

ORIGINAL ARTICLE

Food Allergy & Anaphylaxis

Parent and child perception of quality of life in a randomized controlled peanut oral immunotherapy trial

Tonje Reier-Nilsen^{1,2}  | Karin C. Lødrup Carlsen^{1,2} | Merethe Melbye Michelsen^{1,2} | Sebastian Drottning¹ | Kai-Håkon Carlsen^{1,2} | Chi Zhang³ | Magnus P. Borres^{4,5}  | Geir Håland^{1,2}

¹Division of Pediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway

²Institute of Clinical Medicine, University of Oslo, Oslo, Norway

³Department of Biostatistics, Faculty of Medicine, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway

⁴Thermo-Fisher Scientific, Uppsala, Sweden

⁵Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

Correspondence

Tonje Reier-Nilsen, Division of Pediatrics and Adolescent Medicine Ullevål, Oslo University Hospital, Postboks 4956 Nydalen, 0424 Oslo, Norway.

Emails: tonjre@ous-hf.no; tonje.nilsen@medisin.uio.no

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Abstract

Background: Improved quality of life (QoL) after oral immunotherapy (OIT) in peanut allergic children is often reported by their parents, while the child's perspective is less clear.

Objective: We aimed to explore whether 2 years of OIT improved QoL in children with peanut allergy and to identify factors influencing change in QoL.

Methods: In the open-labeled TAKE-AWAY peanut OIT trial including children with anaphylaxis to peanuts, 57 were randomized to OIT and 20 to observation. The Pediatric Quality of Life Inventory Version 4.0 was completed by parents and children at enrollment (Y_0), after 1 year (end of up dosing; Y_1) and after 2 years (Y_2) of OIT. Minimally clinically important difference (MCID) is ≥ 5.3 . Perceived treatment burden was recorded by visual analogue scales, including adverse events (AEs). An open food challenge (OFC) was performed at Y_2 .

Results: At Y_2 , 18 children had discontinued OIT and 2 of 39 OIT children refused OFC, while 35 of 37 were desensitized to 7500 mg peanut protein. From Y_0 to Y_2 , the mean change (95% confidence intervals) in QoL was 4.4 (0.5, 8.3) among child self-reports and twice as large among parental proxy reports (9.3 [4.3, 14.3]; both $P < 0.0001$), without significant improvement among the controls. The change in QoL was significantly different from the controls for the parental proxy reports only ($P = 0.002$). Neither treatment burden nor AEs significantly predicted changes in QoL.

Conclusion: Two years of OIT improved child-QoL as reported by parents, but not by the children, suggesting that parents may overestimate improvement in child-QoL by OIT.

Abbreviations: %CD63+, allergen-induced basophil reactivity (proportion of activated basophils); AEs, adverse events; BAT, basophil activation test; CAPT, conjunctival allergen provocation test; CI, confidence interval; DBPCFC, double-blind placebo-controlled food challenge; FAQL-PB, Food Allergy Quality of Life-Parental Burden; GI, gastrointestinal; OFC, oral food challenge; OIT, oral immunotherapy; PedsQL 4.0, Pediatric Quality of Life Inventory Version 4.0; PRO, patient-related outcome; QoL, quality of life; s-IgE/s-IgG/s-IgG₄, specific immunoglobulin E, G, G₄; SPT, skin prick test; SU, sustained unresponsiveness; TAKE-AWAY trial, The "Take-Away food allergy; inducing tolerance in children allergic to peanut" trial; VAS, visual analogue scale; Y_0 , at screening (enrollment); Y_1 , at completed up dosing, approximately after 1 year of treatment, 1 year for controls; Y_2 , at 1 year of maintenance treatment/after 2 years of treatment.

The study was performed within the ORAACLE (Oslo Research group of Asthma and Allergy in Children; the Lung and Environment), Oslo University Hospital and the University of Oslo.

Clinical trial registration: ClinicalTrials.gov number NCT02457416.

KEYWORDS

child, desensitization, double-blind placebo-controlled food challenge, oral immunotherapy, peanut allergy, perceived treatment burden, quality of life, self- and proxy reports, visual analogue scale

1 | INTRODUCTION

Peanut oral immunotherapy (OIT) appears promising for inducing desensitization (no allergic reaction while regularly exposed to the allergen),¹⁻⁵ which is the first step to sustained unresponsiveness (SU) after OIT discontinuation. In line with recommendations, measurements of treatment effect should include patient-reported outcomes (PROs)⁶ such as QoL assessments.

Improved QoL has been reported in children after OIT^{1,7-12} despite adverse events (AEs).¹³ Most studies on QoL after OIT are based on parents' assessments of their child's QoL,^{1,7-10} sometimes referred to as proxy reports.^{14,15} In a recent study of 0- to 18-year-old children with peanut, hazelnut, or egg allergy, parents assessed their children's QoL better than did the children themselves,¹⁶ questioning the appropriateness of relying on parental proxy reports alone. Even though one study demonstrated improved QoL after OIT by both parental proxy reports and child self-reports, the lack of a control group limited the possibility to assess whether this was OIT-related.¹¹ Information of one-dimensional PROs using, for example a visual analogue scale (VAS) of treatment burden, is largely lacking.

Peanut OIT is projected soon to become available as a treatment for peanut allergy. However, a recent editorial¹⁷ raised concerns regarding OITs in children highly sensitized to peanuts, based upon recent results from our ongoing 4-year peanut OIT; "Take-Away food allergy: Inducing tolerance in children allergic to peanut" trial (the TAKE-AWAY trial).⁵ This open-labeled randomized controlled trial has an overall objective to assess whether 4 years of OIT induces SU 1 year after cessation of treatment in children with primary peanut allergy. In the present study, we explored the effect of OIT on desensitization and PROs reported by the children and their guardians. Our primary aim was to explore whether peanut OIT improved child-QoL as reported by the parents and/or the children themselves. Secondarily, we aimed to explore whether factors including perceived treatment burden influenced change in QoL from pre-treatment to second year of treatment. Finally, we aimed to explore whether OIT ineligibility affected QoL 1 year later.

2 | METHODS

2.1 | Study design

As shown in Figure S1, the TAKE-AWAY trial^{5,18} has four phases: screening for eligibility (Y_0), the OIT up dosing phase ending after 50-78 weeks (Y_1), 36-months maintenance therapy with desensitization assessed after 2 years OIT (Y_2), and the follow-up of 12 months with SU assessed at Y_5 (to be completed in 2020).

Key Message

What is already known about this topic?

The improved quality of life (QoL) observed in children with peanut allergy undergoing OIT is predominantly based on parents' assessment. Discrepancies between the children's and the parents' assessments of the children's QoL may impact the use of patient-reported outcomes (PROs) in oral immune therapy (OIT).

What does this article add to our knowledge?

The present randomized controlled peanut OIT study includes child self-reports and parental proxy reports to assess QoL. Compared with the children's reports, parents reported a 2-fold increase in their children's QoL from before to after 2 years of OIT, and the improved QoL was significantly associated with OIT for these parental proxy reports only.

How does this study impact on current management guidelines?

Evaluation of OIT efficacy based upon PROs may be more appropriate using the child-reported rather than the parents' proxy-reported QoL which may overestimate improvement in QoL with this treatment.

The present study reports QoL assessed at Y_0 , Y_1 , and Y_2 .

Children 5-15 years old with sensitization to peanut by a peanut skin prick test (SPT) ≥ 3 mm and/or a specific IgE (s-IgE) to peanut ≥ 0.35 kUA/L or with a history of systemic reactions to peanut were screened for study enrollment at the Department of Pediatric and Adolescent Medicine, Oslo University Hospital, Ullevål, Norway, from February 2014 to June 2015, as previously described.¹⁸

Enrollment required a positive double-blind placebo-controlled food challenge (DBPCFC) defined by objective symptoms in ≥ 2 organ systems and a reactivity threshold >3 mg peanut protein¹⁸. Anaphylaxis was defined according to the European Academy of Allergy and Clinical Immunology criteria.¹⁹ Children with a reactivity threshold ≤ 3 mg peanut protein were deemed ineligible for randomization. Exclusion criteria were non-controlled asthma or severe chronic disease including severe atopic eczema and diabetes mellitus.

The screening investigations, described in detail in Appendix S1, included a structured interview, standardized QoL questionnaires, serological and immunologic analyses, lung function measurements,²⁰ SPT, and conjunctival allergen provocation test,²¹ followed by a DBPCFC.

Randomization to peanut OIT or controls (observation only) had a block size of 2:1, which restarted when the OIT starting dose was decreased from 5 to 1 mg peanut protein, as described in Appendix S1 and Table S1. The OIT followed a biweekly step-up protocol with a pre-defined high maintenance dose of 5000 mg, as described in Appendix S1.

The QoL assessments and all tests from the screening except the DBPCFC were repeated in all children still participating at Y_1 and Y_2 , while the OIT children only fulfilled a VAS of perceived treatment burden at Y_1 and Y_2 . The QoL of 19 OIT-ineligible children was reassessed only at Y_1 .

Desensitization was assessed at Y_2 by an open food challenge (OFC) with a maximum cumulated dose of 7500 mg peanut protein, as described in Appendix S1.

Written parental informed consent was obtained after detailed oral and written study information.

The TAKE-AWAY trial was approved by the Regional Committee for Medical and Health Research Ethics (number 2013/430) with regular communications in case of severe or unexpected AEs and registered at ClinicalTrials.gov (number NCT02457416).

2.2 | Study population

As previously reported,⁵ 96 children (5-15 years of age) had a positive DBPCFC at Y_0 with objective symptoms in minimum two-organ systems and fulfilled the EAACI criteria for anaphylaxis. Fifty-seven children were randomized to OIT and 20 to controls, whereas 19 were deemed ineligible for enrollment (Figure 1). The 77 children enrolled had primary sensitization to peanut with a mean (95% CI) s-IgE to Ara h2 of 103.0 (75.8, 130.3) kUA/L. Baseline characteristics are given in Table 1 and were similar among OIT children ($n = 57$), controls ($n = 20$), and ineligible children, except that significantly more of the

OIT children needed adrenaline during DBPCFC ($P = 0.03$).⁵ Of the 57 OIT children, 43 completed Y_1 and 39 Y_2 , while all 20 controls attended investigations at both Y_1 and Y_2 .

2.3 | Quality of life measurements

Children completed the validated,^{14,22} age-adapted (age 5-7, 8-12, and 13-18 years) generic Pediatric Quality of Life Inventory Version 4.0 (PedsQL 4.0) applying a 5-point Likert scale (0 = never, 4 = almost always) for 8- to 18-year-olds, and a simplified 3-point scale for 5- to 7-year-olds. The 13 items are reverse-scored (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0) reporting the mean sum of each item, as recommended.²² The minimal clinically important difference is defined as the smallest change that the patient perceives as important, which is 5.3 and 5.5 for the child self-report and the parental proxy report, respectively.¹⁴ The present study includes QoL scores for Psychosocial Functioning as this is found to be most relevant for food allergies,²³ please find details in Appendix S1.

Parents completed both the PedsQL 4.0 proxy report as well as the Food Allergy Quality of Life-Parental Burden (FAQL-PB) Questionnaire^{24,25} for parents' own QoL, both described in Appendix S1. The scores of the FAQL-PB 7-point Likert scale (1 = not troubled, 7 = extremely troubled) for each question are summated, reporting the sum ranging from 17 to 119.

Improved QoL is indicated by higher scores in the PedsQL 4.0 but lower scores in the FAQL-PB.

2.4 | Measurement of perceived treatment burden

A VAS form was developed to obtain one-dimensional reports of perceived treatment burden during the last 12 months

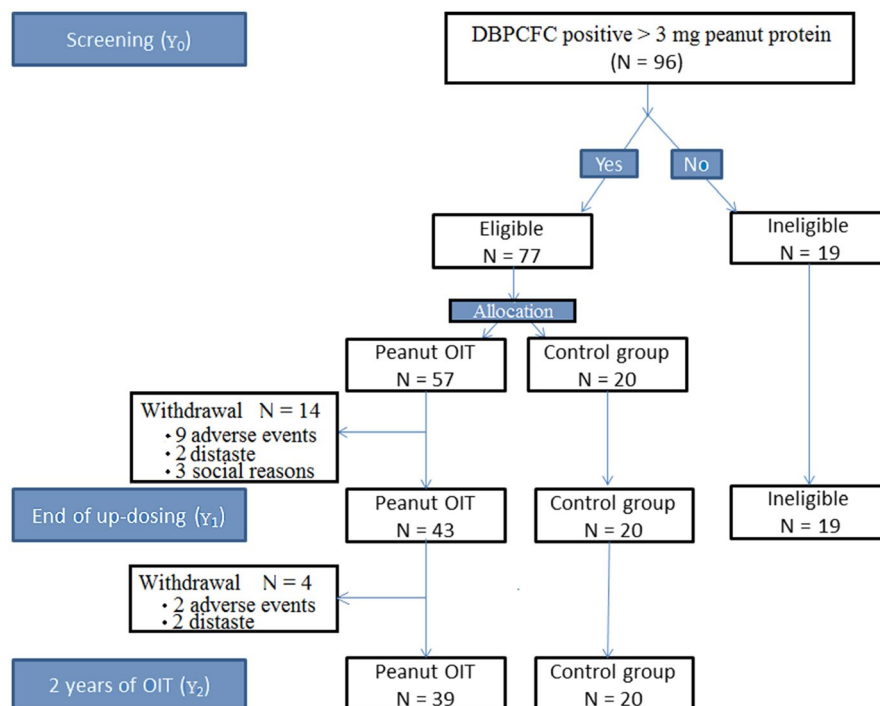


FIGURE 1 Flowchart from screening to second year of oral immunotherapy in the TAKE-AWAY trial [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Baseline characteristics of children randomized to peanut OIT or controls, and children ineligible for enrollment

	Active (n = 57)	Controls (n = 20)	Ineligible (n = 19)	Overall P-value
Age	9.3 (5.2, 15.2)	9.3 (5.1, 13.3)	10.9 (5.6, 14.6)	0.08
Male	31 (54.4)	13 (65.0)	6 (31.6)	0.10
History of systemic reaction to peanut	45 (78.9)	18 (90.0)	17 (89.5)	0.55
Current asthma	24 (42.1)	9 (45.0)	11 (57.9)	0.47
Allergic rhinitis	15 (26.3)	8 (40.0)	5 (26.3)	0.83
Atopic dermatitis	47 (82.5)	14 (73.9)	13 (68.4)	0.40
Allergy to tree nuts	20 (35.1)	7 (36.8)	9 (53.0)	0.37
Allergy to other food than nuts	27 (47.4)	11 (57.9)	11 (61.1)	0.57
Parental atopic disease ^a	50 (87.7)	16 (80.0)	17 (89.5)	0.84
Parental food allergy ^b	21 (36.8)	6 (30.0)	11 (57.9)	0.17
FEV1% predicted	101.2 (97.6, 105.0)	95.5 (88.3, 107.2)	93.3 (85.8, 102.3)	0.15
Pos s-IgE (≥ 0.35 kUA/L)				
Tree nuts ^c	52 (91.2)	16 (80.0)	19 (100.0)	0.07
Other food ^d	54 (94.7)	19 (95.0)	19 (100.0)	0.65
Peanut SPT (mm)	9.8 (8.6, 11.0)	9.3 (7.4, 11.7)	9.8 (8.2, 12.1)	0.97
S-IgE (kUA/L)				
Peanut	110.6 (70.4, 173.8)	52.2 (20.3, 134.4)	128.8 (74.1, 218.8)	0.34
Ara h 2	56.2 (37.2, 87.1)	22.4 (8.4, 58.9)	63.6 (38.0, 102.3)	0.13
Peanut s-IgE/total IgE (kUA/L)	0.3 (0.2, 0.4)	0.2 (0.1, 0.4)	0.3 (0.2, 0.5)	0.39
Peanut s-IgG ₄ /s-IgE (ng/mL)	117.5 (82.9, 165.9)	97.7 (46.3, 208.8)	104.7 (42.4, 263.0)	0.39
QoL child self-report	82.1 (79.1, 85.2)	83.4 (75.4, 91.4)	81.8 (75.8, 87.7)	0.81
QoL parental proxy report	79.8 (76.3, 83.3)	80.7 (73.6, 87.7)	80.0 (69.6, 90.4)	0.62
Baseline DBPCFC				
Anaphylaxis severity grade				
Modified EAACI	1.6 (1.4, 1.7)	1.7 (1.5, 2.0)	1.7 (1.5, 1.7)	0.50
Sampson	2.6 (2.4, 2.8)	2.8 (2.5, 3.2)	1.8 (1.5, 2.0)	0.25
Use of adrenaline	30 (52.6)	5 (25.0)	8 (42.1)	0.10
LOAEL (mg peanut prot [ppt])	18.4 (11.8, 28.6)	16.6 (6.2, 44.7)	NA	0.34
Reactivity threshold (mg ppt)	46.2 (29.7, 72.0)	75.9 (33.1, 173.8)	NA	0.06

Note: Continuous variables are given as geometric mean (95% CI) or n (%), except age which is given as median (min, max) and QoL which is given as mean (95% CI).

One-way ANOVA was applied to determine statistically significant differences between group means.

Chi-square test was applied to determine statistical differences between categorical data.

Anaphylaxis severity was graded by two grading systems according to the modified EAACI position papers¹⁹, Ref. 28 in Supporting Information) ranging from 1 to 3 and the method of Sampson (Grading of Food-Induced Anaphylaxis According to Severity of Clinical Symptoms; Ref. 29 in Supporting Information) ranging from 1 to 5.

Reactivity threshold was defined as the cumulated peanut protein (mg) ingested at positive DBPCFC.

Quality of life scores were given by the generic Pediatric Quality of Life Inventory version 4.0 (PedsQL 4.0).^{14,22}

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; Ig, immunoglobulin; LOAEL, lowest observed adverse effect level (amount of peanut eliciting mild, objective symptoms); LOAEL, lowest observed adverse effect level; OIT, oral immunotherapy; QoL, quality of life; SPT, skin prick test.

^aAtopic disease includes asthma, allergic rhinitis, atopic dermatitis, allergic conjunctivitis.

^bAll food allergy including peanut and tree nut allergy.

^cHazelnut, almond, cashew nut, pistachio nut, walnut, pecan nut, brazil nut, and macadamia nut.

^dFenugreek, soybean, pea, red kidney bean, lupin seed, and wheat.

within three domains: Gastrointestinal (GI)-related AEs (stomach ache, nausea/vomiting, and oral itching), taste and amount of daily peanut dose, and time spent on OIT (up dosing at hospital and ingestion of OIT doses at home), with details in Appendix S1.

2.5 | Outcomes and explanatory factors

The primary outcome was change in child self-reported QoL scores from Y_0 to Y_2 , while the secondary outcome was the corresponding parental proxy reports.

The level of desensitization was defined as the highest cumulated dose of peanut protein eaten without eliciting allergic reactions corresponding to a positive Y_2 OFC.

Factors that potentially could influence the change in QoL included level of desensitization, AEs, maintenance dose at Y_1 , and perception of treatment burden (mean of the three domains: GI-related AEs, taste/amount of peanuts, and time spent on OIT) at Y_1 and Y_2 .

2.6 | Statistical analyses

Baseline characteristics are reported as geometric means with 95% confidence interval (95% CI) or means (95% CI) for non-normal and normal distributions of continuous data, respectively. Statistically significant group differences were assessed using mixed-models analyses for repeated measures followed by Scheffe's test, the Mann-Whitney U test for continuous data, and the chi-square test for categorical data.

The TAKE-AWAY study population size was determined by statistical power analysis outlined in Appendix S1. A treatment group of 40 and a control group of 20 subjects would provide a statistical power of 80% to observe a difference in SU at a five percent significance level between the two groups.

Analyses in the present study were explorative. Mixed-models analyses were applied to assess changes in QoL scores from Y_0 to Y_2 using QoL score at Y_0 , Y_1 and Y_2 , age, gender, and randomization group as independent variables.

A paired t test was applied assessing changes in VAS from Y_1 to Y_2 .

As the normality assumptions for the multiple linear regression analysis were not fulfilled, multivariate robust regression analyses with Huber's M-estimator were used to assess associations between possible factors influencing QoL and change in QoL from Y_0 to Y_2 as outlined in Appendix S1.

Bivariate unadjusted analyses were performed with Spearman correlation analyses (r_s = Spearman correlation coefficient).

A P -value of ≤ 0.05 was considered statistically significant.

Randomization to OIT or controls was performed using Statistical Analysis System (SAS, version 9.3, SAS Institute Inc), and statistical analyses were performed with the IBM Statistical Package for Social Sciences (IBM SPSS Statistics, version 23, Armonk, NY: IBM Corp).

3 | RESULTS

By Y_2 , 18 of 57 (31.6%) children had withdrawn from OIT with their baseline characteristics as well as QoL scores at Y_0 given in Table S2. All 20 controls attended Y_0 , Y_1 , and Y_2 . The mean (SD; min, max) daily maintenance dose of peanut protein was 3322 (1376) (350, 5000) mg.

The Y_2 OFC was refused by 2 of the remaining 39 OIT children out of concern for allergic reactions. Among 37 challenged children, tolerance to 7500 mg peanut protein was confirmed in 35 (94.6%), as described further in Appendix S1.

As shown in Figure 2, the children's self-reported mean (95% CI) QoL scores improved significantly from Y_0 (82.1 [79.1, 85.2]) to Y_2 (86.7 [83.6, 89.7]) within the OIT group ($P < 0.0001$), whereas the QoL scores among controls did not change significantly from the 83.4 (75.4, 91.4) at Y_0 to 82.2 (76.0, 88.4) at Y_2 ($P = 0.80$). However, the mean (95% CI) QoL change of 4.4 (0.5, 8.3) from Y_0 to Y_2 in the OIT group was not significantly different from the -0.9 (-7.9 , 6.11) change observed among the controls ($P = 0.12$; Figure 2).

The parental proxy-reported mean (95% CI) QoL score improved significantly from Y_0 (78.7 [73.6, 83.7]) to Y_2 (88.0 [85.2, 90.8]) within the OIT group ($P < 0.0001$), which was significantly higher than the corresponding improvement in QoL among the controls from Y_0 (81.7 [74.6, 88.8]) to Y_2 (82.1 [75.8, 88.4]; $P = 0.90$), as shown in Figure 2.

In contrast to the child reports, the 2-fold larger mean (95% CI) change in parental proxy-reported QoL of 9.3 (4.3, 14.3) in the OIT

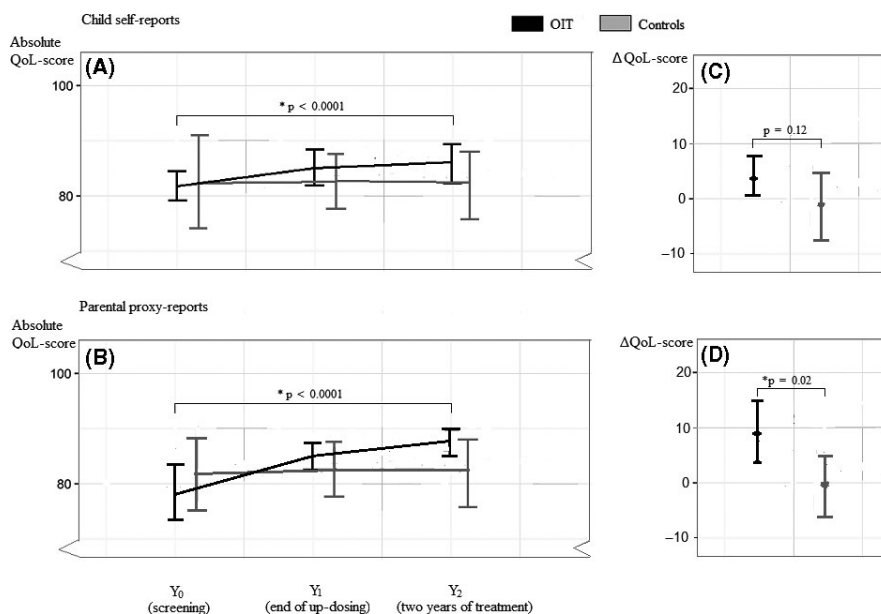


FIGURE 2 The absolute quality of life (QoL) scores (y-axis) in 43 children who receive oral immunotherapy (OIT) and the 20 controls at Y_0 (screening), Y_1 (after 1 y of up-dosing), and Y_2 (after second year of treatment), as reported by the PedsQL 4.0 child self-reports (A) and the parental proxy reports (B). Increased score reflects improved QoL. The change in QoL scores (Δ QoL) from Y_0 (screening) to Y_2 (second year of treatment; y-axis) among the child self-reports (C) and the parental proxy reports (D)

TABLE 2 The perceived treatment burden at Y_1 (after updosing) and Y_2 (after 1 y of maintenance treatment)

	1 y of treatment (Y_1) (N = 43)	2 y of treatment (Y_2) (N = 37)	P-value
Overall	3.9 (3.1, 4.8)	3.7 (2.9, 4.6)	0.84
GI-domain	2.6 (1.9, 3.3)	1.4 (1.0, 1.8)	0.001
Oral itching	3.4 (2.5, 4.4)	2.1 (1.3, 2.9)	0.02
Stomach ache	2.6 (1.7, 3.5)	1.4 (0.8, 2.0)	0.008
Nausea or vomiting	1.6 (0.8, 2.5)	0.6 (0.3, 0.9)	0.02
Taste-/amount-domain	6.5 (5.5, 7.3)	5.3 (4.3, 6.3)	0.02
Taste	7.0 (5.9, 8.0)	6.1 (4.9, 7.3)	0.10
Amount	5.8 (4.8, 6.7)	4.3 (3.3, 5.2)	0.01
Time spent domain	2.9 (2.1, 3.7)	2.2 (1.5, 2.9)	0.06
At home	2.5 (1.6, 3.4)	2.5 (1.5, 3.6)	0.94
At hospital (updosing/visits)	3.0 (2.2, 3.)	1.7 (1.2, 2.3)	0.005

Note: Values are given as mean with 95% confidence interval (CI).

Unpaired t test was applied to determine statistically significant difference between means.

The GI-domain represents average of how AEs like stomach ache, nausea/vomiting, and oral itching are perceived.

The taste-/amount-domain represents average of perceived taste and amount of peanut eaten.

The time spent domain represents perceived average of time spent on eating OIT doses at hospital for updosing visits and at ingesting OIT doses at home.

group was significantly different from the parental controls (0.4 [−7.1, 8.0]; $P = 0.02$; Figure 2).

For OIT children, number of AEs was not significantly associated with change in QoL from Y_0 to Y_2 in bivariate analyses, neither was maintenance dose or any of the three perceived treatment burden domains at Y_1 or Y_2 (Table 2), as shown in the final regression model (Table 3). Including children who discontinued OIT and time spent on OIT did not change the results (data not shown).

Parents' QoL reported by the FAQL-PB improved significantly among both the OIT group and controls from Y_0 to Y_2 (Figure S3).

The QoL was similar among OIT-ineligible children and controls at Y_0 and Y_1 (Figure S4), while the QoL of parents of ineligible children was significantly ($P = 0.048$) poorer compared with parents of the controls at Y_1 , despite being similar at Y_0 (Figure S5).

4 | DISCUSSION

By 2 years of OIT, 18 children had discontinued treatment, while most children with 2 years of OIT were desensitized to 7500 mg peanut regardless of maintenance dose. The child-reported QoL improvement after 2 years OIT was not significantly different between OIT children and the controls. In contrast, the corresponding 2-fold larger improvement in child-QoL reported by the parents of OIT children was significantly larger than that reported by control parents, likely to represent a clinically meaningful difference.¹⁴ Neither AEs nor perception of treatment burden reported by the children, level of desensitization, or maintenance dose significantly influenced the change in QoL. The QoL of OIT-ineligible children was similar to that of controls at enrollment and Y_1 , while the QoL of their parents was poorer after 1 year compared with control parents.

Our finding that parental proxy-reported, but not child self-reported QoL, improved significantly with 2 years of OIT, is to the best of our knowledge novel. Discrepancies between child self-reported and parental proxy-reported QoL have been demonstrated for chronic diseases²² including children with food allergies.¹⁶ In line with these reports,^{16,22} the pre-treatment parentally reported child-QoL of 78.7 was poorer than the children's self-reported score of 82.1. The increase in parentally reported child-QoL to 88.0 after 2 years of OIT is consistent with a change from “chronically ill” to “healthy” in the original Varni paper.²² Although we found that child-QoL improved after 2 years OIT in both the parental proxy reports and the child self-reports, the significant OIT-related improvement in child-QoL was observed among the parental proxy reports only and is probably due to the 2-fold larger improvement compared with child self-reports. The larger improvement in the parental proxy reports may reflect improved QoL among the parents, regardless of study group. Parents may thus be more influenced by their child's well-being than the child itself and respond more positively than their children to general study participation^{7,10,11} including going through the OFC.²⁶ This study supports the suggestion²² that in addition to include parental proxy reports as is commonly done,^{1,7,10,12} it is important to include the child self-reported QoL.

Neither perception of treatment burden, level of desensitization, maintenance dose, nor AEs influenced change in QoL from baseline to 2 years OIT, in line with previous reports.^{10,16,27} Thus, perceived treatment burden may be disassociated from the number and severity of AEs during OIT.^{10,16}

Reduced QoL in parents by ineligibility for OIT is in contrast to a previous report of improved QoL after OFC.²⁶ The poorer QoL may reflect the finding of severe peanut allergy with a very low reactivity threshold, including loss of hope for therapy.

TABLE 3 Multivariate robust regression analyses for associations between factors that may influence change in quality of life from Y_0 (screening) to Y_2 (second year of treatment)

	PedsQL 4.0 child	P-value	PedsQL 4.0 parents	P-value	FAQLPB (parents)	P-value
Age	-0.49 (-2.17, 1.19)	0.56	1.50 (0.24, 3.23)	0.09	0.02 (-0.06, 0.10)	0.63
Gender	-8.90 (-18.55, 0.76)	0.07	-5.90 (-16.29, 4.50)	0.26	0.23 (-0.25, 0.71)	0.34
Maintenance dose (mg)	-0.00 (-0.01, 0.00)	0.48	-	-	-	-
Perceived burden of						
Adverse events	-0.22 (-0.59, 0.15)	0.23	0.19 (-0.17, 0.56)	0.29	-0.02 (-0.04, 0.00)	0.10
Taste/amount of peanuts	0.15 (-0.02, 0.32)	0.09	-	-	0.01 (-2.02, -0.13)	0.09

Note: Associations are given as the relative change (β) related to each unit increase by the in QoL score. $N = 37$, including only children still receiving OIT at Y_2 with no missing data. Change in QoL is given by the Pediatric Quality of Life Inventory Version 4.0 (PedsQL 4.0) child self-report and parental proxy report, or the Food Allergy Quality Of Life-Parental Burden (FAQLPB). Decreasing values of PedsQL and increasing values of FAQLPB reflect poorer QoL. Perceived treatment burden was reported by VAS (range 0-10; 0 = no burden, 10 = massive burden) within the domains: adverse events (stomach ache, nausea/vomiting, and oral itching) and taste and amount of daily peanut OIT.

4.1 | Strengths and limitations

The study strengths include the standardized QoL assessments completed by both children and parents, the control group, close follow-up, and detailed information of AEs and a VAS of perceived treatment burden.

The study limitations include allocating controls for observation only, which excludes expectations of treatment effect caused by placebo. This may bias the result toward a larger difference between the OIT children and controls.

The larger variation in QoL observed among the child reports as well as the limited sample size may have contributed to the non-significant differences observed among the children's self-reports.

We did not capture QoL assessment in the 32% of OIT children who discontinued treatment. Expecting a lower QoL in these children, this bias may overestimate the positive effect on QoL by OIT, supporting our interpretation that peanut OIT did not significantly improve child-reported QoL.

5 | CONCLUSION

Among the two-thirds of children who completed 2 years of peanut OIT, QoL improved compared with controls as reported by the parents, but not by the children themselves, indicating that parents may overestimate improvement in QoL by OIT.

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CONFLICT OF INTEREST

Karin C. Lødrup Carlsen has received governmental and non-governmental research grants. Magnus P. Borres is employed by Thermo Fisher Scientific. The other authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

G. Håland, K. C. Lødrup Carlsen, and K-H. Carlsen designed the project. M. M. Michelsen, G. Håland, and T. Reier-Nilsen included patients and collected data, and S. Drottning carried out the updosing protocol. M. P. Borres contributed in carrying out immunologic tests. The analytic approaches were designed by G. Håland, K. C. Lødrup Carlsen, K-H. Carlsen, C. Zhang, and T. Reier-Nilsen, while the main statistical analyses were performed by T. Reier-Nilsen in collaboration with the statistician C. Zhang. T. Reier-Nilsen is the lead author with significant contribution from all authors who read and approved the submitted manuscript.

ORCID

Tonje Reier-Nilsen  <https://orcid.org/0000-0001-8184-0607>

Magnus P. Borres  <https://orcid.org/0000-0002-9045-2304>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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SUPPLEMENTARY TABLES

Supplement Table 1. Baseline characteristics in children with peanut OIT starting dose 1 mg and 5 mg peanut protein.

	OIT starting dose 1 mg peanut protein (n = 40)	OIT starting dose 5 mg peanut protein (n = 17)	p-value
Age	9.7 (5.4, 15.0)	10.4 (6.3, 15.1)	0.26
Male sex	23 (57.5)	8 (47.5)	0.47
Ever had eczema	32 (80.0)	15 (88.2)	0.46
Current asthma	20 (50.0)	11 (64.7)	0.56
Allergic rhinitis	10 (25.0)	5 (29.4)	0.77
Parental atopic disease*	38 (90.5)	12 (70.6)	0.01
Parental food allergy**	15 (37.5)	6 (35.3)	0.87
Peanut SPT (mm)	9.8 (4.0, 36.3)	9.4 (4.0, 22.9)	0.88
Positive SPT other nuts (≥ 3 mm)***	22 (55.0)	6 (35.3)	0.17
S-IgE (kUA/L)			
Peanut	92.8 (9.8, 2290.9)	102.3 (3.1, 955.0)	0.86
Ara h 2	46.8 (9.9, 489.8)	61.7 (2.5, 457.1)	0.60
Positive s-IgE (kUA/L)			
other nuts***	38 (95.0)	14 (87.5)	0.33
other food****	38 (95.0)	16 (100.0)	0.36
Peanut s-IgE/total IgE (kUA/L)	9.5 (8.0, 10.0)	9.5 (9.1, 9.9)	0.46
Peanut s-IgG ₄ /s-IgE (ng/ml)	4.7 (9.2, 288.4)	4.7 (9.9, 42.7)	0.72
BAT (%CD63+), pos *****	63.1 (16.2, 93.3)	64.6 (37.2, 91.2)	0.80
CAPT positive (dilution) *****			
1/160	5 (12.5)	2 (11.8)	0.59
1/80	11 (27.5)	2 (11.8)	
1/40	12 (30.0)	9 (52.9)	
1/20	11 (27.5)	2 (11.8)	
1/10	11 (27.5)	2 (11.8)	
Pre-OIT DBPCFC			
Use of adrenaline	23 (57.5)	7 (41.2)	0.26
Anaphylaxis severity modified EAACI	1.7 (1.0, 2.0)	1.4 (1.0, 2.0)	0.10
Reactivity threshold	42.8 (3.0, 933.3)	93.7 (12.9, 1584.9)	0.12

*Atopic disease includes asthma, allergic rhinitis, atopic dermatitis, allergic

conjunctivitis

**All food allergy including peanut and treenut allergy

***Hazelnut, almond, cashewnut, pistachionut, walnut, pecannut, brazilnut and macadamianut

****Fenugreek, soybean, pea, red kidney bean, lupin seed and wheat

***** The CAPT was recorded positive ranging from dilution level 1 (1:160) to 5 (1:1).

***** N=50. The BAT was not performed in 7 children due to technical causes (n=5) and non-reponders were excluded from the analyses (n=2).

14 Anaphylaxis severity was graded according to the modified EAACI position papers (19, 28)
15 ranging from 1 to 3 and the method of Sampson (Grading of Food-Induced Anaphylaxis
16 According to Severity of Clinical Symptoms) (29) ranging from 1 to 5.
17

18 SPT, skin prick test; BAT, basophil activation test; CAPT, conjunctival provocation test;
19 Ig - immunoglobulin; LOAEL - lowest observed adverse effect level; OIT – oral
20 immunotherapy; DBPCFC – double blind placebo controlled food challenge; LOAEL -
21 lowest observed adverse effect level (amount of peanut eliciting mild, objective symptoms)

22 Supplement Table 2.

	Patients completing OIT up- dosing (n = 43)	Patients dis- continuing OIT (n = 14)	p-value		
Age (median, min-max)	9.0 (5.2, 15.2)	11.1 (5.4, 15.1)	0.13		
Male	21 (48.8)	10 (71.4)	0.14		
History of anaphylaxis to peanuts	32 (74.4)	13 (92.8)	0.41	6 (42.9)	0.82
				8 (57.1)	0.37
Current asthma	16 (69.6)	8 (57.1)	0.26		
Allergic rhinitis	13 (30.2)	2 (14.3)	0.53		
Atopic dermatitis	36 (83.7)	11 (78.6)	0.64		
Allergy to tree-nuts	20 (48.8)	0 (0.0)	0.002		
Allergy to other food than nuts	25 (59.5)	2 (14.3)	0.003		
Parental atopic disease*	36 (83.7)	14 (100.0)	0.16		
Parental food allergy**	14 (32.6)	7 (50.0)	0.51		
FEV1% predicted	102.7 (98.6, 106.7)	99.7 (94.0, 105.8)	0.58		
SPT tree-nuts ≥ 3 mm	25 (58.1)	3 (21.4)	0.02		
Pos s-IgE (≥ 0.35 kUA/L): tree-nuts***	40 (95.2)	12 (85.7)	0.08		
other food****	41 (95.3)	13 (92.9)	0.63		
Peanut SPT (mm)	10.3 (8.7, 11.9)	12.1 (8.3, 15.8)	0.48		
Total IgE (kUA/L)	570.6 (405.1, 736.2)	713.9 (314.1, 1113.6)	0.51		
<u>S-IgE (kUA/L):</u> Peanut	197.5 (12.8, 270.1)	472.8 (120.2, 825.3)	0.09		
Ara h2	99.0 (62.7, 135.2)	177.1 (85.9, 268.4)	0.05		
Peanut s-IgE/ total IgE (kUA/L)	0.3 (0.3, 0.4)	0.5 (0.4, 0.7)	0.009		
Peanut s-IgG4/ s-IgE (ng/ml)	27.4 (10.5, 44.4)	9.7 (1.9, 21.3)	0.22		
QoL child self-report	78.6	81.7	0.80		

	(75.6, 81.7)	(77.6, 86.3)	
QoL parental proxy-report	82.7 (80.0, 85.4)	82.1 (75.5, 88.8)	0.71
<i>At baseline DBPCFC:</i>			
Number of anaphylaxis:	43 (100.0)	14 (100.0)	C
Anaphylaxis severity grade: modified EAACI	1.7 (1.6, 1.8)	1.6 (1.4, 1.9)	0.70
Sampson	2.7 (2.3, 2.9)	2.7 (2.3, 3.1)	0.94
Use of adrenaline	22 (51.2)	8 (57.1)	0.70
LOAEL (mg peanut protein)	113.3 (12.4, 214.3)	82.9 (16.3, 149.5)	0.11
Reactivity threshold (mg peanut protein)	155.4 (48.9, 261.9)	250.1 (60.9, 439.3)	0.07

Variables are given as mean (95% CI) or n (%), except age which is given as median (min, max).

Bold values are statistically significant ($p < 0.05$).

C Not able to compute – anaphylaxis at DBPCFC is a constant.

*Atopic disease includes asthma, allergic rhinitis, atopic dermatitis, allergic conjunctivitis

**All food allergy including peanut and treenut allergy

***Hazelnut, almond, cashewnut, pistachionut, walnut, pecannut, brazilnut and macadamianut

****Fenugreek, soybean, pea, red kidney bean, lupin seed and wheat

*****The CAPT was recorded positive ranging from dilution level 1 (1:160) to 5 (1:1).

Anaphylaxis severity was graded by two grading systems according to the modified EAACI position papers (19, 28) ranging from 1 to 3 and the method of Sampson (Grading of Food-Induced Anaphylaxis According to Severity of Clinical Symptoms) (29) ranging from 1 to 5. LOAEL is defined as the cumulated peanut protein (mg) ingested eliciting mild, objective symptoms

Reactivity threshold is defined as the cumulated peanut protein (mg) ingested at positive DBPCFC, with at least two moderate objective symptoms in one or more organ systems symptoms according to Bock's criteria (33, 34, 42).

Quality of life scores was given by the generic Pediatric Quality of Life Inventory Version 4.0 (PedsQL 4.0) (14, 22).

SPT, skin prick test; Ig - immunoglobulin; LOAEL - lowest observed adverse effect level; OIT – oral immunotherapy; DBPCFC – double blind placebo controlled food challenge; LOAEL - lowest observed adverse effect level (amount of peanut eliciting mild, objective symptoms); QoL – quality of life

SUPPLEMENTARY FIGURE LEGENDS

Supplement Figure 1

Overall study design. The “Take away food allergy; inducing tolerance in children allergic to peanut” trial (TAKE-AWAY trial) established in 2012 consists of four phases; the screening phase (three days of eligibility screening), up-dosing phase (50-78 weeks), maintenance phase (36 months) and follow-up phase (12 months). Defined time-points in the study was Y_0 – at screening, Y_1 - after one year of OIT (the end of up-dosing phase), Y_2 , Y_3 , Y_4 after two, three and four years of OIT (one, two and three years of maintenance treatment) respectively and Y_5 - one year after cessation of 4 years of OIT, with assessments expected to be completed in 2020.

Supplement Figure 2

Correlation between change in perceived treatment burden from end of up-dosing (Y_1) to second year of treatment (one year of maintenance) (Y_2) (Δ) (Y-axis) and perceived burden at Y_1 (X-axis). Perceived treatment burden is reported as mean score per domain ranging from 0–10 (0=no burden, 10=massive burden) within overall burden (A), as well as within three domains: Adverse events (stomach ache, nausea/vomiting and oral itching) (B), taste and amount of daily peanut oral immunotherapy (OIT) (C) and time spent on OIT (D).

Supplement Figure 3

A: The absolute quality of life (QoL) scores (Y-axis) in 43 parents of children receiving oral immunotherapy (OIT) and the 20 controls at Y_0 (screening), Y_1 (after one year of up-dosing) and Y_2 (after second year of treatment) using the FAQL-PB. Decreased value reflects improved QoL.

B: The change in QoL-scores (Δ QoL) from Y_0 (screening) Y_2 (second year of treatment) (Y-axis).

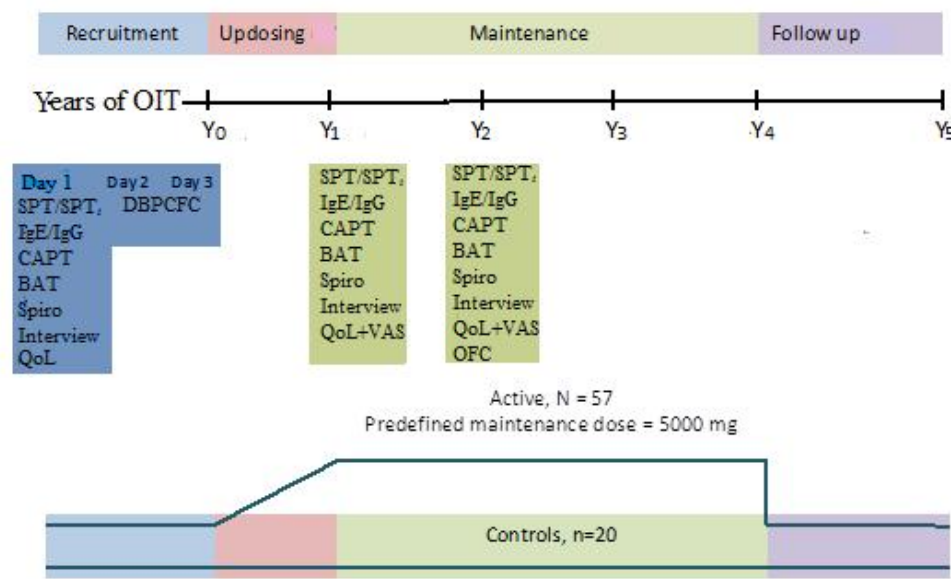
Supplement Figure 4

The absolute quality of life (QoL) scores (Y-axis) in 19 children ineligible for oral immunotherapy (OIT) and the 20 controls at Y_0 (screening) and Y_1 (after one year of up-dosing), as reported by the PedsQL 4.0 child self-reports (A) and the parental proxy-reports (B). Increased score reflects improved QoL.

Supplement Figure 5

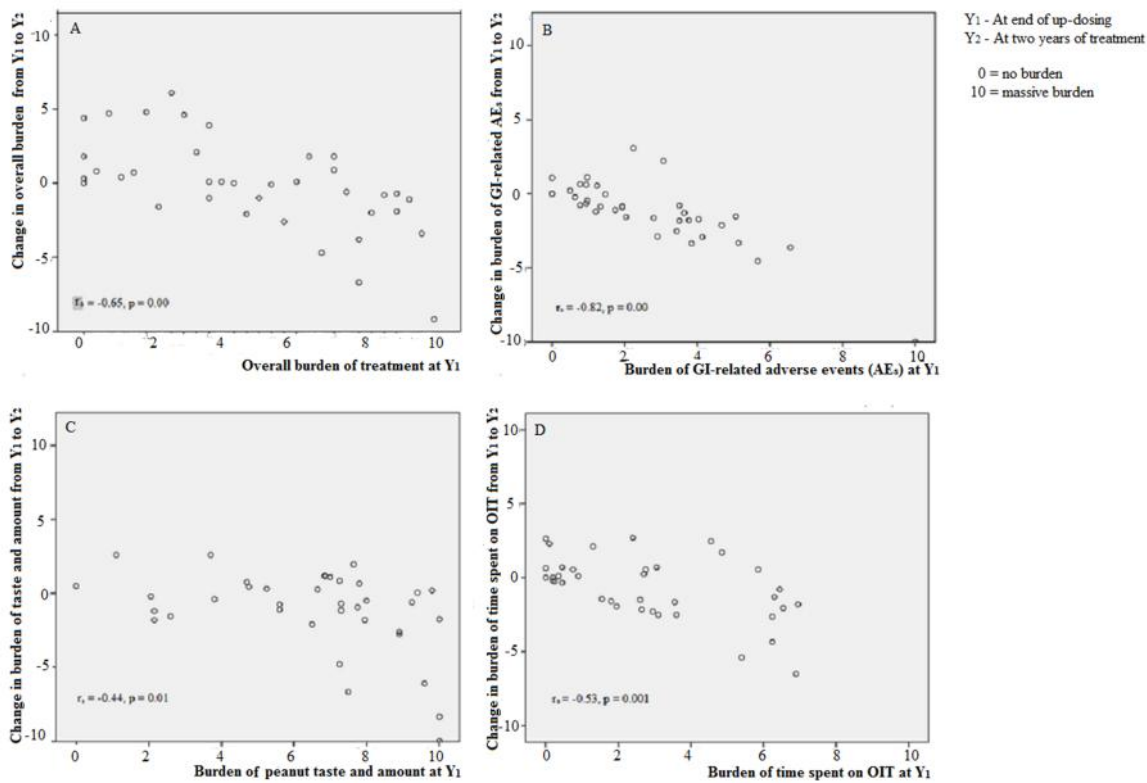
The absolute quality of life (QoL) scores (Y-axis) in 19 parents of children ineligible for oral immunotherapy (OIT) and the 20 controls at Y_0 (screening) and Y_1 (after one year of up-dosing). Decreased score reflects improved QoL.

84 **Supplement Figure 1**



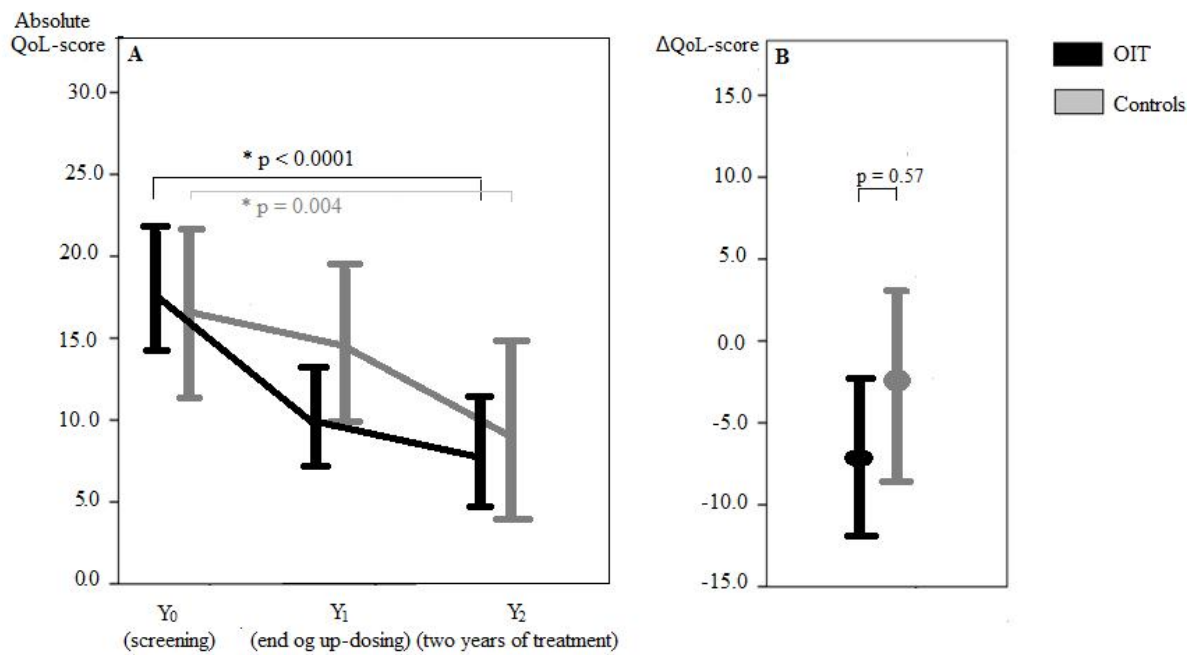
BAT – basophil activation test; CAPT – conjunctival allergen provocation test;
DBPCFC – double-blind placebo-controlled food challenge; OFC – oral food
challenge; Spiro – spirometry with reversibility testing; SPT – skin prick test; SPT_t –
titrated skin prick test; VAS*; visual analogue scale form of perceived treatment
burden; QoL – standardized quality of life questionnaires
*only in the OIT children

93 **Supplement Figure 2**



94

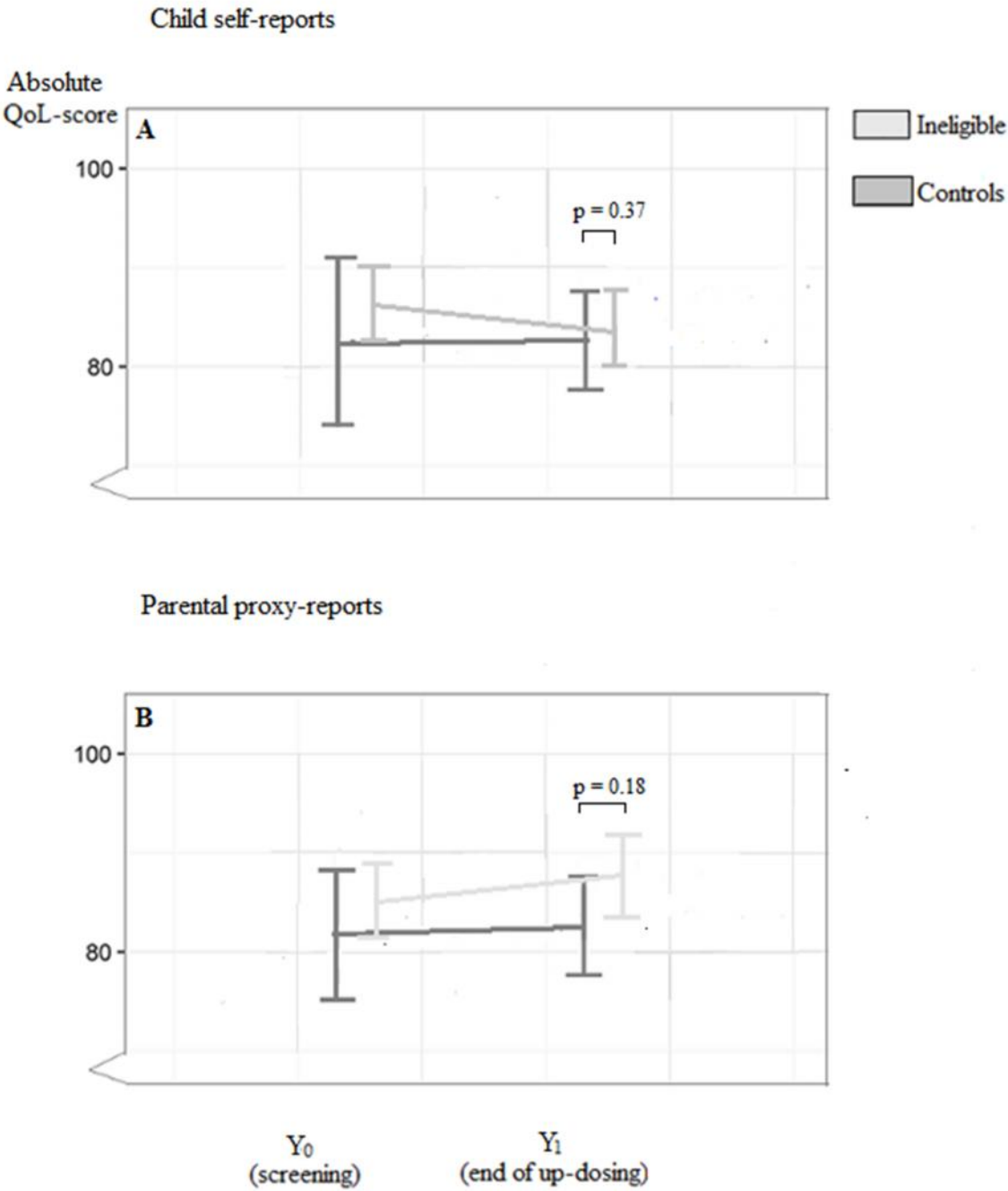
95 **Supplement Figure 3**



96

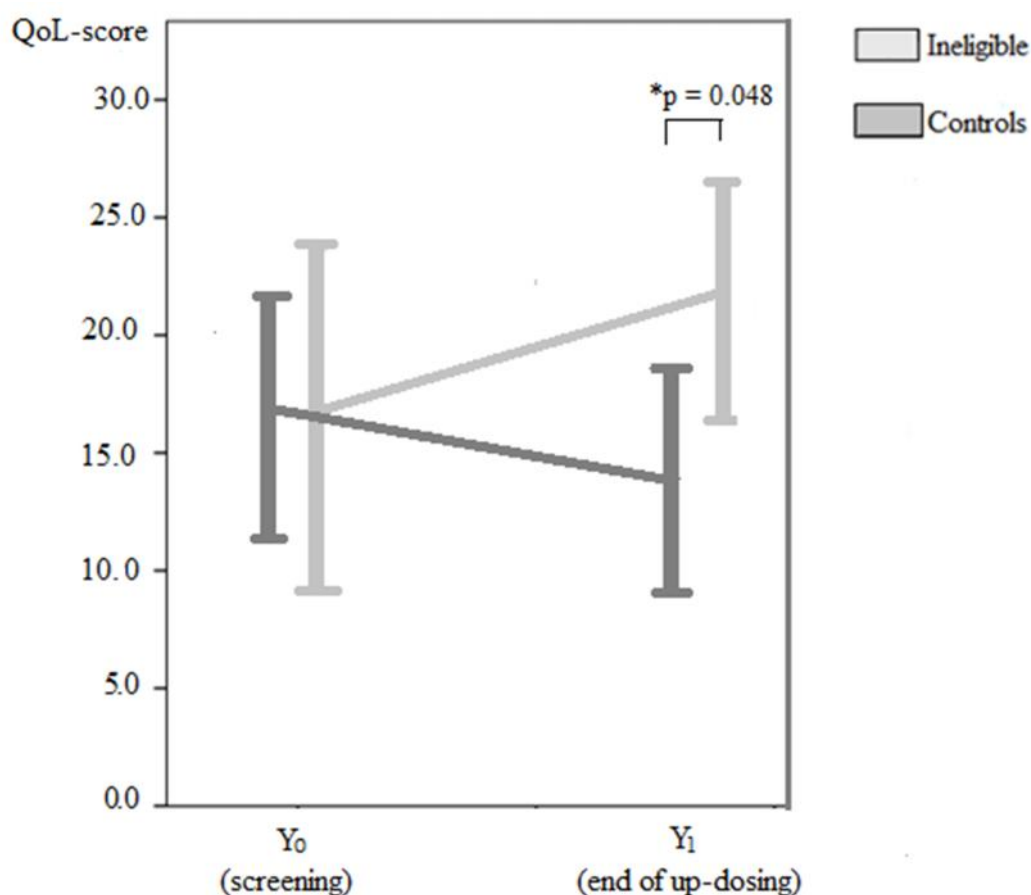
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98 **Supplement Figure 4**



99

100

101 **Supplement Figure 5**

102

103 **SUPPLEMENTARY REFERENCES**

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SUPPLEMENTARY MATERIAL

METHODS

Study design

Inclusion criteria for screening in the Take-Away trial were age 5-15 years, a history of systemic reactions to peanut or sensitization to peanut by a peanut specific skin prick test (SPT) ≥ 3 mm or a specific immunoglobulin E to peanut (s-IgE) ≥ 0.35 kUA/L, and living within acceptable distance from the Oslo University Hospital to ensure feasibility of a possible OIT. Exclusion criteria were non-controlled asthma, allergy or intolerance to any other ingredients in the peanut DBPCFC vehicle (ginger bread), current or previous allergen specific immunotherapy, cardiac disease, severe atopic skin disease, diabetes mellitus or other severe diseases that might interfere with adherence to study protocol. Children with severe atopic eczema were excluded due to the challenges of observing skin reactions during food challenges and during OIT.

The eligibility criterion of a positive DBPCFC at screening with a reactivity threshold >3 mg peanut protein had to occur within the cumulated dose of 6443 mg peanut protein given.

The OIT starting dose was initially 5 mg of peanut protein based on previously published studies (2, 21, 30), but lowered to 1 mg of peanut protein after including 26 children (17 active vs 9 controls) due to low reactivity threshold in the referred patients (18). Lowering the starting dose was approved by the ethical committee, and results from statistical analyses comparing children with a different OIT starting dose of 5 mg vs 1 mg of peanut protein ($n = 17$ vs 40), allowed that all children on active OIT could be assigned as one intervention group

Immunoglobulin assessments and skin prick test

Specific IgE was analyzed for peanut and peanut allergen components (Ara h1, Ara h2, Ara h3, Ara h8, Ara h9), hazelnut and hazelnut allergen components (Cor a1, Cor a8, Cor a9, Cor a14), almond, cashew nut, pistachio, walnut, pecan nut, brazil nut, macadamia nut, fenugreek,

soy bean, lupine seed, wheat, latex, common silver birch, timothy and mugwort with positive tests defined as s-IgE $\geq$ 0.35 kUA/L. Specific IgG and IgG₄ were analyzed for peanut and Ara h 2 with positive tests defined as IgG $>$ 2.0 mg_A/L and IgG₄ of $>$ 0.07 mg_A/L. Immunoglobulins were analyzed using the Phadia CAP-System FEIA (Thermo Fisher, Uppsala, Sweden). Lung function measurements included predicted forced expiratory volume in one second (FEV₁%) (20).

The SPT was performed according to European guidelines (31) and included peanut, hazelnut, almond, soy, birch, grass (timothy), mugwort, cat, dog, mite and mold (cladosporium herbarium) (ALK SQ extracts from ALK Abello (Hørsholm, Denmark), pea positive control (histamine) and negative control (Allergopharma (Reinbek, Germany)).

Anaphylaxis definition and grading

Anaphylaxis was defined as objective symptoms from at least two-organ systems in line with European Academy of Allergy and Clinical Immunology (EAACI) task force position papers (19, 28), modified for children by Vetander et al. (32). Severity of anaphylaxis was also graded in line with the EAACI position papers (19, 28) scoring from 1-3 (mild-moderate-severe) in addition to the method of Sampson (Grading of Food-Induced Anaphylaxis According to Severity of Clinical Symptoms) ranging from one to five (extremely severe reaction) (29).

Up-dosing protocol of the oral immunotherapy

For the lowest doses, the allergen source was peanut flour (Golden Peanut Company, Alpharetta, GA, USA). Since larger amounts of flour was found hard to eat, all but one child switched to roasted peanuts at OIT doses of 65-500 mg peanut protein. Each up-dosing period started with the incremented OIT dose ingested under observation at the hospital, followed by daily intake of a specific peanut dose at home for 14 days. In case of ongoing

infections, asthma exacerbations, excessive tiredness or vaccinations we advised to postpone the daily OIT dose to the next day. The OIT was resumed at home if less than three consecutive doses were missing, and in hospital if three or more doses were missed. Exercise within two hours after ingesting the OIT dose was strongly discouraged.

Registration of peanut intake, AEs, use of medication and accidental exposure to peanut were based upon daily symptom diary recordings. An independent safety board was contacted if unexpected severe AEs occurred. All participants received prescriptions of adrenaline auto-injectors and antihistamines, a written treatment plan for AEs, and had around-the-clock access to the private cell-phone numbers of the study personnel.

The AEs were classified as mild, moderate and severe (including anaphylaxis) according to the modified Bock's criteria (33, 34). Mild skin symptoms include occasional scratching, less than three hives, mild lip oedema, or a few areas of erythema, whereas moderate include scratching for more than two continuous minutes, more than three but less than ten hives, significant face oedema or areas of erythema, and severe skin symptoms include excoriations or generalized erythema or urticaria. Mild respiratory symptoms include rare sneezing or sniffing, expiratory wheezing by auscultation or less than three episodes of throat clearing, whereas moderate include less than ten bursts of sneezing, frequent sniffing, conjunctivitis, inspiratory and expiratory wheezing by auscultation or hoarseness, and severe respiratory symptoms include persistent rhinorrhea, use of accessory muscles or audible wheezing or stridor. Mild GI-symptoms include complaints of nausea or stomach ache or one episode of emesis or diarrhea, whereas moderate include frequent complaints of nausea and stomach ache with normal activity and two to three episodes of emesis or diarrhea or one of each, and severe GI-symptoms include complaints of nausea or stomach ache with change of activity level or more than three episodes of emesis or diarrhea or two of each. Mild cardiovascular include subjective weakness or tachycardia, whereas moderate include more than 20 % drop

in baseline blood pressure, and severe cardiovascular symptoms include signs of impaired circulation.

The oral immunotherapy protocol

The peanut OIT followed a biweekly step-up protocol with a fixed starting dose and a pre-defined maximum maintenance-dose (MMD) of 5000 mg peanut protein as previously reported (18). Each increment of peanut dose was based upon an agreement between the participating child, parents and the study pediatrician. In case of distaste for peanuts, intolerable AEs or three consecutive unsuccessful up-dosing attempts due to AEs, the current dose would represent the individual maintenance-dose. Withdrawal was initiated by self-discontinuation, severe AEs or more than two anaphylactic reactions.

Grading of AEs was in line with the modified Bock's criteria (33-35) (further described in online supplements).

Quality of life measurements

The generic PedsQL 4.0 allows QoL to be compared across groups of people (23). Even though the PedsQL 4.0 is classified by Physical Health Score (Physical Functioning) and Psychosocial Health Summary Score (Emotional, Social and School Functioning), the Total Scale Score is the most suitable for comparing outcomes between active intervention groups and healthy controls (22, 23). However, physical health is not affected in studies of food allergies (23) and other diseases like diabetes mellitus (36), and the intercorrelation between child self-reports and parental proxy-reports in Psychosocial Functioning is superior to that of the Physical Functioning. Hence, the present study includes QoL-scores for Psychosocial Functioning. Translation into Norwegian has been validated for PedsQL 4.0 (37).

Measurement of perceived treatment burden

The VAS developed to obtain one-dimensional reports of perceived treatment burden during the last 12 months included eight individual VAS items and was completed by OIT-children together with their parents at Y_1 and Y_2 . One item referred to overall perception of treatment burden, whereas seven items referred to treatment burden within three domains: Gastro-intestinal (GI) related AEs (stomach ache, nausea/vomiting and oral itching), taste and amount of daily peanut dose, and time spent on OIT (up-dosing at hospital and ingestion of OIT doses at home). Each VAS item ranged from 0–10 (0=no burden, 10=massive burden), reporting the mean score per domain.

Oral food challenge at Y_2

The daily maintenance-dose was withheld on the day of the Y_2 OFC. The first dose of the OFC protocol however, equaled the maintenance-dose. A cumulated dose of 7500 mg peanut protein was reached after maximum six doses, ingested with a 30 minutes interval.

Statistical analyses

The statistical power analysis at onset of the TAKE-AWAY trial was based upon reports desensitization of up to 80% of peanut allergic children using a step-up peanut OIT (3, 4) and spontaneous tolerance development in up to 20% (38). Assuming that desensitization would be less successful in children with severe peanut allergy, we estimated that with a desensitization rate of 57%, a treatment group of 40 and a control-group of 20 subjects would provide a statistical power of 80% at a five percent significance-level.

As the underlying assumptions for the multiple linear regression analysis were not fulfilled, multivariate robust regression analyses with Huber's M-estimator was used to assess associations between possible factors influencing QoL (as independent variables), and change in QoL from Y_0 to Y_2 in the PedsQL 4.0 or the FAQL-PB (as dependent variables). Hosmer's

step down multivariate analysis (39) retaining age and gender in the analysis included all variables significant at the 0.35 level in the bivariate analyses and the final model was tested for confounding with all excluded variables. Confounding was considered significant if including the variable caused a minimum of a 25% change in the result (39).

RESULTS

At Y₂ OFC, two children had allergic reactions during challenge. One child reacted with conjunctivitis and urticaria at 7500 mg peanut protein (maintenance-dose 1500 mg), and the other child (maintenance-dose 1250 mg) with a 3-month treatment discontinuation before resuming OIT the last three months before OFC had moderate anaphylaxis (erythema, urticaria and wheezing) at 4444 mg peanut protein.

The change in QoL from Y₀ to Y₂ was not significantly associated with the number of AEs in unadjusted bivariate analyses, neither as reported by the children ($p=0.76$) nor by the parental proxy-reports ($p=0.90$). Among the OIT-children, perceived treatment burden was significantly lower at Y₂ compared with Y₁ for the GI-domain and the taste-/amount-domain, but not for the time spent-domain from Y₁ to Y₂ (Table 2). The associations between changes in perceived treatment burden from Y₁ to Y₂ vs baseline VAS reports at Y₁ are shown in Supplement Figure 2. Although maintenance-dose altered the effect size of the burden of peanut taste/amount >25 % in step-down analyses, neither maintenance-dose, any of the three perceived treatment burden domains at Y₁ and Y₂, nor the level of desensitization were significantly associated with change in QoL in the final regression model (Table 3).

The change in perceived treatment correlated significantly with the VAS reported burden at Y₁ with mean correlation coefficients ranging from -0.82 to -0.44 ($p<0.001$) (Supplement Figure 2).

The parents' QoL improved significantly (decreased score) from Y_0 to Y_2 in both groups as shown in Supplement Figure 3, with a FAQL-PB score decreasing from 2.1 (1.8, 2.3) to 1.5 (1.3, 1.7) ($p < 0.0001$) among the OIT parents and from 1.9 (1.7, 2.3) to 1.4 (1.2, 1.7) ($p = 0.004$) among the control parents. No significant difference in mean change (95% CI) among parents' QoL was observed from Y_0 to Y_2 between the OIT-group (-9.9 (-14.6, -5.3)) and the controls (-9.4 (-15.3, -3.6)) ($p = 0.57$) (Supplement Figure 3).

DISCUSSION

Using VAS to report perceived treatment burden may improve our understanding of patient perceived burden of OIT. The VAS was not pre-validated for the TAKE-AWAY trial, but has previously been validated for pain and nausea (40).

The 32% OIT-children discontinuing treatment, represent a potential bias with missing QoL-assessments and VAS-forms. To correct for the potential bias of missing data, we used mixed-models analyses. The alternative of last observation carried forward analysis was found less appropriate as this would represent an even larger bias in our small sample-size (41).

