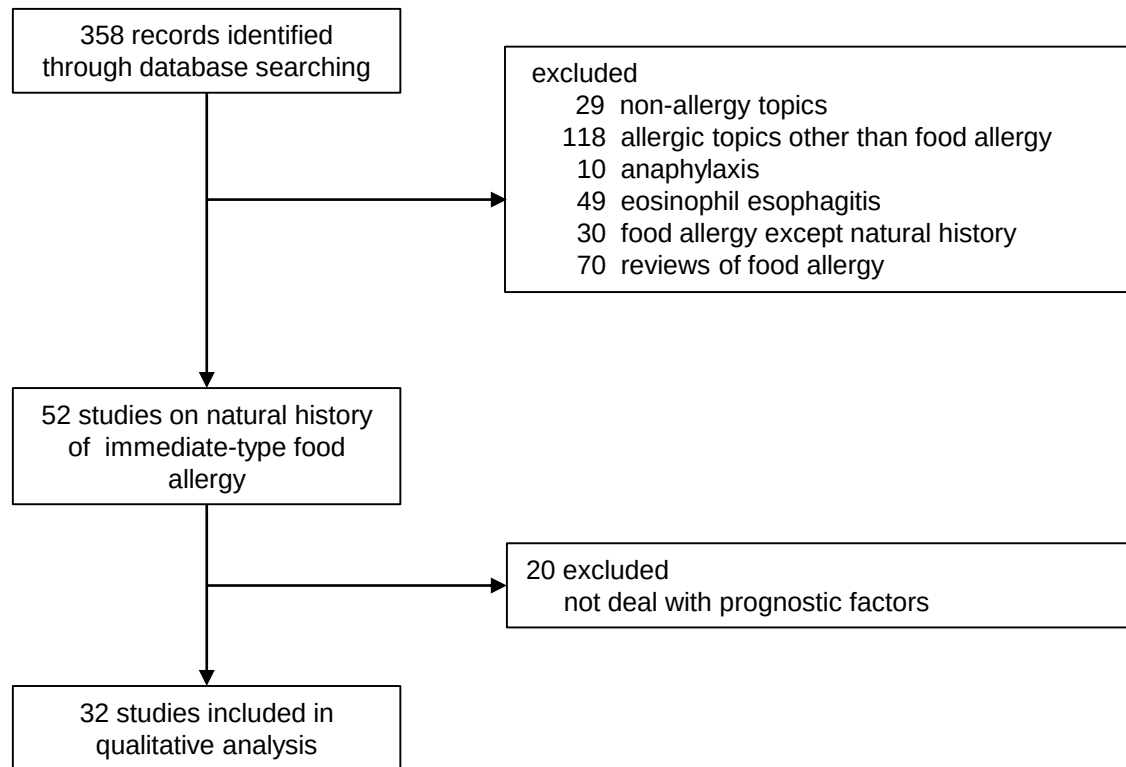


Figure S2

Table S1 FAQLQ–PF scores in Group N and Group O at 1 year after OFC

FAQLQ–PF	All subjects	Group U	Group S	P value
Total score	3.5 (2.7-4.3)	4.5 (4.1-4.9)	3.2 (1.6-3.8)	<0.001
Subscales				
Emotional impact	3.4 (2.2-4.2)	4.5 (3.9-4.7)	3.0 (1.7-3.8)	<0.001
Food anxiety	3.1 (2.1-4.5)	4.9 (3.6-5.3)	3.0 (1.3-3.8)	<0.001
Social dietary limitations	3.7 (2.6-4.5)	4.8 (4.4-4.9)	3.5 (1.9-4.1)	<0.001

Median (IQR)

Table S2 Factors associated with natural history of food allergy

Allergenic food	Predictive factors for persistence of food allergy	Reference(s)
Egg	High specific-IgE levels	1-7
	Systemic symptoms on ingestion	1,4,8,9
	Skin prick test (large wheal)	4,6,10
	Multiple sensitizations	8,11
	History of anaphylaxis	1,3
	Comorbid asthma	3,5
	Comorbid atopic dermatitis	3,5
	Comorbid allergic rhinitis	12
	Intolerance to baked egg	5
	Age at diagnosis of egg allergy ≥ 6 months	3
	Family history of allergic diseases	7
Milk	High specific-IgE levels	7,13-20
	Skin prick test (large wheal)	13,16,18,20,21
	Comorbid asthma	14,15,22,23
	Comorbid atopic dermatitis	14,16,18,22
	Multiple sensitization	8,9,11
	Family history of allergic diseases	9,17
	Systemic symptoms on ingestion	9
	Comorbid allergic rhinitis	15
	Serum IgM	24
	Low threshold	21
	Symptoms at less than 30 days of life	21
	Gut microbiota	18
	Strict avoidance	25
Peanut	High specific-IgE levels	26,27
	Skin prick test (large wheal)	27,28
	History of anaphylaxis	28
	Systemic symptoms on first ingestion	26
	Other food allergies	26
Sesame	Irritability on ingestion	29
Tree nuts	Comorbid atopic dermatitis	30
	Other food allergies	30
Wheat	High specific-IgE levels	31,32

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