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Three-year follow-up after peanut food challenges: Accidental reactions in allergic children and introduction failure in tolerant children



To the Editor:

The gold standard to diagnose peanut allergy is a double-blind, placebo-controlled food challenge (DBPCFC).¹ Children and parents are advised to avoid peanut after a positive DBPCFC result or to introduce peanut after a negative DBPCFC result. Children with confirmed peanut allergy have frequent accidental allergic reactions and often do not recognize and adequately treat

allergic symptoms.² On the other hand, children with a negative DBPCFC result often experience failure to introduce peanut at home.³ Children and parents might benefit from a DBPCFC because our previous systematic review reported that health-related quality of life (HRQL) improved up to 6 months after an oral food challenge, irrespective of the outcome.⁴ Limited data exist on the long-term follow-up after a DBPCFC, including the frequency and treatment of accidental allergic reactions, diet, and HRQL.

We sought to evaluate 1) allergic reactions and HRQL in children with peanut allergy and 2) peanut introduction and HRQL in peanut-tolerant children. The current study is a 3-year follow-up of 83 children who participated in a prospective study in The Netherlands and all underwent a DBPCFC for peanut.⁵ Three years after the DBPCFC, all parents and children aged 8 years or older were contacted by mail and asked to fill out a questionnaire on accidental allergic reactions and current diet and the Food Allergy Quality of Life Questionnaire (FAQLQ). Details on data collection and statistical methods are presented in the Methods section in this article's Online Repository at www.jacionline.org. The study was approved by the ethics committee of the University Medical Centre Utrecht, and written informed consent was obtained before enrollment in the original study.

In total, 69 (83%) of 83 children completed the questionnaire after a positive ($n = 41/48$) or negative ($n = 28/35$) DBPCFC result. Children who completed the questionnaire and children who did not were comparable in age, sex, sensitization, and HRQL and DBPCFC outcomes (data not shown). The mean (SD) age of the children at follow-up was 11.5 (SD, 3.5) years, and 48 (70%) were male. The study flowchart and baseline characteristics are presented in Fig E1 and Table E1 in this article's Online Repository at www.jacionline.org.

Seventeen (41%) of 41 children with peanut allergy had a total of 68 accidental allergic reactions to peanut during the 3-year follow-up. Children with peanut allergy and accidental allergic reactions were comparable with those without accidental allergic reactions (see Table E2 in this article's Online Repository at www.jacionline.org). The characteristics of the most severe reactions are presented in Table 1 (see also Table E3 in this article's Online Repository at www.jacionline.org).⁶ All children had symptoms within 2 hours from ingestion. Five of 17 children had mild or moderate symptoms and used antihistamines at home. Twelve of 17 children reported severe symptoms and used antihistamines ($n = 7$), antihistamines and oral steroids ($n = 1$), bronchodilators ($n = 1$), or no medication at all ($n = 3$). Seven of 17 children reported severe lower respiratory tract symptoms. None of these 7 children used their epinephrine autoinjectors.

Parent-proxy-reported HRQL remained unchanged between baseline and 3-year follow-up in children with peanut allergy (mean difference [MD], 0.05; $P = .823$). On the individual level, HRQL improved in 29% and deteriorated in 39% of children with peanut allergy 3 years after the DBPCFC compared with baseline values. HRQL data are presented in Fig E2 and Table E4 in this article's Online Repository at www.jacionline.org.

Long-term introduction of peanut 3 years after the DBPCFC failed in 9 (32%) of 28 peanut-tolerant children (Fig 1). The reported reasons for failure were aversion ($n = 5$), aversion and fear ($n = 2$), or fear ($n = 2$). Parent-proxy-reported HRQL improved significantly and was clinically relevant during

TABLE I. Characteristics of the most severe allergic reactions during follow-up per patient

Patient no.	Product	Label	All symptoms reported*	S†	Treatment
1‡	Baklava	UNP	Pruritis, oral itch, feel of oral swelling, nausea, diarrhea , abdominal pain, dyspnea , feel of collapse	4	AH
2‡	Peanut skin contact	UNP	Pruritis, swelling eyes , diarrhea , blocked nose , wheezing	4	INH
3	Japanese rice crackers	ING	Pruritis, rash , oral itch, nausea, vomiting , diarrhea , abdominal pain, changed activity	4	None
4‡	Peanut	UNP	Rash , urticaria , swelling eyes , feel of oral swelling, nausea, vomiting , abdominal pain, blocked nose , dyspnea , anxiety	4	AH
5	Chocolate	UNP	Pruritis, rash , urticaria , diarrhea , blocked nose	4	None
6	Fries	UNP	Swelling eyes , oral itch, nausea, diarrhea , abdominal pain	4	AH
7	Cake	UNP	Swelling eyes , vomiting , abdominal pain	2	AH
8‡	Biscuit	ING	Swelling eyes , feel of oral swelling, nausea, abdominal pain, dysphagia , anxiety	4	AH + OS
9	Biscuit	ING	Oral itch, nausea, abdominal pain	2	AH
10‡	Pesto with cashew nut	PAL	Oral itch, feel of oral swelling, nausea, abdominal pain, sneezing , cough , anxiety	4	AH
11	Peanut butter	UNP	Oral itch, abdominal pain	1	AH
12	Unknown	UNP	Nausea, diarrhea , abdominal pain	4	None
13	Potato chips	CON	Pruritis, nausea, dizziness, feel of collapse	4	AH
14	Peanut butter	ING	Pruritis, rash , swelling eyes , itching eye	2	AH
15‡	Biscuit	ING	Oral itch, nausea, abdominal pain, itching eyes, feel of oral swelling, hoarseness , cough , dysphagia , dyspnea , dizziness	4	AH
16‡	Salty sticks	ING	Pruritis, rash , urticaria , swelling eyes , itching eyes, nausea, abdominal pain, blocked nose , sneezing , dyspnea , changed activity	4	AH
17	Biscuit	PAL	Pruritis, rash , urticaria , swelling eyes , oral itch, itching eyes, blocked nose , sneezing , anxiety	3	AH

AH, Antihistamines; CON, contaminated with peanut by other consumers; ING, peanut mentioned as an ingredient; INH, bronchodilator; OS, oral steroids; PAL, precautionary allergen labeling for peanut; UNP, unpacked foods.

*Patient-reported symptoms: objective symptoms are shown in boldface.

†Severity of symptoms according to the Sampson classification of anaphylaxis.⁶

‡Severe lower respiratory tract symptoms requiring use of epinephrine.

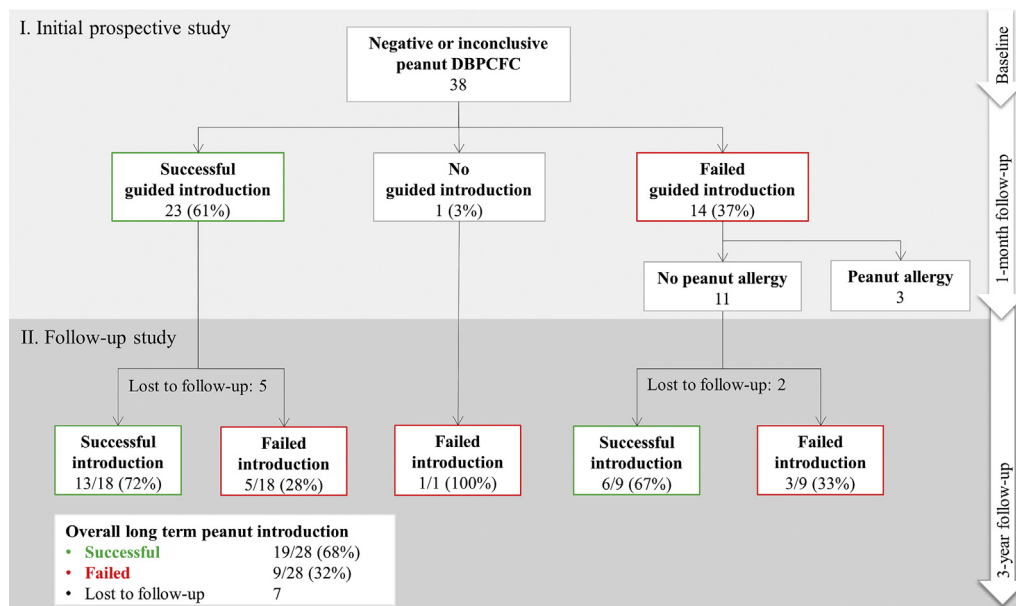


FIG 1. Flowchart of reintroduction to peanut after a negative or inconclusive DBPCFC result for peanut. Values are shown as numbers (percentages).

the 3-year follow-up in peanut-tolerant children (MD, -0.51 ; $P = .025$). A stratified analysis per long-term introduction outcome in peanut-tolerant children showed that HRQL improved significantly and was clinically relevant after successful long-term introduction (MD, -0.70 ; $P = .013$) and not after failed long-term introduction (MD, -0.05 ; $P = .906$). On the individual level, HRQL improved in 52% and deteriorated in

19% of peanut-tolerant children 3 years after the DBPCFC compared with before.

To our knowledge, this is the first study investigating the long-term course after a DBPCFC for peanut in children. In this study we have shown that almost half of children with peanut allergy have accidental reactions during 3 years after a positive DBPCFC result and that severe accidental reactions are not treated with

epinephrine. In addition, peanut-tolerant children often experience failure of peanut introduction into the diet 3 years after a negative DBPCFC result. Our results indicate that HRQL improves in peanut-tolerant children after successful peanut introduction and not after failed peanut introduction or in children with peanut allergy.

The high rate of accidental allergic reactions despite the explicit advice to avoid peanut and inappropriate management despite instructions on how and when to use epinephrine, as seen in this study, is of clinical concern. A recent analysis of the European Anaphylaxis Register demonstrated that more than 85% of patients with severe anaphylaxis did not use their epinephrine autoinjectors, despite clear recommendations.⁷ Children with peanut allergy and their families might benefit from multidisciplinary allergy care, including regular clinical consultations with an experienced physician and dietitian to evaluate any accidental ingestion of peanut and continuing education on peanut avoidance and use of emergency medications.⁸

Almost one third of peanut-tolerant children did not introduce peanut, despite guidance after the DBPCFC. The importance of peanut introduction in peanut-tolerant children is supported by our results that indicate that HRQL improved only in peanut-tolerant children after successful peanut introduction and remained unchanged after failed peanut introduction. Further research and discussion are needed to investigate whether food aversion and anxiety, which were the main reason not to introduce, can be relieved when psychological guidance is provided.

Our study is limited by the relatively small sample size and the possibility of recall bias over a 3-year time period. The study is strengthened by a prospective study design, including a well-defined patient cohort of children who all underwent a DBPCFC for peanut and a high response rate after 3 years of follow-up.

In conclusion, despite adequate diagnostic procedures and guidance, living with peanut allergy remains a challenge during childhood. In peanut-tolerant children peanut introduction often fails. However, peanut introduction is meaningful to improve HRQL.

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Allergy to prebiotic galacto-oligosaccharides: House dust mites—the putative primary sensitizer



To the Editor:

Galacto-oligosaccharides (GOS) have been increasingly used globally to supplement commercially available milk formulations and dairy products for their health benefits.¹ Intriguingly, when GOS were introduced into Southeast Asian countries as an ingredient in milk formula, a few acute allergic reactions and anaphylactic responses to GOS were promptly observed.²⁻⁴ Anaphylaxis to GOS occurred on first consumption in all our patients with allergic reactions, which was an indication of the presence of pre-existing GOS sensitization. GOS allergy is unique because the allergen is a pure carbohydrate. Vivinal GOS (vGOS) (FrieslandCampina, Amersfoort, The Netherlands) is produced with a β -galactosidase enzyme derived from *Bacillus circulans*. The composition of GOS has been shown to contain mostly β -1,4 linkages between glucose and galactose or between galactoses.⁵ However, β -1,6 and β -1,3 linkages are also found in vGOS, although to a lesser extent. GOS does not contain any fucose or sialic acid moieties. In view of the geographic restriction of GOS allergy to Southeast Asian countries when GOS is used to supplement milk formulas globally, we postulated that GOS allergy might be a result of sensitization to an agent that is likely geographically confined to Southeast Asia. We sought to identify the primary sensitizer for GOS allergy.

The clinical symptoms/reactions, skin prick test responses, and basophil activation test results to vGOS in 33 patients with GOS allergy, including 23 subjects who reacted to vGOS after consumption of vGOS-containing milk or water and 10 GOS-sensitized subjects who did not consume GOS before testing, are shown in Table I. Sera from these subjects were tested to determine the sensitization profile to 54 allergens (see Table E1 in this article's Online Repository at www.jacionline.org for the list of allergens) by using the EUROLINE multiplex immunoblot assay (EUROIMMUNE, Lübeck, Germany) and to *Curvularia lunata* and *Aedes communis* by using the

METHODS

Accidental allergic reactions in children with peanut allergy

All parents were asked whether their child had any accidental allergic reactions to peanut since the DBPCFC for peanut. If any allergic reactions to peanut were reported, parents were asked to report the following on the most severe allergic reaction: food ingested, estimated amount consumed, time interval from ingestion of the product to reaction, symptoms, duration, and treatment. Symptoms were categorized according to the PRACTALL consensus report, and severity was categorized according to the Sampson classification of anaphylaxis.^{E1,E2}

Introduction of peanut in peanut-tolerant children

Details collected on the current diet included the question of whether the child consumed whole peanuts or products with visible peanut (category A), products with peanut as an ingredient (category B), or products with precautionary allergen labeling (category C). If children avoided one of the peanut product categories, details on the reasons for avoidance were collected. Successful long-term introduction of peanut was defined as eating category A and/or category B products at least once a month.

HRQL

HRQL was assessed by using the self-reported disease-specific FAQLQ before and 3 years after the DBPCFC. The FAQLQ parent form (FAQLQ-PF) for parents of all children, the child form (FAQLQ-CF) for children aged 8 to 13 years, and the teenager form (FAQLQ-TF) for children aged 13 to 18 years were used.^{E3-E5} All items are scored on a 7-point scale ranging from 1 to 7, with 1 as the best possible score. The relevance of the change in FAQLQ

score was evaluated by using the minimal clinically important difference of 0.50.

Statistical analyses

Data were presented as means (SDs) or medians (interquartile ranges) for continuous data and numbers (percentages) for categorical variables. Differences between allergic and tolerant children and between children with and without allergic reactions during follow-up were statistically evaluated by using the χ^2 test for categorical variables and the Mann-Whitney *U* test for continuous variables, with Bonferroni correction for multiple testing. The difference between FAQLQ scores at baseline and follow-up were compared by using the paired *t* test. All analyses were performed with SPSS for Windows (version 25; SPSS, Chicago, Ill), and a *P* value of less than .05 was considered statistically significant.

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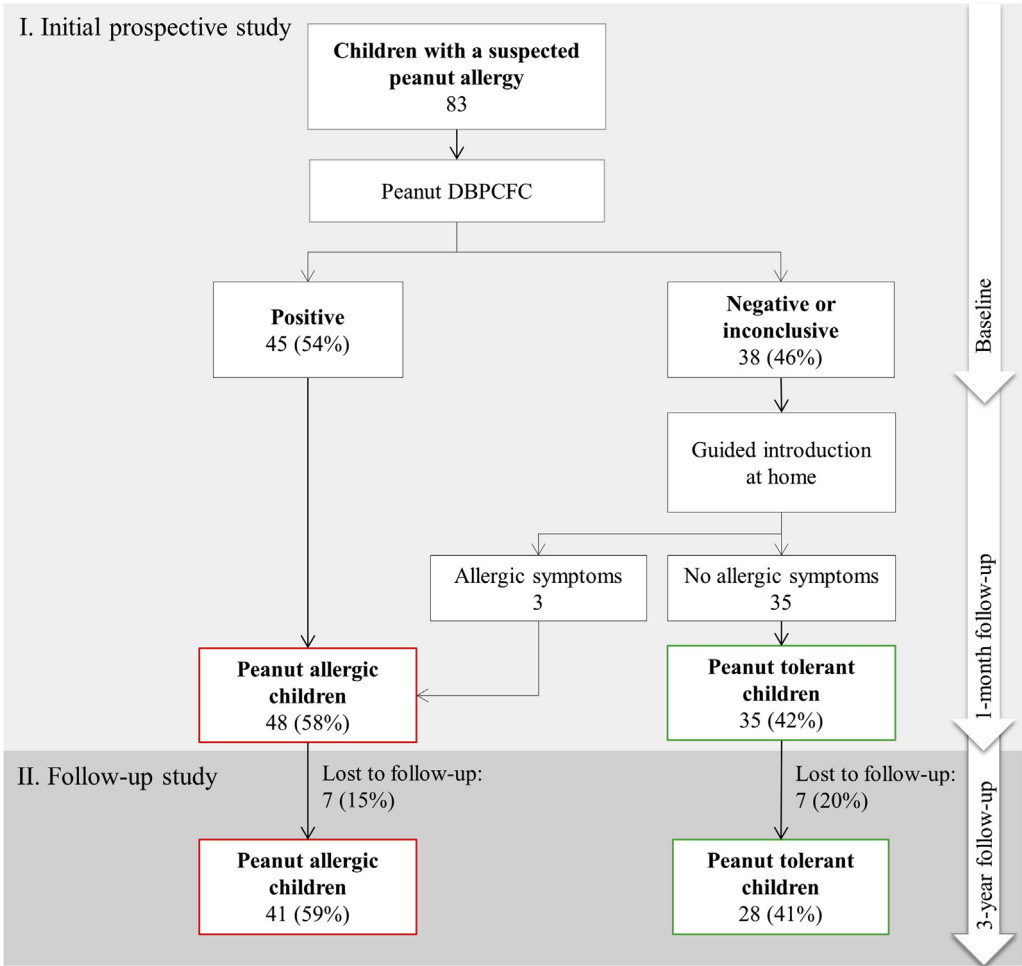


FIG E1. Study flowchart. Values are shown as numbers (percentages).

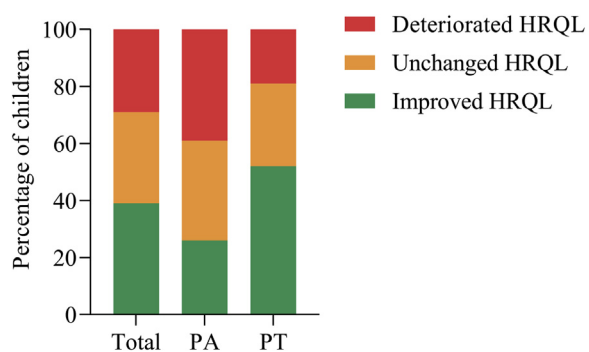


FIG E2. Percentage of children with improved (change, <-0.5), unchanged (change, -0.5 to 0.5), or deteriorated (change, >0.5) HRQL 3 years after a DBPCFC for peanut. *PA*, Children with peanut allergy; *PT*, peanut-tolerant children.

TABLE E1. Baseline characteristics

	All children (n = 69)	Children with peanut allergy (n = 41 [59%])	Peanut-tolerant children (n = 28 [41%])	P value
Baseline characteristics				
Age at DBPCFC (y), mean (SD)	8.4 (3.5)	8.6 (3.4)	8.2 (3.7)	.624
Age at follow-up (y), mean (SD)	11.5 (3.5)	11.7 (3.3)	11.2 (3.7)	.614
Male sex	48 (70)	27 (66)	21 (75)	.417
History of atopy				
Asthma	33 (48)	23 (56)	10 (36)	.096
Allergic rhinitis	41 (59)	27 (66)	14 (50)	.188
Atopic dermatitis	40 (58)	23 (56)	17 (61)	.703
Avoidance of other foods than peanut				.169
0 foods	25 (36)	13 (32)	12 (43)	
1 or 2 foods	10 (15)	6 (15)	4 (14)	
3 or 4 foods	11 (16)	4 (10)	7 (25)	
5 or 6 foods	15 (22)	12 (29)	3 (11)	
≥7 foods	8 (12)	6 (15)	2 (7)	

Values are shown as numbers (percentages), unless otherwise indicated.

TABLE E2. Comparison between children with peanut allergy with and without accidental reactions during follow-up

	Accidental reaction(s), 17 (41%)	No accidental reactions, 24 (59%)	P value*
Baseline characteristics			
Age at follow-up, no. (%)			1.000
4-13 y	11 (65)	16 (67)	
13-18 y	6 (35)	8 (33)	
Male sex, no. (%)	11 (65)	16 (67)	1.000
History of atopy			
Duration of peanut elimination diet, no. (%)			.972
3 to 8 y	6 (35)	9 (38)	
8 to 13 y	7 (41)	9 (38)	
Lifelong	4 (24)	6 (25)	
Previous reaction to peanut,† no. (%)			.615
Never ingested peanut	3 (18)	7 (29)	
Contact	3 (18)	2 (8)	
Grades 1-3	5 (29)	9 (38)	
Grades 4-5	6 (35)	6 (25)	
Elimination diet >1 other allergen, no. (%)	12 (71)	16 (67)	1.000
History of asthma, no. (%)	8 (47)	15 (63)	.358
Sensitization before DBPCFC			
Specific IgE to peanut, median (IQR)	8.3 (2.7-21.45)	7.1 (1.54-43.50)	.853
Specific IgE to Ara h 2, median (IQR)	6.4 (2.36-23.85)	3.45 (0.93-32.50)	.662
DBPCFC			
Reaction during DBPCFC,† no. (%)			.565
Grades 1-3	12 (71)	20 (83)	
Grades 4-5	3 (18)	3 (13)	
Missing	2 (12)	1 (4)	
LOAEL DBPCFC, median (IQR)			
Subjective	65 (1-1950)	100 (20-1000)	.609
Objective	1000 (0-2500)	1000 (38-1000)	.939
Dietary advice: no products with PAL, no. (%)	7 (41)	6 (25)	.322

Values are shown as numbers (percentages), unless otherwise indicated.

IQR, Interquartile range; LOAEL, lowest observed adverse effect level; PAL, precautionary allergen labeling.

*P values of less than .003 were taken to be significant according to Bonferroni correction for multiple testing.

†According to the Sampson classification of anaphylaxis.^{1,2}

TABLE E3. Characteristics of the most severe accidental allergic reactions to peanut in 17 (41%) of 41 children with peanut allergy

	No. (%)
No. of reactions	
1 or 2	9 (53)
3 or 4	4 (25)
≥5	3 (18)
Missing data	1 (6)
Age category	
Children (≤12 y)	11 (65)
Adolescents (>12 y)	6 (35)
Contact	
Ingestion	14 (82)
In oral cavity	1 (6)
Skin	2 (12)
Time from ingestion to symptoms	
≤2 h	17 (100)
>2 h	0
Symptoms according to PRACTALL*	
Skin	10 (59)
Gastrointestinal	16 (94)
Upper respiratory tract	8 (47)
Lower respiratory tract	7 (41)
Cardiovascular/neurologic	9 (53)
Severity of symptoms†	
Mild or moderate	
Grade 1	1 (6)
Grade 2	3 (18)
Grade 3	1 (6)
Severe	
Grade 4	12 (71)
Treatment	
No medicines	3 (18)
Antihistamines	12 (71)
Antihistamines + oral steroids	1 (6)
Epinephrine autoinjector	0
Bronchodilators	1 (6)
Consultation with physician	
No consultation	14 (82)
General practitioner visit	2 (12)
Hospital/emergency department visit	1 (6)

*See Sampson et al.^{E1}†According to the Sampson classification of anaphylaxis.^{E2}

TABLE E4. HRQL before and 3 years after a DBPCFC for peanut

		Before DBPCFC (T1)	Three years after DBPCFC (T2)	Delta score*	
	FAQLQ domain	Mean (SD)	Mean (SD)	Mean	P value†
Parent-proxy-reported HRQL					
All children (n = 44)	Overall	2.38 (0.97)	2.17 (1.00)	−0.22	.187
	FRA	2.66 (1.17)	2.53 (1.18)	−0.14	
	SDL	2.41 (1.08)	2.02 (0.96)	−0.38	
	EI	2.19 (1.17)	2.05 (1.04)	−0.14	
Children with peanut allergy (n = 23)	Overall	2.29 (1.02)	2.35 (0.80)	0.05	.823
	FRA	2.50 (1.22)	2.66 (0.80)	0.16	
	SDL	2.31 (1.17)	2.22 (0.85)	−0.10	
	EI	2.13 (1.08)	2.24 (0.90)	0.11	
Peanut-tolerant children (n = 21)	Overall	2.48 (0.94)	1.97 (1.18)	−0.51	.025
	FRA	2.84 (1.25)	2.38 (1.50)	−0.46	
	SDL	2.50 (1.00)	1.80 (1.05)	−0.69	
	EI	2.25 (1.29)	1.84 (1.15)	−0.40	
Successful introduction (n = 15)	Overall	2.59 (1.06)	1.90 (1.20)	−0.70	.013
	FRA	2.89 (1.38)	2.22 (1.35)	−0.67	
	SDL	2.65 (1.12)	1.80 (1.19)	−0.85	
	EI	2.37 (1.47)	1.76 (1.17)	−0.61	
Failed introduction (n = 6)	Overall	2.21 (0.52)	2.16 (1.20)	−0.05	.906
	FRA	2.71 (0.94)	2.77 (1.89)	0.06	
	SDL	2.11 (0.51)	1.81 (0.71)	−0.30	
	EI	1.94 (0.72)	2.04 (1.18)	0.10	
Child-reported HRQL					
Child Form (n = 6)	Overall	3.72 (1.82)	3.29 (1.72)	−0.42	.648
Teen Form (n = 3)	Overall	4.54 (1.15)	3.85 (1.26)	−0.69	.270
Child Form (T1) + Teen Form (T2 [n = 14])	Overall	3.48 (1.26)	2.85 (1.14)	NA	NA
None (T1) + Child Form (T2 [n = 18])	Overall	NA	3.40 (1.75)	NA	NA

EI, Emotional impact; FRA, food-related anxiety; NA, not available; SDL, social dietary limitations.

*Delta scores in boldface indicate a clinically relevant difference between the 2 time points.

†P values in boldface indicate a significant difference between the 2 time points.