

ORIGINAL ARTICLE

Food Allergy and Gastrointestinal Diseases



WILEY

Quality of life of children aged 8-12 years undergoing food allergy oral immunotherapy: Child and parent perspective

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Funding information

Dr Goldberg is funded by a Kamea grant from the Ministry of Health, Israel. This study was supported by a grant from Allergists for Israel.

Abstract

Background: Oral immunotherapy (OIT) for food allergy improves the quality of life (QOL) of children from parental perspective but little is known about the child perception.

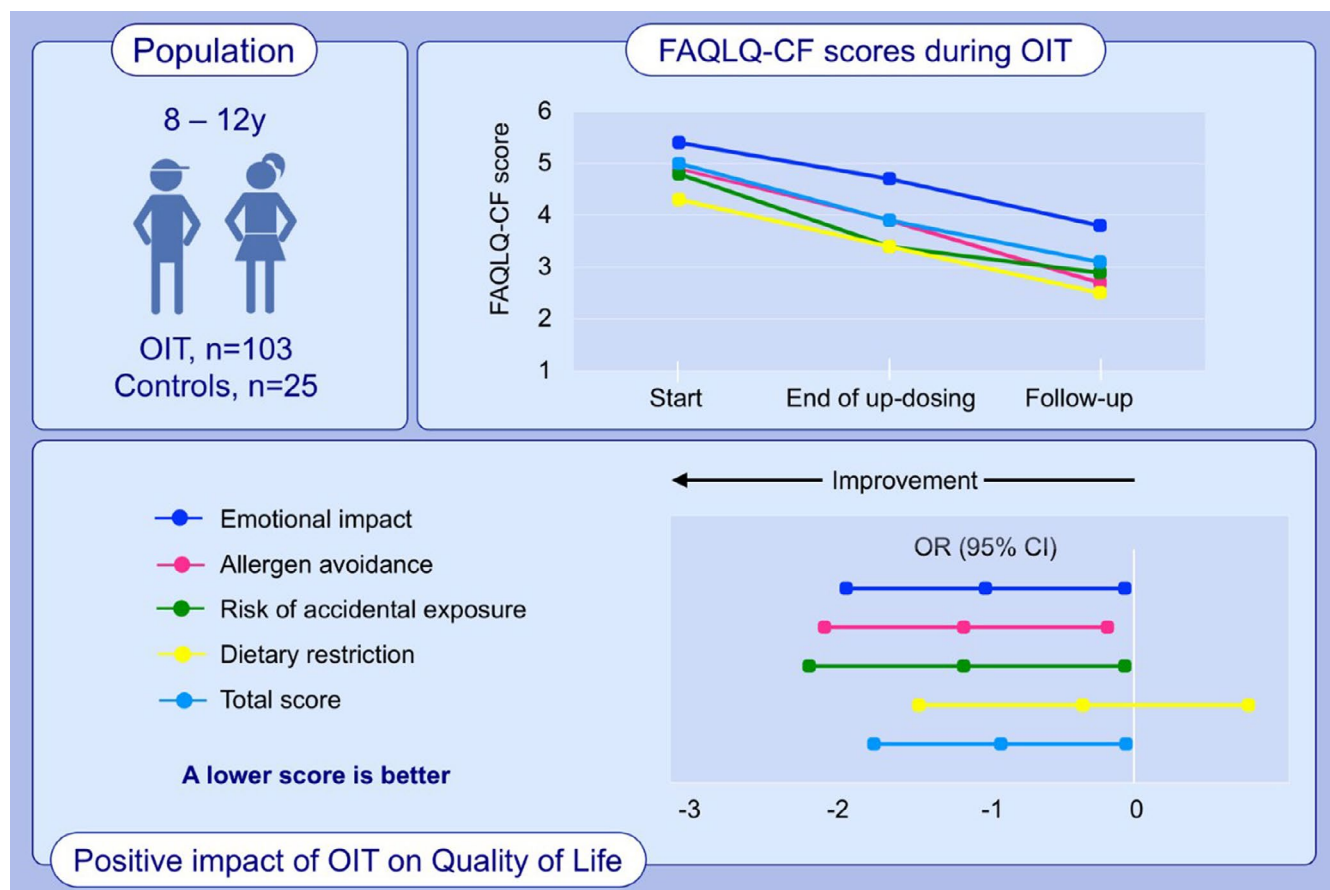
Methods: The Food Allergy Quality of Life Questionnaire—Child Form (FAQLQ-CF) was administered to children aged 8-12 years, and the FAQLQ—Parent Form (FAQLQ-PF) was administered to their parents at the start of OIT for milk, egg, peanut, sesame, or tree nuts, at the end of up-dosing, and after 6 months of follow-up. Food-allergic children not undergoing OIT served as controls. Children QOL scores were compared to their parents.

Results: The total FAQLQ-CF score of 103 children undergoing OIT improved significantly from start of OIT (median (IQR); 4.8, 3.8-5.7) to end of up-dosing (3.9, 3-5.2) ($P < .001$). A greater improvement was noted in the 56 children who reached a follow-up visit, from 5.0 (3.7-5.8) at OIT start to 3.1 (1.8-5.0) on follow-up, ($P < .001$). In contrast, FAQLQ-CF scores of control patients improved mildly and nonsignificantly between the two time points from 5.3 (4.3-5.7) to 4.8 (3.6-6.0), ($P = .13$). The improvement in the total FAQLQ-CF scores from OIT start to follow-up was significantly greater compared to the change in control patients during observation ($P = .015$). Parents reported better QOL scores compared to their children at all stages of OIT (start 4.0, 3.2-5, $P = .004$; end of up-dosing 2.9, 1.9-4.7, $P = .04$; follow-up 2.2, 1.6-3.6, $P = .003$).

Conclusions: QOL of food-allergic children undergoing OIT improves significantly compared to controls. Parents perceive QOL to be better than the perception of the children.

KEYWORDS

desensitization, food allergy, maintenance dose, oral immunotherapy, quality of life



GRAPHICAL ABSTRACT

FAQLQ-CF was administered to 103 children aged 8-12 years undergoing OI for food allergy and to 25 food-allergic controls. Children undergoing OIT experienced a significant improvement in quality of life at maintenance and an additional improvement at 6-month follow-up, a time-point representing the real-world impact of the treatment on their lives. This study demonstrates the positive impact of OIT on the quality of life of children and emphasizes the importance of longitudinal studies

1 | INTRODUCTION

Food allergy is a major worldwide public health problem with increasing prevalence, taking a personal, social, and economic toll on individuals and society.¹⁻⁶ The traditional approach in food-allergic patients, consisting of an elimination diet, is hampered by adverse reactions due to accidental exposures and is associated with significantly impaired quality of life (QOL).⁷⁻¹¹

Oral immunotherapy (OIT) has been shown to be an effective alternative treatment for patients with food allergy¹²⁻²³ and was recently recommended as a treatment option by the European Academy for Allergy and Clinical Immunology.²⁰ However, the treatment itself imposes many difficulties. It requires daily consumption of food which patients learned to avoid and fear, and to which many have developed aversion.²⁴ Moreover, anaphylactic reactions, some requiring injectable epinephrine, as well as nonanaphylactic reactions, are commonly experienced during treatment.^{13,22,25-27} Therefore, to determine whether OIT is justified despite the adverse reactions experienced, evaluating patient-important outcomes is mandatory.²⁸

Few studies have assessed changes in QOL of patients during and following OIT.²⁹⁻³² We previously demonstrated a significant improvement in the QOL of children, as perceived by their parents, throughout the OIT build-up phase, with further improvement during maintenance.³³⁻³⁵ However, when coping with food allergy, children and their caregivers face different difficulties. While children are challenged with the social burden of feeling different or left out, parents are usually preoccupied with anxiety regarding accidental exposure and the ability to adequately treat a life threatening reaction.¹¹ Furthermore, children's perception of QOL differs from the way their parents perceive it.^{36,37} Only a few small studies thus far have examined children's perception of QOL during OIT.³⁸⁻⁴⁰ While the QOL of children aged <8 years is usually assessed by proxy, the FAQLQ-CF (for children 8-12 years) is available for children <12 years. The current study focuses on the changes in QOL of children aged 8-12 years undergoing OIT for food allergy, as compared to QOL of control food-allergic children who continued food elimination. In addition, QOL as perceived by the children themselves and QOL as perceived by their parents was compared.

2 | METHODS

2.1 | Patients

Children aged 8-12 years who began OIT for IgE-mediated food allergy to milk, peanut, egg, sesame, or tree nuts at Shamir Medical Center (formerly Assaf Harofeh), after May 2014 and who reached the end of up-dosing (full desensitization, partial desensitization or failure) by April 2019, were included. Exclusion criteria were uncontrolled asthma or chronic inflammatory disease other than asthma. Only children who completed the FAQLQ-CF at the beginning of OIT were eligible. Epidemiological data, past medical history, and the nature and severity of previous food-related reactions were obtained from the parents of each participant. A control group was comprised of food-allergic patients aged 8-12 years who were followed regularly at our clinic and were eligible for OIT. Each patient could only be represented once in the study. The diagnosis of food allergy was based on a positive skin prick test (SPT) and/or specific serum IgE, together with a positive oral food challenge (OFC), or a clinical history of an allergic reaction following accidental ingestion in the past year. SPTs to food and histamine control (ALK-Abello, Port Washington, NY) were performed in all patients on the volar surface of the forearm and read after 15 minutes. The study was approved by the institutional ethics committee, and informed oral consent was obtained from parents of study participants.

2.2 | Oral immunotherapy

The individual OIT treatment program began with a 4-day dose-escalation phase during which the dose eliciting a reaction in each patient was established, and the single highest tolerated dose (SHTD) which would be the patients' starting dose for the treatment was determined. Treatment subsequently consisted of alternate cycles of up-dosing and home-treatment phases until the food-specific target dose for full desensitization (milk, 7200 mg protein; egg, 6000 mg protein; peanut 3000 mg protein; sesame and tree nuts, 4000 mg protein) was reached, as detailed in the online repository and as previously described.²⁷ Patients who were able to tolerate less than the target dose but an amount of at least 180 mg protein of milk (6 mL), 300 mg peanut (~1 peanut) or tree nuts (>1/4 walnut), 1500 mg egg (1/4 egg) and 240 mg protein of sesame (1 g of Tahini) without adverse reactions, were considered partially desensitized. Patients reported on doses taken at home and adverse reactions via a web-based reporting system.⁴¹ After reaching the target maintenance dose, patients who were fully desensitized were instructed to consume a lower daily dose at home (milk, 4500 mg protein; egg, 6000 mg protein; peanut, sesame, and tree nuts, each 1200 mg protein), as previously described.^{13,22,27} Partially desensitized patients were instructed to consume their maximal tolerated dose. Starting from April 2016, patients who have reached full desensitization

were invited for a routine 6-month evaluation visit. During this visit, all patients were challenged to the full dose reached at the end of up-dosing to validate full desensitization.

2.3 | Food Allergy Quality of Life Questionnaire—Child Form (FAQLQ-CF) and Parent Form (FAQLQ-PF)

The FAQLQ-CF was developed to evaluate the QOL of school-aged food-allergic children aged 8-12 years. The questionnaire contains 24 items and 4 domains: Emotional Impact (EI), Allergen Avoidance (AA), Risk of Accidental Exposure (RAE), and Dietary Restrictions (DR). The scoring method is described in the online repository.⁴²⁻⁴⁴ Patients and their caregivers were administered the FAQLQ-CF and FAQLQ-PF, respectively, at three time points during the treatment program. Initially, at the start of therapy (during the third day of the first week); at the end of the up-dosing period; and, starting April 2016, when patients arrived for a 6-month follow-up visit. Patients who did not answer $\geq 80\%$ of the questions in the FAQLQ-CF/FAQLQ-PF were excluded. Control children were followed at the allergy clinic and filled out the QOL questionnaires at two different visits.

2.4 | Statistical analysis

Statistical analyses were performed using SPSS software (version 20; SPSS, Inc, Chicago, Ill). Values were expressed as medians and interquartile ranges (IQRs) unless otherwise indicated, or counts and percentages, as appropriate. The FAQLQ-CF was translated to Hebrew and validated, as described in the online repository and in Table S1. QOL scores in the different time points were non-normally distributed and were therefore analyzed using the Wilcoxon paired analysis and Mann-Whitney test, respectively. The effect of continuous and categorical variables on changes in QOL scores was assessed by linear regression and Mann-Whitney test, respectively. QOL scores of children and their parents were compared using Wilcoxon paired analysis. Analysis of nominal variables was done using chi-square test. A difference of >0.5 was considered the minimal clinical important difference (MCID) on HRQL questionnaires with a 7-point scale.⁴⁵ All analyses were 2-tailed and a P value of <0.05 was considered significant.

3 | RESULTS

3.1 | Patient characteristics and OIT outcome

A total of 145 patients aged 8-12 years began OIT after May 2014 and completed it by April 2019, of which 117 completed the FAQLQ-CF at the start of OIT and were eligible for the study (Figure 1). The demographics and clinical characteristics of eligible

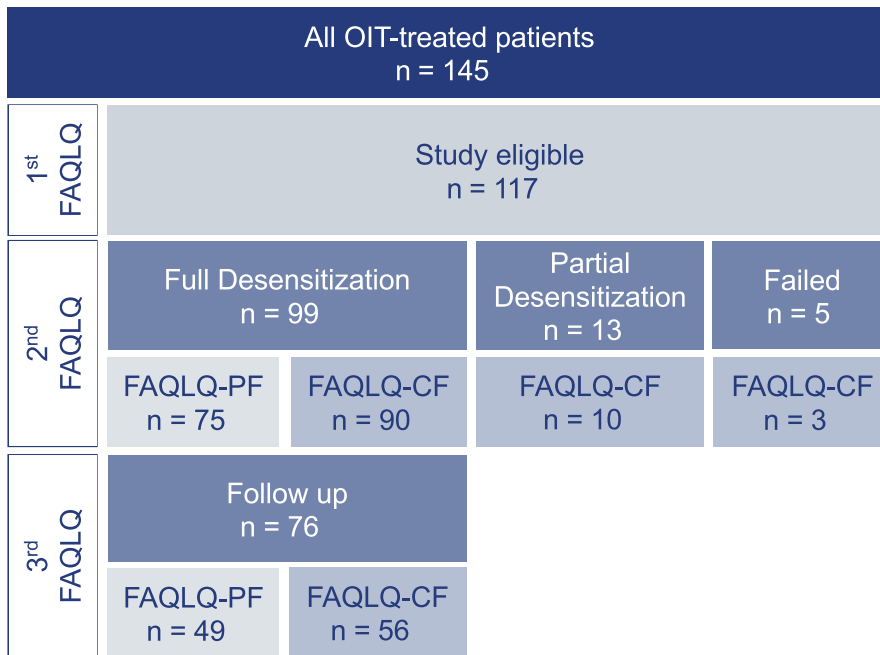


FIGURE 1 Enrollment of study participants. Full desensitization was defined as tolerating the target dose (milk, 7200 mg protein; egg, 6000 mg protein; peanut 3000 mg protein; sesame and tree nuts, 4000 mg protein). Partial desensitization was defined as 10-fold increase in the SHTD but inability to tolerate the target dose. SHTD = Single Highest Tolerated Dose

Category	Variable	Frequency		P value
		Study group N = 103	Control group N = 25	
Demographics	Age (y) ^b	9.0 (8-11)	9.0 (8-10)	.29
	Male gender	59 (57.3%)	13 (52.0%)	.66
	Multiple Food allergies	30 (29.1%)	2 (8%)	.04
	Asthma	51 (49.5%)	5 (21.7%) ^a	.02
Clinical Background	Anaphylaxis	55 (53.4%)	11 (47.8%) ^a	.65
	Epinephrine	34 (33%)	5 (21.7%) ^a	.33
	Emergency department	50 (48.5%)	12 (52.2%) ^a	.82
	Hospitalization	11 (10.7%)	2 (8.7%) ^a	1.0

^aData available for 23 patients.

^bNumerical data presented as median and IQR. The study group had significantly more multiple food allergies than the control group ($P = .04$), as well as a significantly higher rate of asthmatics ($P = .02$).

TABLE 1 Demographic and clinical characteristics of the study and control populations

and noneligible patients were comparable (Table S2). Of the 117 eligible patients, 99 patients (84.6%) reached full desensitization and 90 of them (90.9%) completed a second FAQLQ-CF. An additional 13 (11.1%) patients reached partial desensitization (mean 1006.5 mg, range 240-3000 mg protein for all foods) of which 10 (76.9%) completed a second questionnaire after up-dosing cessation. Three of five patients (60%) who failed treatment completed a second questionnaire after treatment failure (Figure 1). OIT and control patients ($n = 25$) were comparable in demographics and in the severity of reactions upon accidental exposures to the allergenic food before study entry (Table 1). More patients in the OIT group had asthma (49.5% vs 21.7%, $P = .02$) and more had multiple food allergies (29.1% vs 8%, $P = .04$). In the OIT group, the allergens treated

were primarily milk and tree nuts (Figure S1A) and the single highest tolerated dose (SHTD) was ≤ 150 mg of protein in 85 patients (82.5%) (Figure S1B). Eighteen patients (17.5%) experienced allergic reactions requiring injectable epinephrine during OIT up-dosing in clinic, while 15 (14.6%) required epinephrine for reactions to home doses. The median interval between the two time points when the questionnaire was completed by control children was 11.3 months (IQR, 6.7-24.1; range, 1.5-37.3), significantly longer than the median duration of 7.6 months in OIT from start to end of up-dosing ($n = 103$) (IQR, 4.2-19.9, range, 1.9-37.2 months, $P = .005$). However, it was comparable to the interval of 12.6 months from OIT start to follow-up in those fully desensitized ($n = 56$) (IQR, 10.1-16.2; range 7.9-40.3, $P = .7$).

TABLE 2 FAQLQ-CF scores of OIT population at start and maintenance versus controls

FAQLQ-CF scores	OIT group (n = 103)			Control group (n = 25)				OIT Vs Control			
	1st Visit	2nd Visit ^a	Delta	P value 1st-2nd	1st Visit	2nd Visit	Delta	P value 1st-2nd	P value	P value	P value
									1st	2nd	Delta
Emotional impact	5.5 (4-6.5)	4.7 (3.3-6.3)	-0.5 (-1.5-0.7)	.003	5.8 (4.3-6.6)	5.3 (3.9-6.2)	-0.3 (-0.9-0.8)	.44	.94	.35	.82
Allergen avoidance	4.9 (3.6-6.1)	4.2 (2.4-5.4)	-0.4 (-1.3-0.6)	.002	5.4 (4.3-6.1)	4.9 (3.4-6.4)	0 (-1.5-0.9)	.64	.27	.06	.36
Dietary restrictions	4.3 (3.2-5.3)	3.7 (2.3-4.5)	-0.5 (-1.8-0.5)	.001	4.8 (4.0-5.8)	4.3 (2.8-5.3)	-0.5 (-1.6-0.4)	.06	.07	.06	.5
Risk of accidental exposure	4.5 (3.4-5.8)	3.4 (2.6-4.8)	-0.4 (-2.1-0.6)	<.001	5.2 (4.2-5.6)	4.2 (3.7-5.7)	0 (-1.2-0.6)	.44	.32	.024	.19
Total score	4.8 (3.8-5.7)	3.9 (3-5.2)	-0.5 (-1.3-0.3)	<.001	5.3 (4.3-5.7)	4.8 (3.6-6.0)	-0.2 (-0.9-0.4)	.13	.24	.05	.5

Note: Data are represented as medians and interquartile ranges.

^aSecond visit represents the time of reaching maintenance in fully desensitized patient, the time of discontinued up-dosing in partially desensitized patients and the time of treatment cessation in those who failed.

3.2 | Changes in QOL between start and end of up-dosing (OIT vs control)

The baseline FAQLQ-CF scores of control patients ($n = 25$) were higher (worse) than those of OIT-treated patients ($n = 103$) but the difference was not statistically significant (total score 4.8 (3.8-5.7) for OIT-treated patients vs 5.3 (4.3-5.7) for controls, $P = .24$). The FAQLQ-CF scores of OIT-treated patients improved significantly, both statistically and clinically (>0.5 difference), in all domains, from the start of OIT to the end of up-dosing (EI, 5.5-4.7, $P = .003$; AA, 4.9-4.2, $P = .002$; DR, 4.3-3.7, $P = .001$; RAE, 4.5-3.4, $P < .001$, and total score, 4.8-3.9, $P < .001$) (Table 2). These changes were driven by several items in each domain (Figure S2). In contrast, only a mild nonsignificant improvement was noted in controls (EI, 5.8-5.3, $P = .44$; AA, 5.4-4.9, $P = .64$; DR, 4.8-4.3, $P = .06$; RAE, 5.2-4.2, $P = .44$; and total score, 5.3-4.8, $P = .13$) (Table 2). There was no effect for demographics, having asthma, multiple food allergies, prior allergic reactions, the food treated, the SHTD, reactions during therapy or treatment duration, on the changes in the total FAQLQ-CF score during treatment (Tables S3, S4). Patients who required epinephrine for adverse reactions (either in clinic or at home) ($n = 27$) experienced a significantly larger improvement in the total FAQLQ-CF score compared to patients without such reactions (-0.8 vs -0.3 , $P = .017$), (Table S4). The FAQLQ-CF scores were significantly lower (better QOL) in OIT-treated patients compared to controls at the completion of the second questionnaire for RAE (3.4 vs 4.2, $P = .024$) and with borderline significance for the AA (4.2 vs 4.9, $P = .06$), DR (3.7 vs 4.3, $P = .06$) and total score (3.9 vs 4.8, $P = .05$) (Table 2). Given that the baseline FAQLQ-CF scores of control patients were higher (worse) compared to patients undergoing OIT (although not statistically significant), we compared the change between the 1st and 2nd questionnaires in both groups. No significant differences were noted in the change of QOL scores from the 1st to the 2nd questionnaire between OIT-treated patients and controls (EI, -0.5 vs -0.3 , $P = .82$; AA, -0.4 vs 0 , $P = .36$; DR, -0.5 vs -0.5 , $P = .5$; RAE -0.4 vs 0 , $P = .19$; and total score, -0.5 vs -0.2 , $P = .5$) (Table 2).

3.3 | Changes in QOL for patients according to treatment status (full, partial and no desensitized)

The FAQLQ-CF scores of the 90 patients who reached full desensitization improved significantly in all domains, both statistically and clinically, from the start of OIT to the end of up-dosing (EI, 5.4-4.7, $P = .016$; AA, 4.8-4.2, $P = .006$; DR, 4.3-3.7, $P = .002$; RAE, 4.4-3.4, $P = .001$, and total score, 4.8-3.9, $P = .001$) (Table S5). QOL scores of the 10 patients who reached partial desensitization improved significantly during this period, both statistically and clinically, for the AA (5.3-3.7, $P = .016$) and EI (5.5-4.1, $P = .046$) domains and for the total score (5-3.7, $P = .018$) (Table S5). Interestingly, the degree of improvement in the total FAQLQ-CF scores from start to end of up-dosing was not statistically different between fully desensitized and partially desensitized patients (-0.45 vs -0.65 , $P = .36$). Of the

TABLE 3 FAQLQ-CF scores of OIT population at start and follow-up vs controls

FAQLQ-CF scores	OIT group (n = 56)			P value S-F	Control group (n = 25)			OIT Vs Control			
	Start	Follow-up	Delta		1st Visit	2nd Visit	Delta	P value 1st-2nd	P value S vs 1st	P value F vs 2nd	P value Delta
Emotional impact	5.4 (3.7-6.7)	3.8 (2.7-5.3)	-1.1 (-2.5-0)	<.001	5.8 (4.3-6.6)	5.3 (3.9-6.2)	-0.3 (-0.9-0.8)	.44	.88	.012	.016
Allergen avoidance	4.9 (3.5-6.0)	2.7 (1.7-5.3)	-1.3 (-2.1-(-0.2))	<.001	5.4 (4.3-6.1)	4.9 (3.4-6.4)	0 (-1.5-0.9)	.64	.28	.002	.013
Dietary restrictions	4.3 (3.1-5.5)	2.5 (1.7-5.3)	-0.7 (-2.5-0.5)	.008	4.8 (4.0-5.8)	4.3 (2.8-5.3)	-0.5 (-1.6-0.4)	.06	.09	.034	.57
Risk of accidental exposure	4.8 (3.1-5.8)	2.9 (1.4-4.8)	-0.9 (-2.9-(-0.4))	<.001	5.2 (4.2-5.6)	4.2 (3.7-5.7)	0 (-1.2-0.6)	.44	.41	.004	.012
Total score	5.0 (3.7-5.8)	3.1 (1.8-5.0)	-1.0 (-2.3-(-0.3))	<.001	5.3 (4.3-5.7)	4.8 (3.6-6.0)	-0.2 (-0.9-0.4)	.13	.22	.003	.015

Note: Data represented as median and interquartile ranges.

five children who failed treatment, 3 completed the questionnaire at start and after stopping therapy. No significant changes were noted in any of their QOL scores (RAE, $P = .65$; AA, $P = .11$; EI, $P = .65$; DR, $P = .11$; and total score, $P = .29$).

3.4 | Changes in QOL between start and follow-up (OIT vs control)

Of the 90 fully desensitized patients, 76 were receiving the full maintenance dose for ≥ 6 months at the time of the study. Of those, 56 (73.6%) completed a third questionnaire at their follow-up visit (Figure 1). The rate of asthma (44.6% vs 21.7%, $P = .08$) and of multiple food allergies (28.6% vs 8%, $P = .046$) was higher in OIT-treated patients analyzed at follow-up compared to controls. The change in QOL scores from start to follow-up was significant both statistically and clinically for all domains in OIT-treated patients (EI, 5.4-3.8, $P < .001$; AA, 4.9-2.7, $P < .001$; DR, 4.3-2.5, $P = .008$; RAE, 4.8-2.9, $P < .001$; and total score 5-3.1, $P < .001$) (Table 3, Figure 2). As in the up-dosing period, these changes were driven by most domains (Figure S3). The FAQLQ-CF scores of OIT-treated patients at follow-up were significantly lower compared to controls at their second visit, both clinically and statistically (EI, $P = .012$; AA, $P = .002$; DR, $P = .034$; RAE, $P = .004$; and total score, $P = .003$) (Table 3, Figure 2). Again, given the baseline differences in FAQLQ-CF scores between the two groups, we compared the change between OIT start and follow-up to the change between the 1st and 2nd questionnaires in control patients. The change in the EI, AA, and RAE sub-scales and in the total FAQLQ-CF score in OIT-treated patients, was significantly greater compared to the change in controls (EI, $P = .016$; AA, $P = .013$; RAE, $P = .015$; and total score, $P = .015$) (Table 3). Linear regression analyses including asthma, multiple food allergy and epinephrine-treated reaction before the study as confounders showed that only group assignment to OIT was significantly associated with a greater improvement in QOL scores from start to follow-up (EI, $P = .037$; AA, $P = .021$; RAE, $P = .039$; and total score, $P = .039$) except for DR ($P = .54$).

3.5 | Comparison of QOL between children and their parents

The parents of 75 of the 90 children who were fully desensitized answered the FAQLQ-PF at the start of OIT and the end of up-dosing (Figure 1). There was a significant improvement in all domains of the FAQLQ-PF, from 4 to 2.9 for the mean total score, $P = .003$ (Table S6). Parents of 49 of those children completed the questionnaire also during the follow-up visit (Figure 1). A further improvement, both clinically and statistically significant, was noted in all domains during that time, from 2.9 to 2.2 for the mean total score, $P = .001$ (Table S6). Total QOL scores given by the parents (FAQLQ-PF) throughout the process of OIT were lower (better QOL) than the scores given by the children (FAQLQ-CF), (OIT start, 4.0 vs

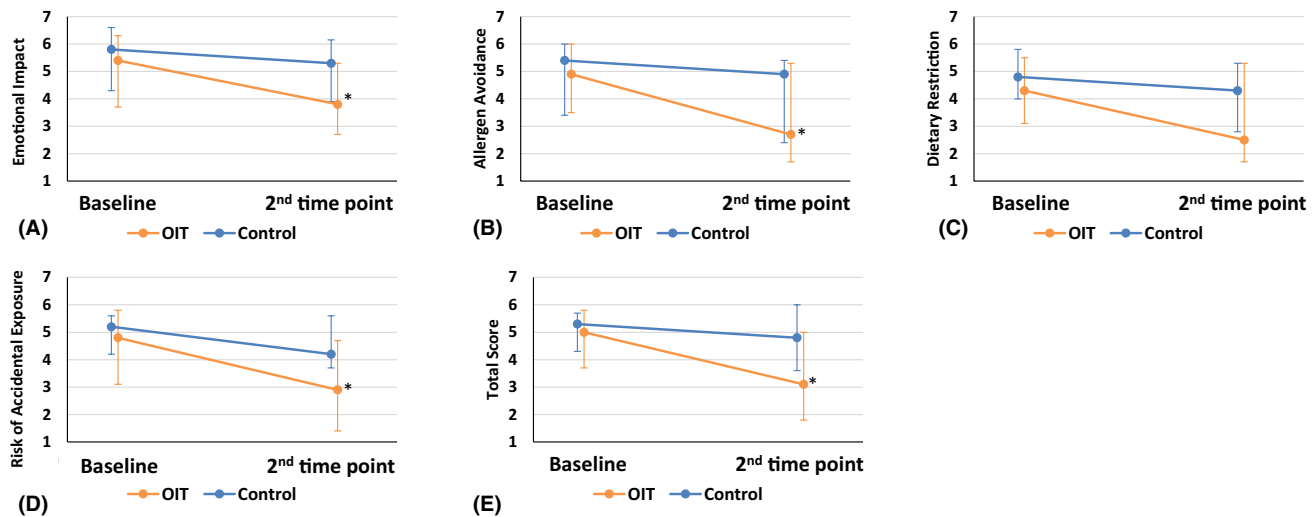


FIGURE 2 Comparison of the change in the FAQLQ-CF total score of 56 OIT-treated patients from start to follow-up and control patients from the 1st to 2nd questionnaire. The scores are shown as medians and IQRs for each domain (Emotional Impact (A), Allergen Avoidance (B), Dietary Restrictions (C) and Risk of Allergen Exposure (D)) and for the total score (E). *Statistically significant difference between the delta from start to follow-up in the OIT-treated patients Vs the delta between the two time points of control patients for the EI domain ($P = .016$), AA domain ($P = .013$), RAE domain ($P = .012$) and total score ($P = .015$)

5.0, $P = .004$; end of up-dosing, 2.9 vs 3.9, $P = .036$; follow-up, 2.2 vs 3.0, $P = .003$) (Figure 3). However, the degree of improvement in QOL during OIT as perceived by both groups was comparable. A good correlation was observed for the change in QOL from start to follow-up between children and their parents (0.4 , $P = .004$).

4 | DISCUSSION

In this study, we examined the changes in QOL of food-allergic children aged 8-12 years undergoing OIT for food allergy. We found that QOL of OIT-treated children improved from start to the end of up-dosing, with further improvement on follow-up, both statistically and clinically. Parents estimated the QOL of their children to be better than the perception of the children themselves but the degree of improvement was perceived similarly by parents and children.

The goal of OIT is to increase the reaction threshold of allergic patients, thereby protecting them from severe reactions in case of accidental exposure. In most patients, some degree of desensitization is achieved, enabling them to consume the allergenic foods and reducing their diet restrictions.^{16,46,47} While the efficacy of OIT has been shown in multiple studies, the process itself is associated with adverse reactions and debate still exists around its risk-benefit ratio.²⁸ Studies that focus on patient-important outcomes, such as QOL, are critical for understanding patient needs.⁴⁶ Several studies have shown improvement in QOL of patients who completed OIT, usually through the viewpoint of their parents using the FAQLQ-PF.²⁹⁻³⁵ However, data on QOL of children undergoing OIT, from the child perspective, is limited to small or uncontrolled studies.³⁸⁻⁴⁰ In the largest group of children studied thus far, we found a significant improvement, both statistically and clinically, in QOL from start to the end of up-dosing of OIT. This improvement was

exhibited for all domains, and was not related to the clinical history nor the course of OIT. The change in QOL between these time points was not significant when compared to controls. This could reflect insufficient improvement in QOL of children during the up-dosing phase of OIT. Alternatively, it could reflect the fact that most control patients in our study were tree nut allergic and underwent several OFCs between the administration of the first and the second questionnaire. This could have facilitated a less rigid elimination diet, reformed their understanding of food allergy and its treatment, and improved their QOL.^{49,50}

The QOL of OIT-treated children continued to improve significantly, both clinically and statistically, as the process proceeded and they reached follow-up. At this time point, the change in QOL scores of OIT-treated patients was significantly greater compared to the change in controls. The continued improvement at follow-up may reflect reduced adverse reactions during this time point,⁴⁸ as well as adaptation to regular dose consumption and accommodation to a new routine. In addition, secondary benefits of this process, such as a richer diet and ability to attend social events with less anxiety may play a role. This finding emphasizes that if studies wish to best reflect the effects of OIT, they need to examine not only its short-term outcomes, but rather analyze data after sufficiently long time-periods.

We found that patients who were partially desensitized also had a statistically significant improvement in their total FAQLQ-CF score as well as the EI and AA domains, emphasizing the psychological benefit of daily consumption of the allergenic food, even if at lower doses. Patients who failed treatment did not experience a significant change (for better or worse) in QOL. However, the findings in these two sub-groups should be interpreted with caution given the small sample sizes.

It has previously been shown that children and parents might differ in their perception of QOL.^{9,36} Our results support these

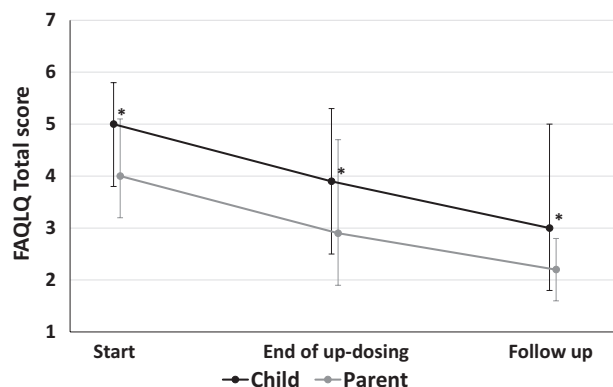


FIGURE 3 Comparison between the FAQLQ-CF and FAQLQ-PF total scores at the different stages of OIT. The Scores are shown as medians and IQRs. * Significant difference between the total score of children and their parents at the different time points ($P = .004$, $.036$, $.003$ when comparing the total score at start, end of up-dosing and follow-up, respectively). The degree of improvement in QOL as perceived by parents and by children were comparable (start to end of up-dosing $P = .9$; maintenance to follow-up, $P = .6$; start to follow-up, $P = .5$)

findings, showing that parents estimated the QOL of their children to be consistently better than the way QOL was depicted by the children themselves, throughout all phases of OIT. It is important to take into consideration that these questionnaires are not identical. Still, these differences might reflect the different concerns, challenges, and insights between children and their parents. While parents are mostly concerned with safety aspects, alleviating uncertainty as well as the perception of actively insuring treatment, improves their QOL.⁴⁷ Children, on the other hand, are forced to cope with consuming food they dislike and may not fully understand the long-term benefits of treatment. This also stresses the importance of supporting the children through this process, explaining the different stages of therapy in concepts children can understand and relate to, as well as actively engaging them and encouraging them to succeed.

Our study has several limitations. First, we did not randomly assign patients for OIT and control groups. Control patients were all eligible for OIT and the main factor for group assignment was the waiting time for OIT. A few control patients (6/25) did not enlist for OIT as the treatment does not fit everyone. Various reasons could account for that and those could potentially affect patient QOL. However, these are likely to primarily affect parental rather than the child's QOL and are unlikely to affect the change in QOL overtime. Regardless, both study and control groups were comparable for both the severity of food allergy and for epidemiological data. Second, control patients had worse (although not statistically) QOL scores at baseline. To correct for that, we compared the change in QOL scores during OIT between both groups. These differences could lead to a regression to the mean phenomenon but that would bias against rather than in favor of our findings. In addition, the time intervals chosen do not represent fixed time points but rather fixed stages in treatment. However, these better reflect real-world effect of the treatment on patient QOL. Last, we did not collect data on

the gender of the parent answering the FAQLQ-PF. While parental gender can impact the perception of different sub-scales of QOL,⁵¹ it does not appear to affect the total QOL scores.⁹

In summary, we demonstrate the beneficial effects of OIT on QOL of children aged 8-12 years and show that QOL continues to improve over time. This study emphasizes the utility of long-term outcomes when assessing OIT and adds support for the use of OIT in clinical practice. Additionally, we found differences in QOL between children and their caregivers which might reflect the different obstacles they face during treatment. For the success of OIT, patients and their caregivers must be addressed with adequate support and reinforcement, as well as tools for overcoming difficulties. Future studies should focus on exploring the benefits of such tools in terms of success of OIT and improvement in QOL.

ACKNOWLEDGMENTS

We would like to thank the large staff of the Shamir Medical Center Allergy Clinic in their daily work and efforts: nurses, dieticians, respiratory technicians, laboratory workers and secretaries. We would also like to thank Allergist for Israel for the grant we received. Finally, we would also like to thank our patients and their parents for participating in this study.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Arnon Elizur and Na'ama Epstein Rigbi contributed to conception and design of the study, acquisition, analysis, and interpretation of data, and drafting the article; Michael R Goldberg, Liat Nachshon, and Michael B Levy contributed to interpretation of data and drafting the article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Epstein-Rigbi N, Goldberg MR, Levy MB, Nachshon L, Elizur A. Quality of life of children aged 8-12 years undergoing food allergy oral immunotherapy: Child and parent perspective. *Allergy*. 2020;00:1-10.
<https://doi.org/10.1111/all.14350>

APPENDICES MATERIAL

OIT protocol

Each patient underwent a single food OIT. The initial up-dosing round consisted of 4 days, during which the dose eliciting a reaction in each patient was established, and the single highest tolerated dose (SHTD) which would be the patients' starting dose for the treatment was determined. The SHTD was then consumed once daily during the home treatment round until the next up-dosing cycle 24 days later. Additional up-dosing rounds were performed until the target maintenance dose was reached (milk, 7200 mg protein; egg, 6000 mg protein; peanut 3000 mg protein; sesame and tree nuts, 4000 mg protein). Our food allergy center at Shamir Medical center consists of allergists, nurses and dietitians as well as medical clowns. This staff provides support in cases of reactions and setbacks.

FAQLQ questionnaires

The FAQLQ-CF was developed to examine the self-reported QOL of children aged 8-12 years (42). Items are scored on a 1-7 scale, ranging from not troubled (1) to extremely troubled (7). A higher score represents a higher impact or burden and hence, worse health related quality of life. The total FAQLQ-CF score is the sum of all items divided by the number of the items and ranges from 1 (minimally impaired QOL) to 7 (extremely impaired QOL). The Food Allergy Independent Measure- Child Form (FAIM-CF) was originally developed as an independent measure of food allergy QOL in order to evaluate and validate the FAQLQ-CF (43). The FAQLQ-PF was developed to examine QOL in children aged 0-12 years, as assessed by their parents. The questionnaire is divided into 3 domains: Emotional Impact (EI), Food Anxiety (FA), and

Social and Dietary Limitations (SDL). It has the same 15 questions for all 3 age groups, but additional questions are included for 4-6 years (26 questions in total) and for 7-12 years (30 questions in total). The scoring is similar to the FAQLQ-CF, from 1 to 7, as mentioned above. The FAQLQ-PF has been previously translated to Hebrew and validated (33).

Translation

The FAQLQ-CF and the FAIM were translated from English to Hebrew according to standardized guidelines. The translation was then back-translated to English and the meaning of each question in the back-translation was examined against the same question in the original questionnaire, as prescribed by the World Health Organization (44).

Construct validity

Construct validity was examined for the translated FAQLQ-CF with the use of the translated FAIM. Correlation coefficients were calculated between the total FAQLQ-AF score and the total FAIM score, between individual FAQLQ-CF items and the total FAIM score. Moderate correlation coefficients (0.3 – 0.5) were expected. In addition, Cronbach's α was used to measure the internal consistency of the FAQLQ-CF and its sub-scales. A cutoff α value equal to or greater than 0.7 was used to determine good internal consistency (43).

SUPPLEMENTARY RESULTS

Validation of the FAQLQ-CF:

For validation of the FAQLQ-CF, OIT-treated and control patients who completed both the FAQLQ-CF and the FAIM questionnaires (n=125), were analyzed. The FAQLQ-CF showed moderate-high correlation with the total FAIM score in all domains ranging from 0.484 to 0.554 ($p < 0.001$ for all domains) (**Table S1**). All individual items of the translated FAQLQ-CF, with the exception of item No. 1, showed moderated correlation (>0.3) with the total FAIM score. Item 1 showed moderate correlation with at least 1 FAIM item. Cronbach's α coefficient demonstrated excellent internal consistency, ranging from 0.748 to 0.934 (**Table S1**).

Table S1. Correlation and internal consistency between FAQLQ-CF and FAIM, n=125

FAQLQ-CF	Cronbach α *	FAIM	
		Rho **	P value
Total Score	0.934	0.554	<0.001
Emotional Impact	0.834	0.484	<0.001
Allergen Avoidance	0.872	0.524	<0.001
Dietary Restrictions	0.792	0.501	<0.001
Risk of Accidental Exposure	0.748	0.520	<0.001

* Analysis performed using Cronbach Alpha Analysis

** Analysis performed using Spearman correlation coefficient

Table S2. Demographic and clinical characteristics of OIT-treated patients who were and who were not study eligible

Category	Variable	Frequency		P value
		Study eligible N=103	Not study eligible N=42	
Demographics	Age (y) [†]	9 (8-11)	9.5 (8.9-10.9)	0.44
	Male gender	59 (57.3%)	25 (59.5%)	0.85
	Multiple Food allergies	30 (29.1%)	13 (31%)	0.84
	Asthma	51 (49.5%)	20 (47.6%)	0.86
Clinical	Anaphylaxis	55 (53.4%)	19 (45.2%)	0.46
Background	Epinephrine	11 (10.7%)	4 (9.5%)	1.0
	Emergency department	50 (48.5%)	16 (38.1%)	0.28
	Hospitalization	11 (10.7%)	4 (9.5%)	1.0
OIT	SHTD (mg) [*]	60 (15-120)	68 (20-128)	0.56
	Epinephrine during first week	18 (17.5%)	6 (14.3%)	0.81

*SHTD = Single Highest Tolerated Dose

Table S3. The effect of continuous variables on the change in total FAQLQ-CF from OIT start to end of up-dosing*

Continuous Variable	Delta Total FAQLQ-CF	
	Coefficient (95% CI)	P value
Age	0.11 (-0.1 -0.31)	0.3
SHTD**	0 (-0.002 – 0.001)	0.7
Reactions	-0.04 (-0.13 – 0.06)	0.47
Duration	0.04 (-0.02 – 0.1)	0.19

*Refers to full or partial desensitization or treatment failure

**SHTD = Single Highest Tolerated Dose

Table S4. The effect of categorical variables on the change in total FAQLQ-CF from OIT start to end of up- dosing*

Categorical Variable		Delta Total FAQLQ-CF	
		Median (IQR)	P value
Gender	Male (n=59)	-0.5 (-1.4 – 0.3)	0.38
	Female (n=44)	-0.2 (-1.3 – 0.3)	
Asthma	No (n=52)	-0.7 (-1.8 – 0.3)	0.17
	Yes (n=51)	-0.2 (-1.1 – 0.3)	
>1 food allergies	No (n=73)	-0.5 (-1.5 – 0.3)	0.3
	Yes (n=30)	-0.2 (-1.2 – 0.3)	
Anaphylaxis	No (n=48)	-0.5 (-1.3 – 0.2)	0.73
	Yes (n=55)	-0.5 (-1.5 – 0.4)	
Epinephrine use	No (n=69)	-0.4 (-1.5 – 0.3)	0.84
	Yes (n=34)	-0.6 (-1.2 – 0.4)	
Emergency room	No (n=53)	-0.4 (-1.5 – 0.3)	0.59
	Yes (n=50)	-0.5 (-1.3 – 0.4)	
Hospitalization	No (n=92)	-0.45 (-1.3 – 0.3)	0.94
	Yes (n=11)	-0.8 (-1.5 – 0.4)	
Food treated	Milk (n=36)	-0.2 (-1.2 – 0.6)	0.37
	Egg (n=10)	0.2 (-2 – 0.9)	
	Peanut (n=22)	-0.9 (-1.6 – (-0.2))	
	Tree nuts (n=22)	-0.4 (-1.2 – 0.3)	
	Sesame (n=13)	-0.5 (-1.3 – 0.4)	
Epinephrine in OIT	No (n=76)	-0.3 (-1.2 – 0.5)	0.017
	Yes (n=27)	-0.7 (-2.0 – (-0.10))	

*Refers to full or partial desensitization or treatment failure

Table S5. Change in FAQLQ-CF scores of 90 fully and 10 partially desensitized patients.

FAQLQ-CF Scores	Full desensitization (n=90)				Partial desensitization (n=10)				Full vs. Partial
	1 st Visit	2 nd Visit*	Delta	P value 1 st -2 nd	1 st Visit	2 nd Visit*	Delta	P value 1 st -2 nd	P value Delta
Emotional Impact	5.4 (4-6.5)	4.7 (3.3-6.2)	-0.5 (-1.5-0.7)	0.016	5.5 (3.6-6.8)	4.1 (2.6-5.1)	-0.5 (-1.8-0)	0.046	0.09
Allergen Avoidance	4.8 (3.4-6.0)	4.2 (2.4-5.4)	-0.4 (-1.3-0.6)	0.006	5.3 (3.9-6.4)	3.7 (2.5-4.4)	-0.95 (-2.9-(-3.3))	0.016	0.52
Dietary Restrictions	4.3 (3.1-5.2)	3.7 (2.3-4.5)	-0.5 (-2.1-0.5)	0.002	4.4 (3.7-6.5)	4.2 (3.3-4.8)	-0.45 (-1.8-0.5)	0.21	0.5
Risk of accidental exposure	4.4 (3.3-5.6)	3.4 (2.5-4.8)	-0.4 (-1.9-0.6)	0.001	4.5 (3.3-7.0)	3.2 (2.3-4.9)	-0.45 (-2.8-0.1)	0.09	0.99
Total Score	4.8 (3.8-5.7)	3.9 (3-5.2)	-0.5 (-1.3-0.3)	0.001	5.0 (4.1-6.2)	3.7 (3.3-4.3)	-0.65 (-2.2-0.08)	0.018	0.36

Numbers represent medians (IQR)

* Second visit represents the time of reaching maintenance in fully desensitized patient and the time of discontinued up-dosing in partially desensitized patients.

Table S6. Change in FAQLQ-PF at the different stages of OIT (n=49).

FAQLQ-PF	Start	End of Up-dosing	Follow-up	P value Start - E	P value E - FU	P value Start - FU
Emotional Impact	4.2 (3.1-4.8)	3.2 (2.2-4.5)	2.5 (1.8-3.6)	0.026	0.003	<0.001
Food Avoidance	4.4 (3.1-5.8)	3.4 (2.1-5.2)	2.4 (1.4-3.6)	0.001	0.001	<0.001
Social and Dietary Restrictions	4.0 (2.1-5.0)	2.2 (1.4-4.6)	1.7 (1.0-3.2)	0.021	0.002	<0.001
Total Score	4.0 (3.2-5.0)	2.9 (1.9-4.7)	2.2 (1.6-3.6)	0.003	0.001	<0.001

Numbers represent medians (IQRs)

E= End of up-dosing; FU = Follow-up

Figure S1. Distribution of food allergies treated and of the SHTD in patients undergoing OIT.

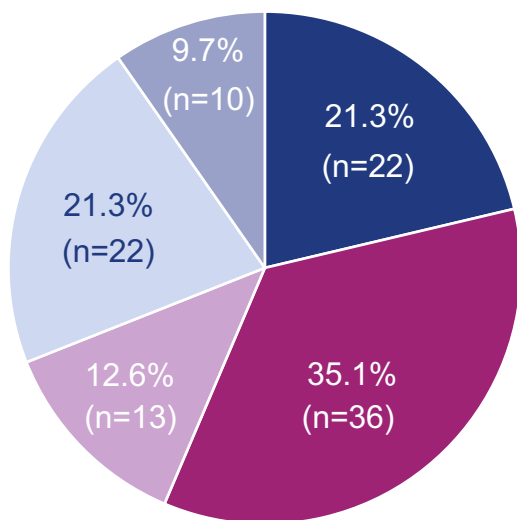
The percentage of patients treated for each food (A) and the distribution of their SHTD (B) at the start of OIT. SHTD = Single Highest Tolerated Dose

Figure S2. Change in individual FAQLQ-CF questions, by domain from baseline to end of up-dosing (n=103). The mean $\pm$ SEM change in each of the FAQLQ-CF questions, grouped by domains, from baseline to maintenance.

Figure S3. Change in individual FAQLQ-CF questions, by domain from baseline to follow-up (n=56). The mean $\pm$ SEM change in each of the FAQLQ-CF questions, grouped by domains, from baseline to follow-up.

(A)

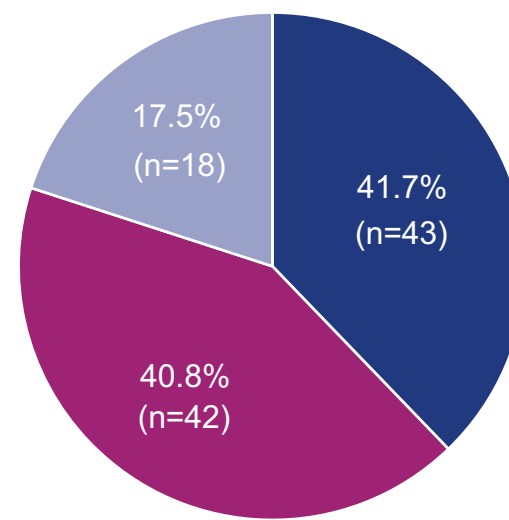
Foods treated in OIT



■ Peanut ■ Milk ■ Sesame ■ Treenuts ■ Egg

(B)

Distribution of SHTD



■ <40 mg ■ 40-150 mg ■ >150 mg

