

Health-related quality of life in patients who had partaken in milk oral immunotherapy and comparison to the general population

To the Editor,

Living with a food allergy may influence the health-related quality of life (HRQoL) of children and their families. Both have been reported to score worse in specific HRQoL domains compared to normative data.¹ The importance of measuring HRQoL has previously been discussed.²

Cow's milk allergy (CMA) is a common food allergy in young children that usually resolves by school age.³ Severe CMA, however, tends to be more persistent.³ Oral immunotherapy (OIT) may promote desensitization, allowing a patient to consume the food protein that previously caused the allergic reaction.⁴ The main aim of this study was to

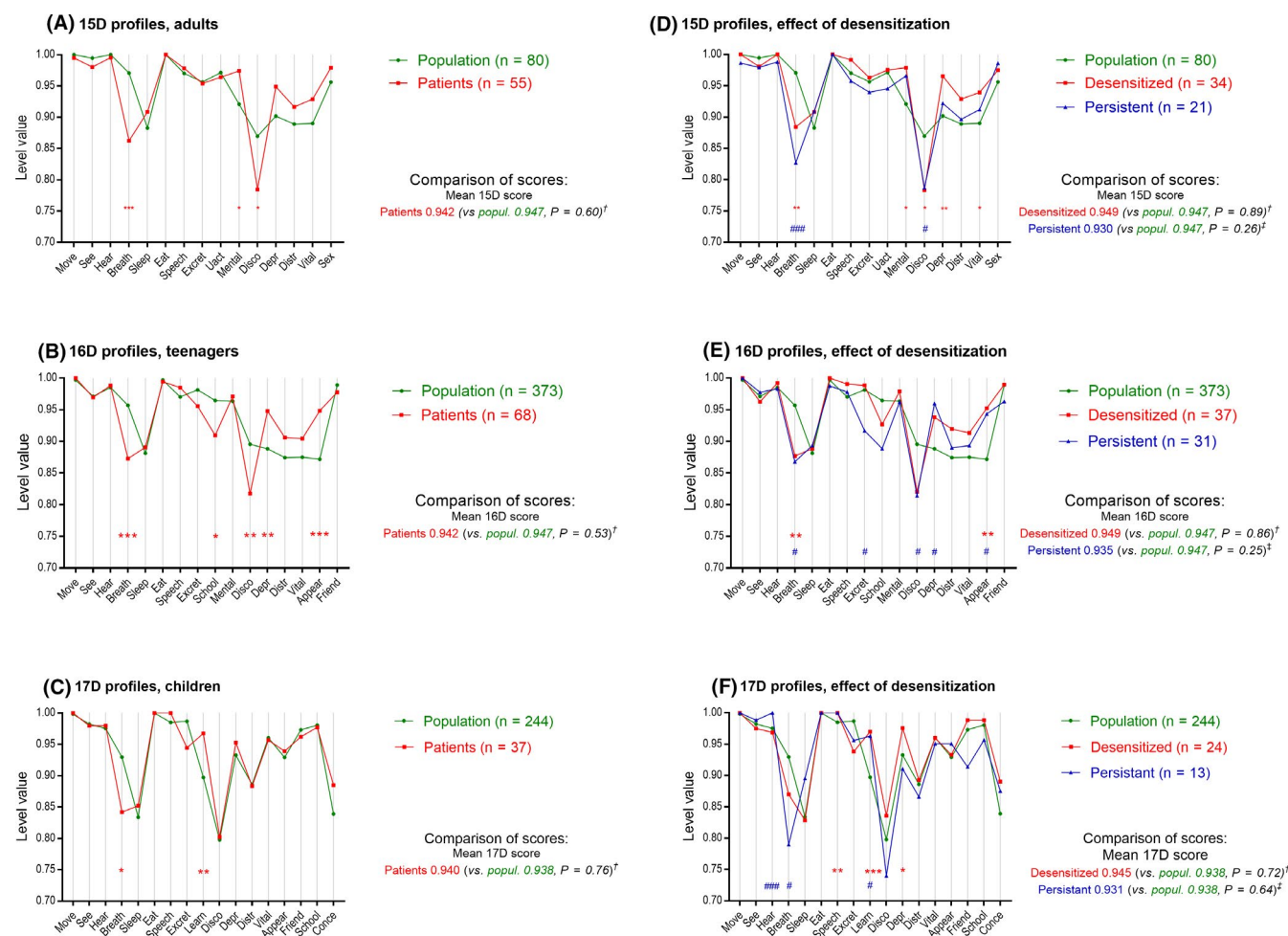


FIGURE 1 Mean health-related quality of life profiles from (A) 15D, (B) 16D, and (C) 17D milk OIT patients and (D) 15D, (E) 16D, and (F) 17D patients divided into the desensitized and persistent group compared to the age- and gender-standardized general populations. [†]/_‡ Comparison between the [†]desensitized or [‡]persistent patients and the general population in the means of each dimensions and the total scores. Statistical differences presented with # or *P < .05, ** or ††P < .01, *** or †††P < .001 (independent sample t test).

explore HRQoL in patients with persistent CMA who had partaken in the milk OIT and the effect of desensitization toward milk on their generic HRQoL compared to age- and gender-standardized samples from a general population in a cross-sectional study. We used the generic HRQoL instruments 15D, 16D, and 17D (Online Repository).⁵ We also collected answers from the milk OIT patients to the food allergy quality of life (FAQL) questionnaires (FAQLQs)⁶ (Online Repository) and studied the effect of desensitization on the FAQL.

The patients were recruited as participants from a milk OIT study between January 2016 and October 2017, 295 patients were recruited, and 160/295 (54%) returned the generic HRQLQs (Table S1). All subjects provided written informed consent. We divided the patients depending on their self-reported milk consumption at the time

when they answered the questionnaire into the desensitized (consuming ≥ 200 mL of milk daily) and persistent (consuming < 200 mL of milk or none at all) groups; the majority (95/160; 59%) were desensitized. Additional atopic diseases were prevalent: 120/158 (76%) had atopic dermatitis, 108/158 (68%) had allergic rhinitis, and 106/160 (66%) had asthma. Likewise, additional food allergies were common, and 87/158 (55%) of the patients had an egg allergy (Table S1). Asthma was more common among persistent milk-allergic children (17D) compared to desensitized children. Persistent milk-allergic adults (15D) had more egg allergy compared to desensitized adults (Table S1). Answers from the general population were collected from the Finnish National Health Survey (15D) or previous studies (16D, 17D) (Online Repository E2-E4).

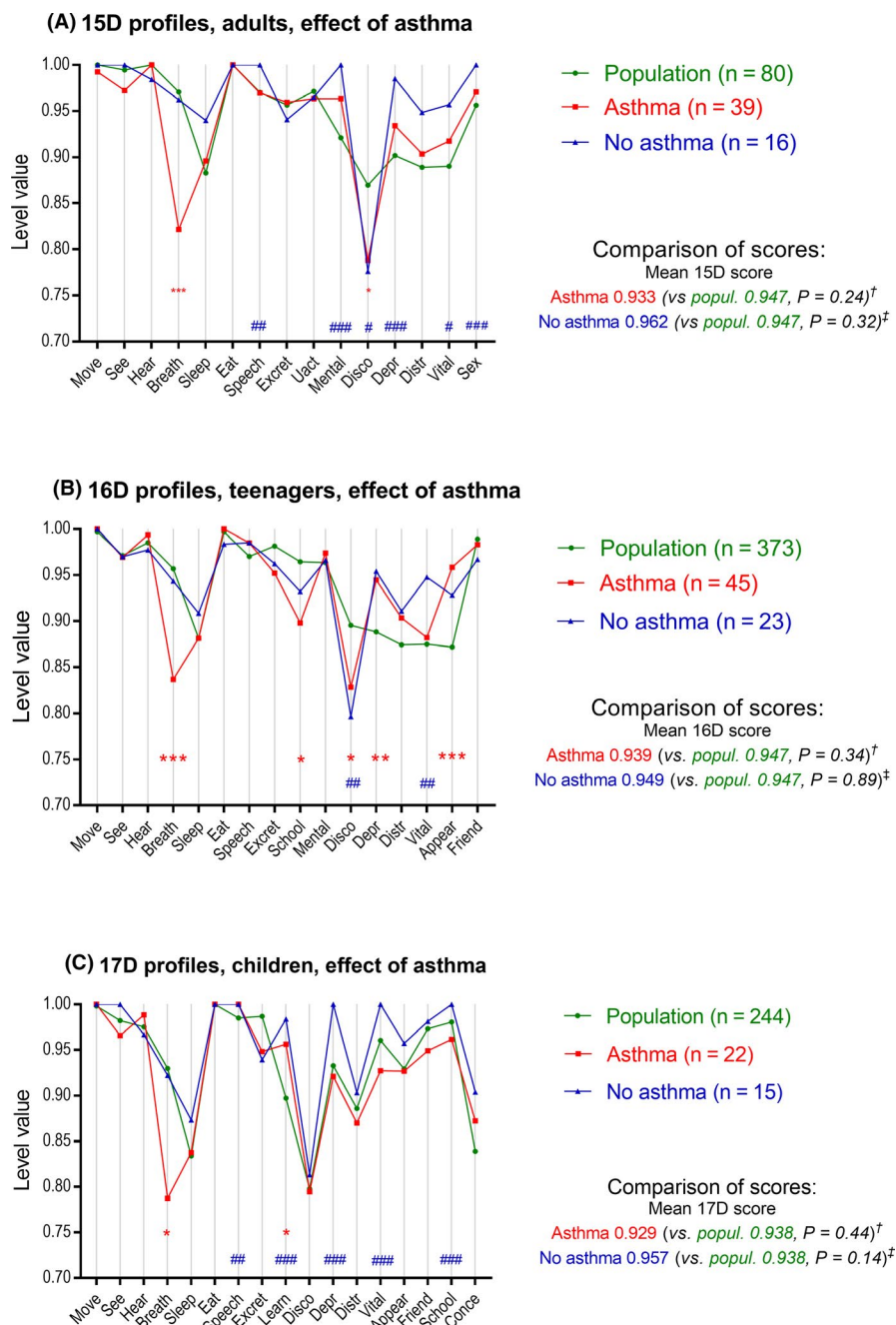


FIGURE 2 Mean health-related quality of life profiles (A) 15D, (B) 16D and (C) 17D from milk OIT patients with or without additional asthma, compared to the age- and gender-standardized general populations. [†]/[‡] Comparison between [†]asthmatic or [‡]nonasthmatic patients and the general population in the means of each dimensions and the total scores. Statistical differences presented with # or * $P < .05$, ## or ** $P < .01$, ### or *** $P < .001$ (independent sample t test).

The total mean HRQoL scores of the patients and the age- and gender-standardized general population were not statistically different in any of the age groups (Figure 1). The total mean HRQoL scores were also not significantly different between the desensitized or persistent patients and the general population (Figure 1). Comparing the HRQoL between the desensitized and persistent groups did not show statistical differences in total mean score or any dimensions, except that the persistent group had a lower excretion score in the 17D questionnaire (Figure S1). There were differences in the patients' HRQoL profiles versus the general population. The breath dimension was statistically lower in all groups, except desensitized children, but they had less asthma. To explore the reason for the breath dimension scores, we divided the patients into asthmatic and non-asthmatic groups. The asthmatic patients had a statistically lower score in the breath dimension, but non-asthmatic patients were at the same level as the general population (Figure 2). The presence of atopic dermatitis (AD) lowered the dimension of discomfort in children and adults compared to the non-AD patients. The presence of allergic rhinitis did not have a clear effect on the HRQoL (Figure S2).

The FAQLQs were answered by 142/295 (48%) patients (Table S2). Desensitization was associated with a statistically significantly better FAQL (lower mean scores) compared to that of the persistent children and adolescents (FAQLQ-children, $n = 47$, score 1.7 versus 2.8, $P = .001$, FAQLQ-teenager, $n = 64$, score 2.1 versus 2.9, $P = .04$, FAQLQ-adult, $n = 31$, score 2.3 versus 2.7, $P = .25$, articles Figure S3). We observed an inverse correlation between the FAQLQ-children and 17D mean scores (Pearson's $r = -.501$ because of opposed scales; $P = .002$), but a significant correlation was not observed between the FAQLQ-teenagers and 16D scores or FAQLQ-adults and 15D scores (Table S3). The desensitized children had lower FAQLQ-children scores and less asthma compared to the persistent children, which might affect the correlation between the FAQLQ and 17D.

Concerns have been raised about anxiety in food allergy patients.³ However, none of our analyses indicated increased levels of depression, mental function, or distress; the result was sometimes the opposite (Figure 1). These results might have been affected by selection bias because patients had participated in the milk OIT study, which may imply a certain psychological health.

Several allergy-related variables have been linked to poor FAQL, including having to avoid several foods, having to avoid commonly served foods and previous severe reactions.^{2,4} However, diagnostic food challenges, OIT^{7,8} and educational interventions have been shown to improve FAQL.^{2,4} A peanut OIT study reported improved FAQL during peanut OIT; otherwise, FAQLQs have not been studied in Finland.⁷

Our study had limitations. The response rate was 54% among generic HRQoLQ and 48% among FAQLQ. There was no statistically significant difference between the gender, age, milk desensitization, or presence of additional atopic diseases of the nonrespondents and study participants in either group (Table S4). The general population's medical records were not available. The sample size was small in some subgroups, especially among the respondents to the FAQL-AF, and there might be some confounders, which might have affected our results. The strength of our study is the comparison

between the OIT patients and the general population in different age groups. Furthermore, this study combines the generic HRQL and FAQL, revealing a possible link between these two associated with the presence of asthma.

In conclusion, the total HRQoL among milk OIT patients was not statistically significantly different from that of the age- and gender-standardized general population. Desensitization to milk was not associated with improved generic HRQoL compared to the general population or persistent patients, but the presence of asthma lowered the breath dimension. Desensitization was associated with better FAQL among children and adolescents compared to the persistent patients.

ACKNOWLEDGMENTS

Dr Kauppila, Dr Pelkonen, Dr Roine, Dr Paasilta, Dr Kukkonen, and Dr Makela have nothing to disclose. Dr Sintonen reports that he is the developer of the 15D and obtains royalties from its electronic versions.

FUNDING INFORMATION

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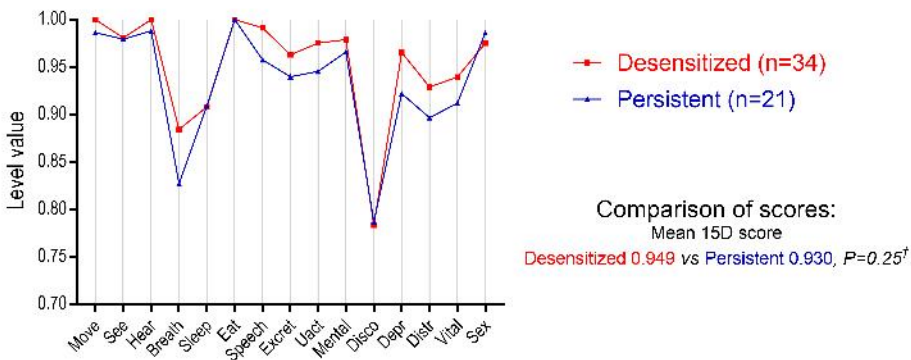
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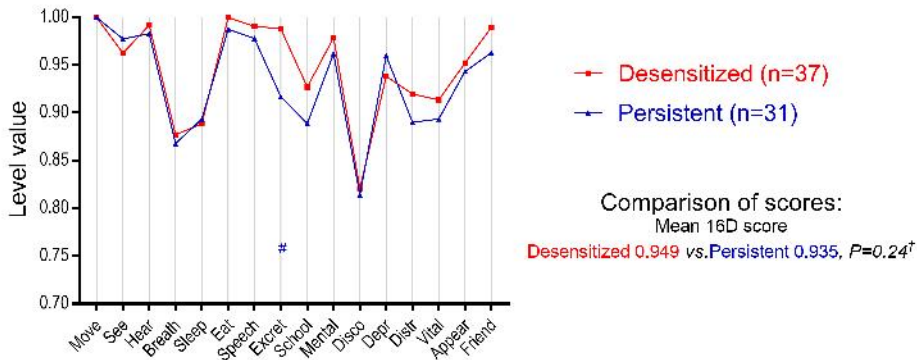
SUPPORTING INFORMATION

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

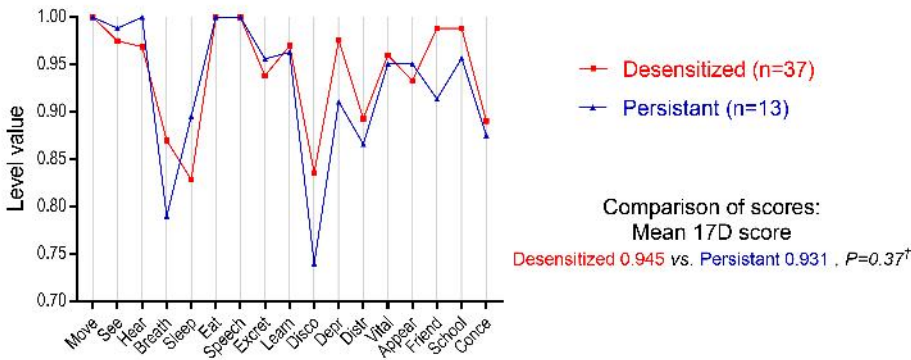
A. Patients 15D profiles, effect of desensitization



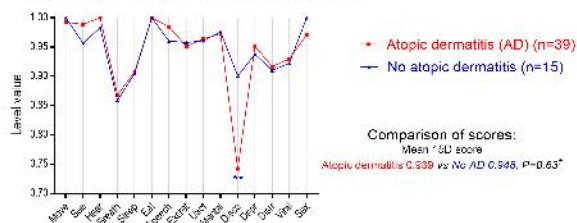
B. Patients 16D profiles, effect of desensitization



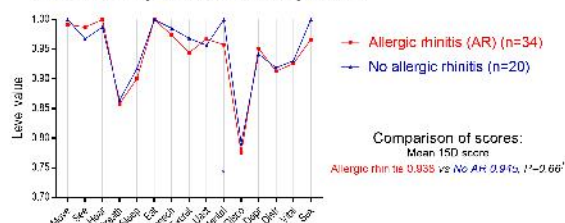
F. Patients 17D profiles, effect of desensitization



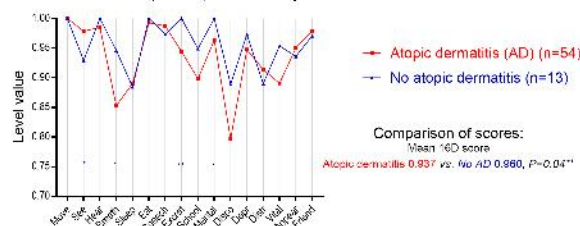
A. Patients 15D profiles, effect of atopic dermatitis



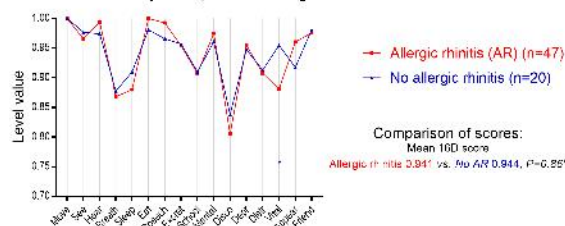
D. Patients 15D profiles, effect of allergic rhinitis



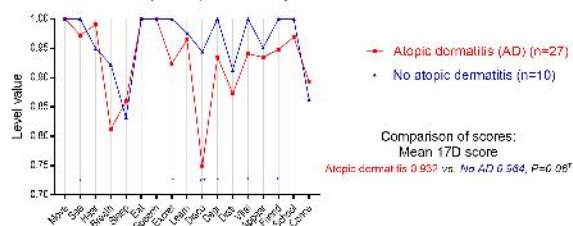
B. Patients 16D profiles, effect of atopic dermatitis



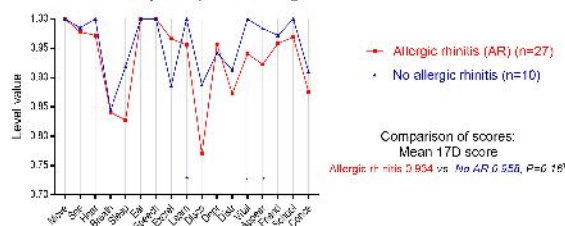
E. Patients 16D profiles, effect of allergic rhinitis

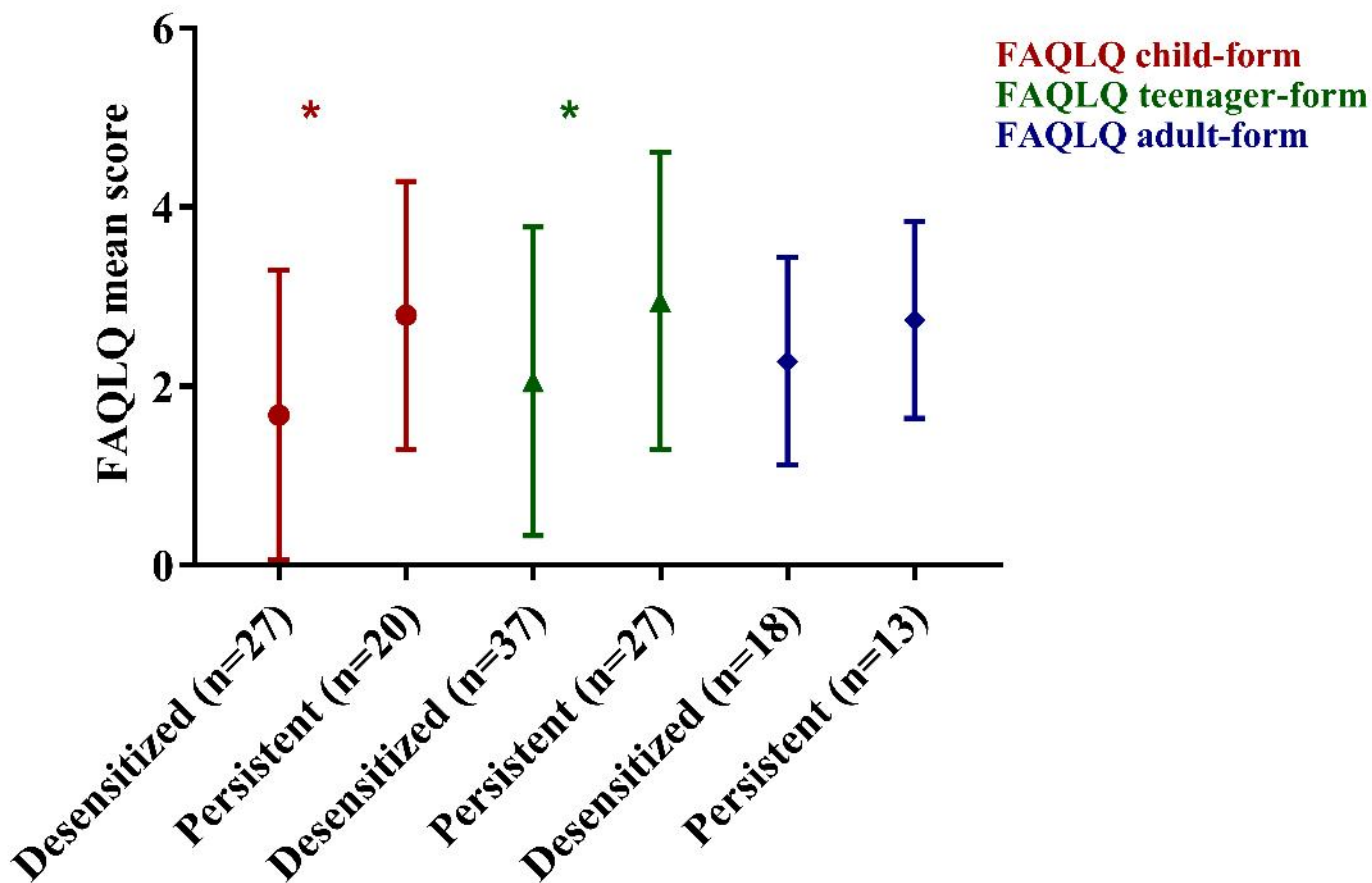


F. Patients 17D profiles, effect of atopic dermatitis



G. Patients 17D profiles, effect of allergic rhinitis





Online Repository

Study population

This study was performed at the Skin and Allergy Hospital of the Helsinki University Hospital, Finland and in the Department of Pediatrics, Tampere University Hospital, Finland between January 2016 and October 2017 to measure health-related quality of life (HRQoL) and food allergy quality of life (FAQL). The patients were recruited as participants in a milk oral immunotherapy (OIT) study. The patients participated in the Finnish milk OIT follow-up study and had received milk OIT treatment between the years 2005 - 2015 ^{E1}. We used HRQoL instruments, FAQL questionnaires (FAQLQs) and a self-made questionnaire that surveyed the patient's baseline characteristics, current allergic comorbidity, and milk consumption, as well as patient records.

The inclusion criteria for milk OIT were as follows: immunoglobulin E-mediated milk allergy at ≥ 5 years old with the diagnosis originally made with an open milk challenge and confirmed by repeated milk challenge or based on a severe recent reaction to milk before starting the OIT. Briefly, the patients had milk escalating doses daily. The starting dose and some additional doses were administered at the hospital, but the patients mainly took doses home during the four-month buildup phase. The starting dose was 0.5 μ g of milk protein (liquid milk diluted in water), and the target maintenance dose was 6.4 g of milk protein (approximately equal to 200 ml of milk). After reaching the maintenance dose, the patients were considered desensitized to milk protein and advised to continue the 200 ml dose daily.

The age- and gender-standardized general population used in this study was based on data from Finnish adults who responded to the 15D questionnaires as a part of the 2011 Finnish National Health Survey ^{E2}. The adolescent population 16D data came from a survey of a sample of adolescents in the Helsinki area

in 2013 ^{E3}. The child population 17D data came from a sample of school children in the Helsinki Metropolitan area in 1996 ^{E4}.

The institutional ethics committees of the University Hospitals of Helsinki and Tampere approved the original OIT study protocol and the follow-up study. The study was registered at ClinicalTrials.gov (number NCT02640014). Written-informed consent was obtained from all subjects and their parents prior to enrollment.

HRQoL 15D (> 16 years of age), 16D (12–15 years) and 17D (8–11 years)

The 15D is a generic HRQoL instrument developed for adult populations ^{E5}. It compares favorably with other generic HRQoL instruments ^{E6}. Using the 15D as a template, other versions have been developed for adolescents aged 12–15 years (16D) ^{E7} and for children aged 8–11 years (17D) ^E. With proxy administration, the 17D can also be used for younger children. The 15D questionnaire measures 15 life dimensions, including breathing, mental function, speech (communication), vision, mobility, usual activities, vitality, hearing, eating, excretion, sleeping, distress, discomfort (and other symptoms), sexual activity and depression. The 16D questionnaire includes 16 questions representing the dimensions of mobility, vision, hearing, speech, breathing, sleeping, eating, excretion, usual activities (school and hobbies), friends, physical appearance, mental function, discomfort (and related symptoms), depression, distress and vitality. In 17D, the distress dimension has been replaced by a dimension representing the ability to concentrate and a dimension representing learning ability and memory. Each dimension has one question with five answer options. The maximum score is one (no problems in any of the dimensions), and the minimum score is zero (the patient is deceased). The questionnaire can be used as both a profile and a single-index score measure. All these questionnaires are standard and have been validated ⁴.

FAQLQ child-form (FAQLQ-CF, 8–12 years), teenager-form (FAQLQ-TF 13–17 years) and adult-form (FAQLQ-AF $\geq$ 18 years)

FAQLQs are available for adults, adolescents and children. These questionnaires have been validated for different age groups, and their reliability has been demonstrated ^{E8, E9, E10}. A Finnish FAQLQ was previously used in a peanut OIT study ⁹. FAQLQs measure aspects of allergen avoidance, the risk of accidental exposure, emotional impact and dietary restrictions. The FAQLQ-CF contains 24 items, the FAQLQ-TF contains 23 items, and the FAQLQ-AF contains 29 items. The questionnaire items are scored on a seven-point scale ranging from zero to six, with lower scores indicating a better FAQL.

Statistical analyses

A difference of ≥ 0.015 in the 15D score is considered clinically important, an indication that a person can, on average, detect the difference ^{E11}. Comparisons of continuous variables between groups were performed using an independent sample t-test (for two groups) or Mann-Whitney-U test. The distributional differences in the clinical variables were compared using Fisher's chi-square test or Mann-Whitney U test. Reported *P* values are two-tailed, when applicable, and *P* values less than 0.05 were considered statistically significant. SPSS Statistics version 24.0 and 25.0 (IBM Corporation, Armonk, NY, USA) and the Prism6 software (GraphPad) were used for the analyses.

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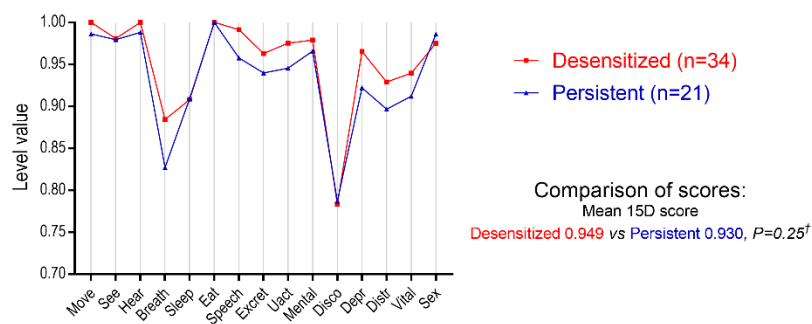
Online Repository Tables and Figures

Table E1: Characteristics of the generic health-related quality of life responders categorized by their self-reported milk consumption and divided into the 15D (adults), 16D (teenagers), and 17D (children) responder subgroups. Comparison between the desensitized group (consuming ≥ 200 ml of milk daily) and persistent group (less than 200 ml of milk or none).

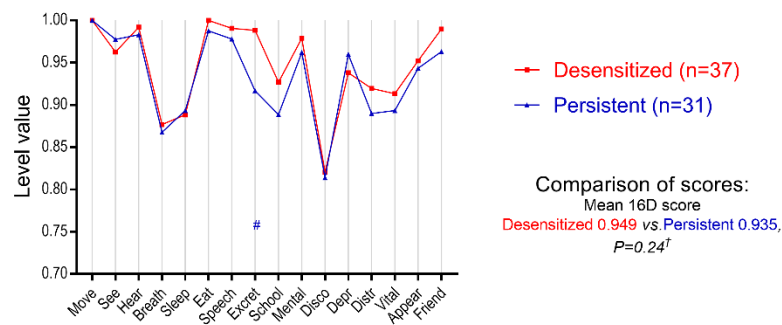
Characteristics	All (n=160)	Desensitized (n=95)	Persistent (n=65)	P value
Age years, mean (SD)	14.3 (3.9)	14.5 (4.1)	14.1 (3.6)	0.67
Range (min-max)	18 (7-25)	17 (8-25)	16 (7-23)	
Male gender	87 (54)	51 (54)	36 (55)	0.87
Additional asthma	106 (66)	57 (36)	49 (75)	0.06
Additional rhinitis	108/158 (68)	63/93 (68)	45 (69)	0.86
Additional atopic dermatitis	120/158 (76)	68/94 (72)	52/64 (81)	0.26
Additional food allergy				
Peanut	79/158 (50)	45/94 (48)	34/64 (53)	0.63
Egg	87/158 (55)	46/94 (49)	41/64 (64)	0.07
Wheat	31/159 (19)	14/94 (15)	17 (26)	0.10
Other	81/157 (52)	47/93 (50)	34/64 (53)	0.87
17D questionnaire	All (n=37)	Desensitized (n=24)	Persistent (n=13)	P value
Age years, mean (SD)	9.5 (1.0)	9.7 (1.0)	9.0 (1.2)	0.06
Male gender	24 (65)	17 (71)	7 (54)	0.47
Additional asthma	22 (59)	10 (42)	12 (92)	0.04
Additional rhinitis	27 (73)	17 (71)	10 (77)	1.00
Additional atopic dermatitis	27 (73)	15 (63)	12 (92)	0.07
Additional food allergy				
Peanut	10/36 (28)	6 (25)	4/12 (33)	0.70
Egg	17 (46)	10 (42)	7 (54)	0.51
Wheat	6 (16)	3 (13)	3 (23)	0.64
Other	18 (49)	10 (42)	8 (62)	0.31
16D questionnaire	All (n=68)	Desensitized (n=37)	Persistent (n=31)	P value
Age years, mean (SD)	13.5 (1.6)	13.7 (1.9)	13.3 (1.2)	0.59
Male gender	41 (60)	20 (54)	21 (68)	0.32
Additional asthma	45 (66)	24 (65)	21 (68)	1.00
Additional rhinitis	47/67 (70)	25/36 (69)	22 (71)	1.00
Additional atopic dermatitis	54/67 (81)	27/36 (75)	27 (87)	0.24
Additional food allergy				
Peanut	37/67 (55)	19/36 (53)	18 (58)	0.81
Egg	39/66 (59)	21/36 (58)	18/30 (60)	1.00
Wheat	14/67 (21)	7/36 (19)	7 (23)	0.77
Other	33/66 (50)	19/36 (53)	14/30 (47)	0.81
15D questionnaire	All (n=55)	Desensitized (n=34)	Persistent (n=21)	P value
Age years, mean (SD)	18.5 (2.4)	18.7 (2.7)	18.2 (1.9)	0.66
Male gender	22 (40)	14 (41)	8 (38)	1.00
Additional asthma	39 (71)	23 (68)	16 (76)	0.56
Additional rhinitis	34/54 (63)	21/33 (64)	13 (62)	1.00
Additional atopic dermatitis	39/54 (72)	26/34 (76)	13/20 (65)	0.53
Additional food allergy				
Peanut	32 (58)	20 (59)	12 (57)	1.00
Egg	31 (56)	15 (44)	16 (76)	0.03
Wheat	11 (20)	4 (12)	7 (33)	0.08
Other	30/54 (56)	18/33 (55)	12 (57)	1.00

102 Figure E1.

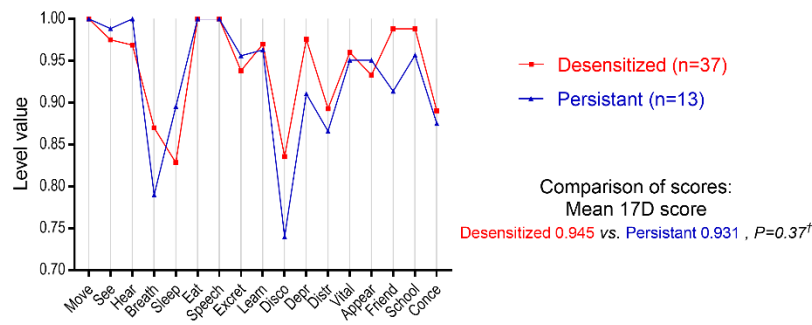
A. Patients 15D profiles, effect of desensitization



B. Patients 16D profiles, effect of desensitization



F. Patients 17D profiles, effect of desensitization



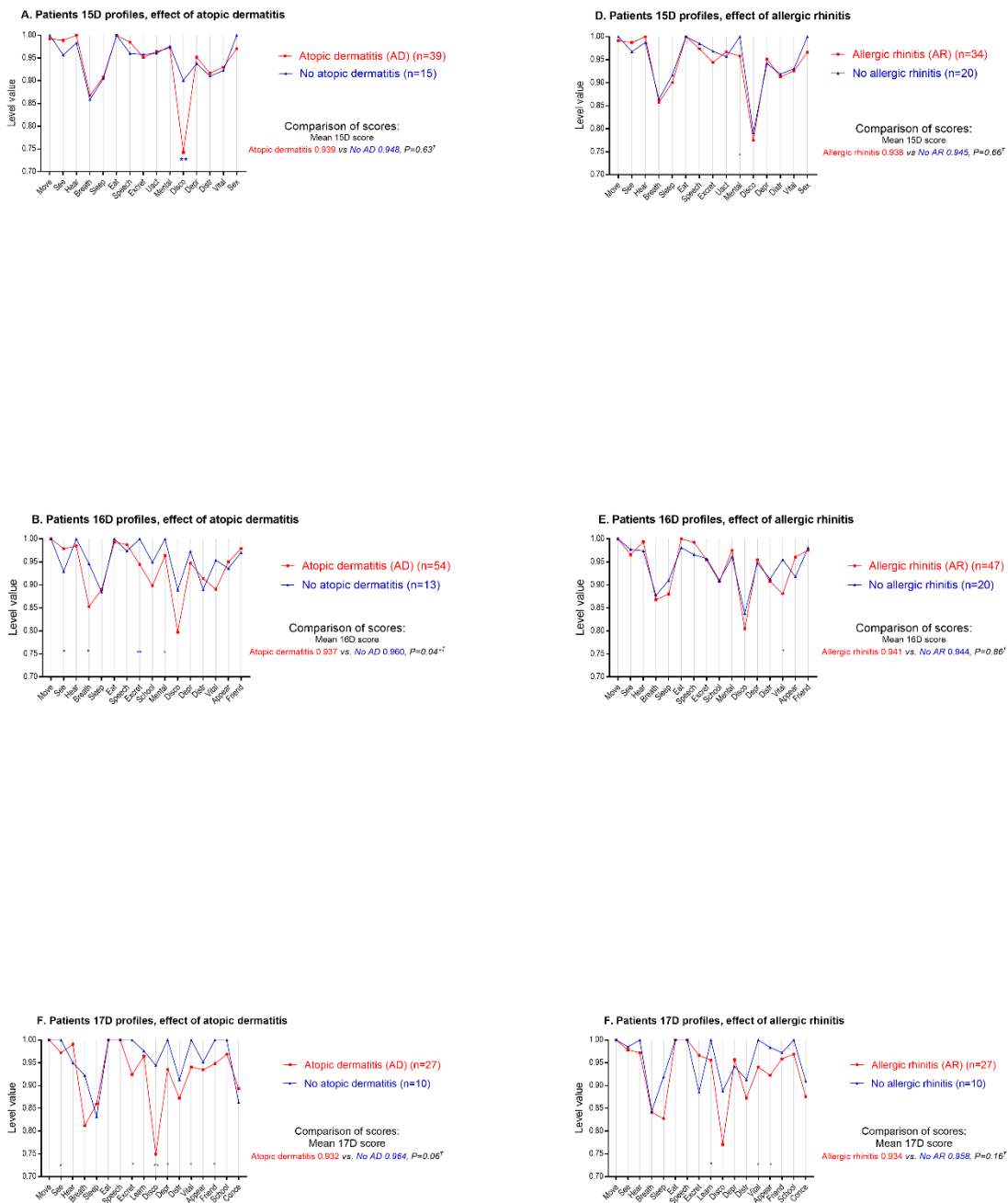
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105 Figure E1. Mean health-related quality of life profiles (A) 15D, (B) 16D, and (C) 17D from milk OIT
106 patients divided into the milk desensitized and persistent groups.

107 † Comparison between desensitized and persistent patients in the means of each dimension and total
108 scores.

109 Statistical differences presented with [#] P < 0.05, ^{##}P < 0.01, ^{###} P < 0.001 (independent sample t-test).

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113 Figure E2. Mean health-related quality of life profiles of milk OIT patients: (A) 15D, (B) 16D, and (C)
 114 17D with additional atopic dermatitis (AD) compared to those without atopic dermatitis and (D) 15D,
 115 (E) 16D, and (F) 17D allergic rhinitis (AR) compared to those without allergic rhinitis

116 † Comparison between atopic dermatitis or allergic rhinitis patients and patients without atopic
117 dermatitis or allergic rhinitis in the means of each dimension and the total scores

118 Statistical differences presented with *P < 0.05, **P < 0.01 (independent sample t-test)

119

120 Table E2: Characteristics of the food allergy quality of life responders categorized by their self-
121 reported milk consumption and divided into the FAQLQ child-form (FAQLQ-CF), teenager-form
122 (FAQLQ-TF), and adult-form (FAQLQ-AF) responder subgroups. Comparison between the
123 desensitized group (consuming ≥ 200 ml of milk daily) and persistent group (less than 200 ml of milk or
124 none).

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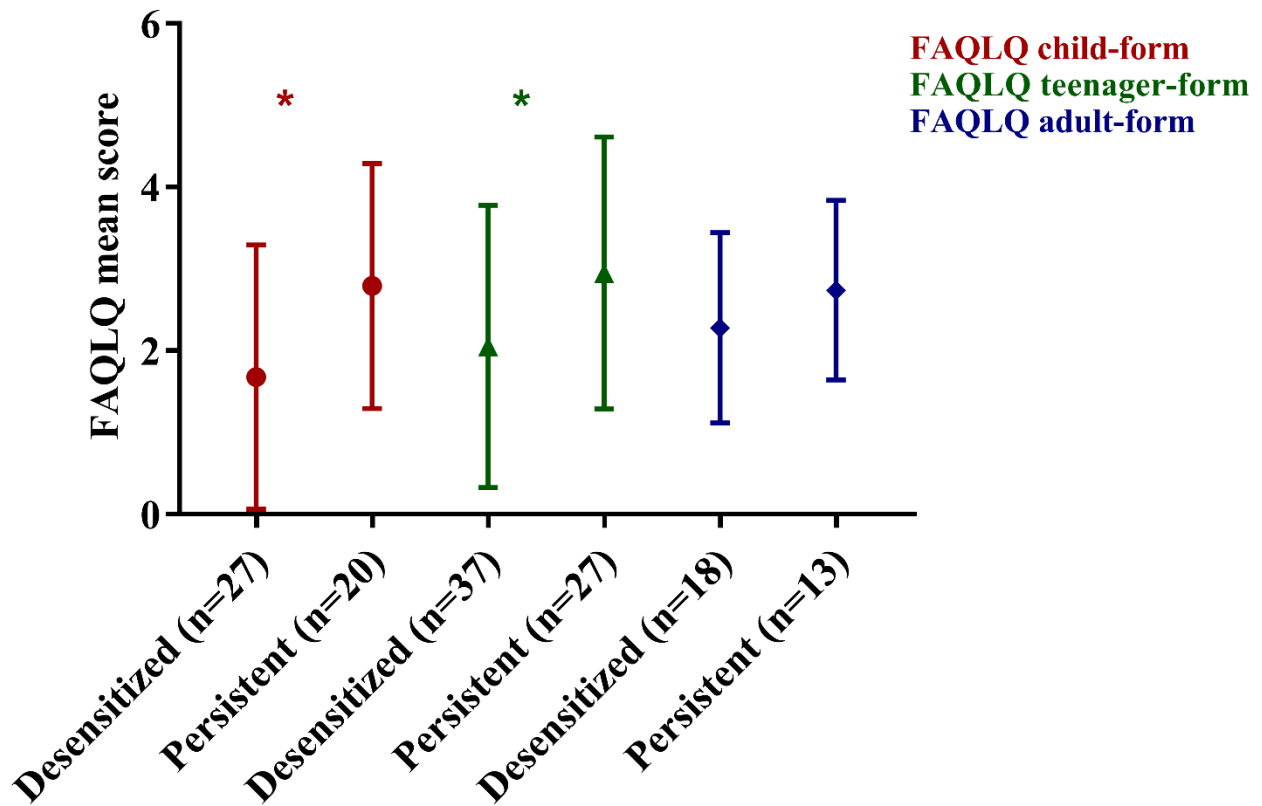
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Characteristics	All (n=142)	Desensitized (n=82)	Persistent (n=60)	P value
Age years, mean (SD)	14.1 (3.7)	14.2 (3.9)	13.9 (3.6)	0.73
Male gender	80 (56)	48 (58)	32 (53)	0.61
Additional asthma	93(65)	48 (58)	45 (75)	0.05
Additional rhinitis	93/140 (66)	53/80 (66)	40 (66)	1.00
Additional atopic dermatitis	103/141 (73)	57/81 (70)	46/60 (76)	0.45
Additional food allergy				
Peanut	69/139 (50)	38/80 (48)	31/59 (53)	0.61
Egg	77/139 (55)	36/80 (45)	41/59 (69)	0.06
Wheat	25/140 (18)	11/80 (14)	14 (23)	0.18
Other	73/139 (53)	42/80 (53)	34/64 (53)	1.0
FAQLQ-child form	All (n=47)	Desensitized (n=27)	Persistent (n=20)	P value
Age years, mean (SD)	10.0 (1.6)	10.1 (1.1)	9.9 (1.6)	0.56
Male gender	27 (57)	17 (63)	10 (50)	0.55
Additional asthma	29 (62)	10 (37)	19 (95)	0.00
Additional rhinitis	34 (72)	19 (70)	15 (75)	1.00
Additional atopic dermatitis	34 (72)	17 (63)	17 (85)	0.11
Additional food allergy				
Peanut	16/46 (35)	7 (26)	9/19 (47)	0.21
Egg	24 (51)	11 (41)	13 (65)	0.14
Wheat	8 (17)	2 (7)	6 (30)	0.06
Other	25 (53)	11 (41)	14 (70)	0.08
FAQLQ-teenager form	All (n=64)	Desensitized (n=37)	Persistent (n=27)	P value
Age years, mean (SD)	14.5 (1.6)	14.6 (1.7)	14.4 (1.4)	0.67
Male gender	39 (61)	24 (65)	15 (56)	0.60
Additional asthma	45 (70)	27 (73)	18 (67)	0.59
Additional rhinitis	42/63 (67)	24/36 (67)	18 (67)	1.00
Additional atopic dermatitis	49/63 (77)	27/36 (75)	22 (81)	0.76
Additional food allergy				
Peanut	36/63 (57)	20/36 (56)	16 (59)	0.80
Egg	37/62 (60)	18/36 (50)	19/26 (73)	0.12
Wheat	11/63 (17)	6/36 (17)	5/27 (19)	1.00
Other	33/62 (53)	21/36 (58)	12/26 (46)	0.44
FAQLQ-adult form	All (n=31)	Desensitized (n=18)	Persistent (n=13)	P value
Age years, mean (SD)	19.3 (1.6)	19.6 (1.9)	18.9 (0.9)	0.16
Male gender	14 (45)	7 (38)	7 (58)	0.48
Additional asthma	19 (61)	11 (61)	8 (62)	1.00
Additional rhinitis	17/30 (57)	19/17 (59)	7 (54)	1.00
Additional atopic dermatitis	20 (65)	13 (72)	7 (54)	0.45
Additional food allergy				
Peanut	17/30 (57)	11/17 (65)	6 (46)	0.46
Egg	16/30 (53)	7/17 (41)	9 (69)	0.16
Wheat	6/30 (20)	3/17 (18)	3/13 (23)	1.00
Other	15/30 (50)	10/17 (59)	5 (38)	0.46

130 Figure E3:



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132 Figure E3: Mean food allergy quality of life (FAQLQ) scores among milk OIT patients categorized by
 133 their self-reported milk consumption and divided into the FAQLQ child-form, teenager-form, and
 134 adult-form responder subgroups. Comparison between the desensitized group (consuming ≥ 200 ml of
 135 milk daily) and persistent group (less than 200 ml of milk or none).

136 * $P < 0.05$ (Mann-Whitney U-test).

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Table E3: Correlations between generic HRQoLQ mean scores (higher scores indicate better HRQoL) and FAQLQ (higher scores indicate worse FAQLQ) mean scores. Correlations are negative because of opposed scales.

Correlation	Pearson's r	P value	Spearman's r	P value
FAQL-CF and 17D	-0.501	0.002	-0.496	0.002
FAQL-TF and 16D	-0.217	0.16	-0.265	0.09
FAQL-AF and 15D	-0.080	0.72	-0.177	0.42

Table E4: Characteristics of the patients who responded or did not respond to the HRQoLQ and FAQLQ and comparison between these two groups.

Characteristic	Responders	Non-responders	P value
Generic HRQoLQ			
Male gender	87/160	88/135	0.07
Age, years, mean (SD)	14.3 (3.9)	14.8 (4.5)	0.44
Achieved desensitization	95/160	41/84	0.14
Number of additional atopic diseases (SD)	2.1 (0.9)	2.2 (0.9)	0.35
FAQLQ			
Male gender	80/142	95/153	0.34
Age, years, mean (SD)	14.1 (3.7)	15.0 (4.6)	0.15
Achieved desensitization	82/142	54/102	0.51
Number of additional atopic diseases (SD)	2.1 (1.0)	2.3 (0.8)	0.08