

ORIGINAL ARTICLE

WILEY

Food Allergy & Anaphylaxis

The impact of oral food challenges for food allergy on quality of life: A systematic review

Hannah M. Kansen¹  | Thuy-My Le² | Yolanda Meijer¹ | Bertine M. J. Flokstra-de Blok^{3,4} | Paco M. J. Welsing² | Cornelis K. van der Ent¹ | André C. Knulst² | Francine C. van Erp²

¹Department of Pediatric Pulmonology and Allergology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, The Netherlands

²Department of Dermatology, University Medical Centre Utrecht, Utrecht, The Netherlands

³GRIAC Research Institute, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

⁴Department of General Practice and Elderly Care Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Correspondence

Hannah M. Kansen, Department of Pediatric Pulmonology and Allergology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, The Netherlands.
Email: h.m.kansen-2@umcutrecht.nl

Edited by: Jennifer Koplin

Abstract

Background: Food allergy significantly impairs health-related quality of life (HRQL). Currently, it is still unknown whether diagnostic interventions for food allergy improve HRQL. We aim to assess the impact of diagnostic interventions for food allergy on HRQL.

Methods: A systematic search was performed in MEDLINE, Embase, Cochrane Library, and CINAHL focused on patients with a (suspected) food allergy who underwent diagnostic interventions (ie, skin prick test, specific IgE, or oral food challenges [OFC]) and in whom HRQL was assessed. The mean difference between HRQL before and after the diagnostic intervention was calculated. A minimal clinically important difference of 0.5 was considered clinically relevant for the food allergy quality of life questionnaire.

Results: Seven of 1465 original identified publications were included in which the impact of an OFC on HRQL was investigated (total patients $n = 1370$). No other diagnostic interventions were investigated. Food allergy-specific parent-reported HRQL improved significantly after an OFC irrespective of the outcome in children with a suspected food allergy in two publications. The change was considered clinically relevant in one of two publications. In addition, parent-reported HRQL improved after an OFC to assess the eliciting dose in children with a confirmed food allergy. The parental burden was significantly reduced after an OFC to assess resolution of food allergy. A meta-analysis could not be performed due to the limited numbers of, and considerable heterogeneity between, eligible publications.

Conclusion: An OFC is associated with an improved food allergy-specific HRQL and a reduced parental burden of food allergy.

KEYWORDS

challenge tests, clinical aspects, diagnostic techniques, food challenge, quality of life

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; FAQL-PB, food allergy quality of life-parental burden questionnaire; FAQLQ-AF, food allergy quality of life questionnaire-adult form; FAQLQ-CF, food allergy quality of life questionnaire-child form; FAQLQ-PF, food allergy quality of life questionnaire-parent form; FAQLQ-TF, food allergy quality of life questionnaire-teen form; HRQL, health-related quality of life; MCID, minimal clinically important difference; MD, mean difference; OFC, oral food challenge; PedsQL™ 4.0, pediatric quality of life inventory 4.0; sIgE, specific immunoglobulin E; SMD, standardized mean difference; SPT, skin prick testing; WHOQOL-BREF, World Health Organization generic quality of life scale.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2018 The Authors. *Pediatric Allergy and Immunology* Published by John Wiley & Sons Ltd

1 | INTRODUCTION

The prevalence of food allergy is thought to be increasing during recent decades.¹ Previous studies have shown that up to 35% of the population reports adverse reactions to food, while between 1% to 3% has a food allergy confirmed by an oral food challenge (OFC).^{2,3}

Currently, no curative treatment for food allergy is available. Patients are advised to follow an elimination diet and to carry emergency medication to avoid or treat possible life-threatening allergic reactions.⁴ Hence, patients with a food allergy are faced with dietary and social restrictions. Due to these restrictions, and fear of an allergic reaction, patients with a food allergy have a significantly impaired food allergy-specific health-related quality of life (HRQL).^{5,6} In addition, patients with a food allergy reported poorer generic HRQL than the general population and patients with diabetes mellitus type 1 but better generic HRQL than patients with rheumatoid arthritis, asthma, and irritable bowel syndrome.⁷ This may be explained by the fact that patients with a food allergy live with constant vigilance and fear of an allergic reaction although they do not have daily chronic symptoms like patients with rheumatoid arthritis, asthma, and irritable bowel syndrome.⁸

An accurate diagnosis of food allergy is highly important to minimize unnecessary elimination diets in non-allergic patients on the one hand and avoid allergic reactions in patients with a food allergy on the other hand. Currently, the diagnostic process for food allergy consists of a careful clinical and dietary history and sensitization tests including the level of specific IgE (sIgE) to the suspected food and/or a skin prick test (SPT).⁹ However, these sensitization tests have a relatively low specificity depending on the allergen.¹⁰ The current reference standard to assess a food allergy, the threshold, and the severity of the clinical reaction is an oral food challenge (OFC). In short, increasing amounts of food allergen or placebo are given with close monitoring in a hospital setting with emergency equipment.^{11,12}

The increasing prevalence of food allergy and the significant impact of food allergy on HRQL of affected patients give cause for careful consideration of current diagnostic strategies. A comprehensive assessment on the impact of diagnostic interventions for food allergy on HRQL of patients is important as these diagnostic interventions might improve HRQL. Therefore, the aim of this review was to provide a systematic synthesis of the current evidence on the impact of diagnostic interventions for food allergy on HRQL.

2 | METHODS

2.1 | Search strategy

This systematic review was conducted according to a previously developed protocol registered on the international prospective register of systematic reviews (PROSPERO) and reported according to the PRISMA checklist.^{13,14}

We developed an extensive search strategy to identify all publications relevant to our research question from electronic bibliographic databases using keywords and Medical Subject

Headings. The search combined keywords and synonyms for the domain (patients with a suspected or a confirmed food allergy), the determinant (diagnostic interventions for food allergy: specific IgE (sIgE), skin prick testing (SPT), oral food challenges (OFC), or component-resolved diagnostics), and the outcome (food allergy-specific or generic HRQL outcome measures). The search strategy was initially developed for the MEDLINE database and then adapted for use on other databases. The full search strategy is published in the Appendix S1. Four databases were searched from inception until July 6, 2017: MEDLINE, EMBASE, the Cochrane Library, and CINAHL. All identified citations were imported into Rayyan for deduplication and title and abstract screening.¹⁵ All identified publications were screened by two authors (HK and FE) independently. Subsequently, all potentially relevant articles were screened full text by the same two authors independently and assessed for eligibility. The references and citations of all the publications that were screened full text were reviewed to identify any additional relevant sources. The citations were analyzed using Scopus.¹⁶ The reasons for exclusion of the publications that were screened full text are listed in the Appendix S2. Any discrepancies between two authors were resolved by discussion and consensus or by consulting a third reviewer (TL) if necessary.

2.2 | Eligibility criteria

We included publications in English, Dutch, German, French, or Spanish and did not restrict on publication year. We excluded publications if no original outcome data were reported, such as other systematic reviews, meta-analyses, or editorials. We included publications of children or adults with a suspected or a confirmed food allergy if a diagnostic intervention for a food allergy was performed and HRQL scores were measured or could be calculated. In patients with a suspected food allergy, the aim of the diagnostic intervention was to confirm or exclude the diagnosis of a food allergy while the aim of diagnostic interventions in patients with a confirmed food allergy was either to assess the threshold, the severity, or the resolution of a food allergy. Publications were only included if a validated food allergy-specific or generic HRQL instrument was used to measure a change before and after a diagnostic intervention or a difference in patients with or without a diagnostic intervention. We contacted the study authors of abstract publications and original publications with incomplete HRQL outcome data to obtain additional information on the study methods and the original data. When we were not able to acquire further details on abstract publications, these publications were excluded. A complete overview of inclusion and exclusion criteria is displayed in the Appendix S3.

2.3 | Quality of paper assessment

The included publications were assessed for risk of bias in duplicate (HK and FE) according to a modified version of the Quality in Prognostic Studies (QUIPS) tool (Appendix S4).¹⁷ The QUIPS tool

considers six domains of potential bias, and every domain comprises several prompting items to consider. All items were scored (yes, partly, no, or unsure) by two authors independently. Subsequently, the six domains of the individual publications were graded for the risk of bias, and finally, each publication as well as the six domains of all publications was graded for the overall risk of bias (*high*, *moderate*, or *low*). Any discrepancies between two authors were again resolved by discussion and consensus or by consulting a third reviewer (TL) if necessary.

2.4 | Outcome assessment

Health-related quality of life can be measured using disease-specific or generic HRQL questionnaires. Disease-specific HRQL questionnaires are able to measure food allergy-related impairments, such as the dietary and social restrictions, and the fear of allergic reactions. In contrast to disease-specific HRQL questionnaires, generic HRQL questionnaires facilitate direct comparison with other populations. We included publications that evaluated disease-specific or generic HRQL before and after a diagnostic intervention and publications that evaluated the difference in disease-specific or generic HRQL in patients with or without a diagnostic intervention.

Disease-specific questionnaires used to evaluate HRQL in food allergic patients in the eligible publications included the self-administered food allergy quality of life questionnaire (FAQLQ) with age-specific adaptations: the child form (FAQLQ-CF) for children 8-12 years of age, the teenager form (FAQLQ-TF) for adolescents 13-17 years of age, and the adult form (FAQLQ-AF) for adults ≥ 18 years of age. In addition, the parent form (FAQLQ-PF) was available to measure parent-reported HRQL of children 0-12 years of age. The FAQLQ-CF contains 24 items and 4 domains (allergen avoidance, risk of accidental exposure, emotional impact, and dietary restrictions), the FAQLQ-TF contains 23 items and 3 domains (allergen avoidance, risk of accidental exposure, and emotional impact), the FAQLQ-AF contains 29 items and 4 domains (allergen avoidance, risk of accidental exposure, emotional impact, and food allergy-related health), and the FAQLQ-PF contains 30 items and 3 domains (emotional impact, food anxiety, and social dietary limitations). The FAQLQ items are scored on a seven-point scale. The longitudinal validity and responsiveness of the FAQLQ have been demonstrated.^{18,19} In addition, the food allergy quality of life-parental burden questionnaire (FAQL-PB) was used to assess the effect of a child with food allergy on caregiver HRQL. The FAQL-PB is a validated questionnaire which contains 17 items.²⁰

Generic questionnaires used to evaluate HRQL in the eligible publications were the pediatric quality of life inventory 4.0 (PedsQL™ 4.0) in children and the World Health Organization generic quality of life scale (WHOQOL-BREF) in parents. The PedsQL™ 4.0 is a validated generic HRQL questionnaire for children 8-12 years of age which contains 23 items and 4 domains (physical, emotional, social, and school). The WHOQOL-BREF is a validated generic HRQL questionnaire for adults which contains 26 items and 4 domains (physical, psychological, social, and environmental).

2.5 | Data analysis

Full details on the publications, patients, diagnostic intervention(s), and outcome (HRQL questionnaire) were gathered. Publications in patients with a suspected food allergy were analyzed separately from publications in patients with a confirmed food allergy because HRQL is associated with perceived disease severity.²¹ Furthermore, the impact of an OFC on HRQL might be profoundly different in patients with a suspected or a confirmed food allergy because the aim of an OFC in patients with a suspected food allergy was to confirm or exclude the diagnosis of a food allergy, while the aim of an OFC in patients with a confirmed food allergy was either to assess the threshold, the severity, or the resolution of a food allergy.

For publications using the food allergy quality of life questionnaires (FAQLQ), we calculated the mean difference (MD) before and after the diagnostic intervention with a 95% confidence interval (95% CI). If the 95% CI of the MD was not available in the original publication and could not be provided by the study authors, we computed this value using the SD of the difference scores.²² To compute the SD of the difference scores in paired data, the correlation coefficient (r) between pre-scores and post-scores is required. We assumed a correlation of $r = .5$ and performed a sensitivity analysis to evaluate the impact of this assumption using a range of plausible correlation ($r = .2$ and $r = .8$). The MD score of the FAQLQ is meaningful as this change score can be interpreted using the minimal clinically important difference (MCID). The MCID is the smallest change score that is considered clinically relevant.²³ The MCID for the FAQLQ is 0.5 as estimated previously using a distribution-based method.¹⁸

For publications using other HRQL questionnaires than the FAQLQ, or if the MD of the FAQLQ could not be calculated, we estimated the standardized mean difference (SMD) before and after the diagnostic intervention with a 95% CI using Cohen's statistics for paired data.²⁴ Again, the correlation coefficient r was imputed to calculate the SD within groups if needed. Based on Cohen's criteria, a SMD of 0.2 is considered small, 0.5 is moderate, and >0.8 is large.²⁴

The MD and SMD were calculated in such a way that their direction was positive. Thus, a positive MD or SMD indicated an improved HRQL. If three or more publications reported HRQL outcomes on the same questionnaire in comparable groups of patients with comparable diagnostic interventions, the results were pooled using the random effects model.²⁵

For publications with a cross-sectional study design, a difference in mean HRQL scores between patients who underwent an OFC and those who did not undergo an OFC was evaluated using the two-sided independent t test.

All data were extracted using standardized pre-piloted data extraction forms in Microsoft Excel 2010, and forest plots were created using GraphPad Prism 7.02 (GraphPad Software, Inc, San Diego, CA).

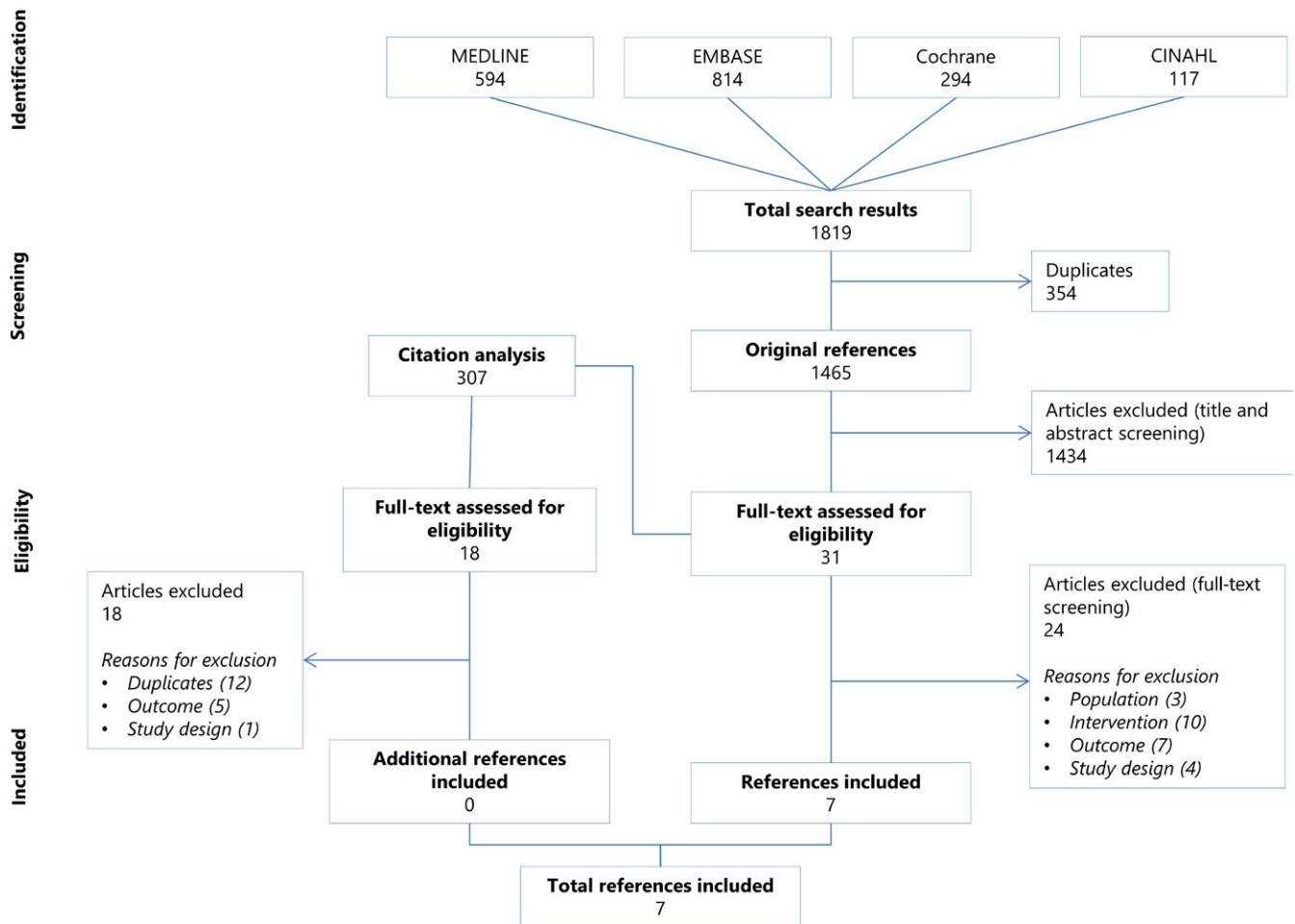


FIGURE 1 PRISMA flowchart of study selection [Colour figure can be viewed at wileyonlinelibrary.com]

3 | RESULTS

3.1 | Selection of eligible publications

The search results are summarized in a flowchart in Figure 1. We selected 31 of 1465 original identified publications for the full-text eligibility screening. Seven eligible publications were included in the final systematic review. Reasons for exclusion after the full-text screening were as follows: no diagnostic intervention was investigated ($n = 10$), the publication did not report original data ($n = 4$), only non-allergic patients were included ($n = 3$), the health-related quality of life (HRQL) questionnaire was not validated ($n = 3$), no HRQL questionnaire was used ($n = 2$), or no change or difference in HRQL was assessed ($n = 2$). No new relevant sources were identified by checking references and analyzing citations.

3.2 | Characteristics of included publications

The characteristics of the seven included publications are summarized in Table 1. Overall, 1370 patients (ranging between 54 and 420 per study) were recruited between 2007 and 2016 in tertiary

care.^{18,26-30} All included publications investigated the impact of an OFC on HRQL. No publications were identified in which the impact of other diagnostic interventions on HRQL was investigated.

Four of seven included publications assessed HRQL in patients with a suspected food allergy.^{18,19,27,29} Three of these four publications compared HRQL before and after an OFC. One of the four publications compared the HRQL between patients who underwent OFC and patients who were on the waiting list for OFC or who were considered food allergic by a physician.¹⁹

Two of seven included publications assessed HRQL before and after an OFC in patients with a confirmed food allergy. The aim of the OFC was to evaluate the eliciting dose²⁶ or to assess resolution of food allergy.³⁰ In one of these two publications, HRQL was also assessed in patients that did not undergo an OFC. These patients were considered food allergic by a physician.³⁰

Finally, one of seven included publications assessed HRQL in patients with a confirmed food allergy at a single point in time in both patients previously diagnosed through an OFC and in patients considered food allergic but who did not undergo an OFC.²⁸

The risk of bias was considered high in three,²⁸⁻³⁰ moderate in three,^{18,19,26} and low in one publication²⁷ (Table 2). The complete results of the risk of bias assessment are published in the Appendix S5.

TABLE 1 Characteristics of included publications

Publication	Study design, geographical area	Participants	Food allergen (n)	Intervention	Control	Outcome
Suspected food allergy						
DunnGalvin ¹⁸	Prospective cohort study in Europe (Ireland)	82 children (≤12 y) with a suspected food allergy (86%) or a suspected tolerance to food (14%). No specific diagnostic criteria reported.	Peanut (26), tree nut (10), milk (24), egg (15), and fish or shellfish (7)	DBPCFC, single-blind or open OFC	NA	FAQLQ-PF at: 1. Day OFC 2. 2 mo after OFC 3. 6 mo after OFC
Soller ²⁹	Prospective cohort study in Europe (Ireland)	54 children (≤12 y) with a suspected food allergy on the waiting list for an OFC. No specific diagnostic criteria reported.	Peanut (17), tree nut (9), milk (10), egg (13), wheat (3), or soy (2)	Open OFC	NA	FAQLQ-PF at: 1. 2 mo before OFC 2. Day OFC 3. 2 mo after OFC 4. 6 mo after OFC
van der Valk ²⁷	Prospective cohort study in Europe (the Netherlands)	112 children (≤17 y) with a suspected cashew nut allergy and their parents. A suspected cashew nut allergy was based on (i) sensitization (positive skin prick test or sIgE) and a clinical history of previous positive reaction to cashew nut or (ii) unknown exposure.	Cashew nut (112)	DBPCFC	NA	FAQLQ-PF, FAQLQ-TF, and FAQLQ-CF at: 1. Before OFC 2. 6 mo after OFC
van der Velde ¹⁹	Prospective cohort study in Europe (the Netherlands)	57 children (8-12 y), 46 adolescents (13-17 y), and 53 adults (≥18 y) with a suspected food allergy on the waiting list for an OFC (expected waiting time < 6 mo) who were challenged during follow-up were compared to 20 children, 25 adolescents, and 20 adults with a suspected food allergy on the waiting list for an OFC (expected waiting time > 6 mo) or with a confirmed food allergy by a physician based on skin prick test or sIgE (no cut-off values reported) who were not challenged during follow-up.	Peanut (68), tree nut (39), milk (17), egg (11), wheat (9), soy (8), sesame (4), or not reported (65)	DBPCFC	No DBPCFC, or other diagnostic testing	FAQLQ-AF, FAQLQ-TF, and FAQLQ-CF at 1. 1 mo before OFC (or baseline) 2. 6 mo after OFC (or 7 mo after baseline)
Confirmed food allergy						
Hourihane ²⁶	Prospective cohort study in Europe (Ireland), the United States (Boston), and Australia (Melbourne)	378 children (≤18 y) with a confirmed peanut allergy. A confirmed peanut allergy was based on (i) a convincing clinical history within 2 y and sensitization (SPT or sIgE), or (ii) a positive OFC (either an open OFC or a DBPCFC) within 2 y, or (iii) no previous ingestion of peanut with sensitization to peanut > 95% PPV (sIgE ≥ 15 kU/L and/or peanut SPT ≥ 8 mm within 2 mo).	Peanut (378)	Single-dose OFC to assess the predicted peanut eliciting dose	NA	FAQLQ-PF and FAQLQ-CF at: 1. Before OFC 2. 1 mo after OFC

(Continues)

TABLE 1 (Continued)

Publication	Study design, geographical area	Participants	Food allergen (n)	Intervention	Control	Outcome
Franxman ²⁸	Cross-sectional study in the United States (Michigan)	115 children (≤18 y) with a positive OFC during the past 11 y were compared to 305 children with a confirmed food allergy by a physician without an OFC. No specific diagnostic criteria reported.	Peanut and/or tree nut (50), milk (42), egg (23), or not reported (305)	NA. Exposure: OFC	NA. No exposure: no OFC	FAQL-PB at: 0-11 y after OFC (or after diagnosis without OFC)
Knibb ³⁰	Prospective cohort in Europe (United Kingdom)	40 children (6-16 y) with a confirmed peanut or tree nut allergy based on clinical history and sensitization (SPT and/or sIgE) were challenged to assess resolution of food allergy and were compared to 103 children (6-16 y) with a confirmed food allergy by a physician based on sensitization (persistent significant SPT wheals or sIgE; no cut-off levels reported) whom were not challenged.	Challenged/unchallenged: peanut (17/19), tree nut (8/8), both peanut and tree nut (15/36)	Open OFC to assess resolution of food allergy	No OFC or other diagnostic testing	FAQL-PB, PedsQL™ 4.0, and WHOQOL-BREF at: 1. Before OFC (or post-clinic) 3-6 mo after OFC (or 3-6 mo after follow-up)

DBPCFC, double-blind placebo-controlled food challenge; FAQLQ, food allergy quality of life questionnaire (different versions: AF, adult form; CF, child form; PB, parental burden; PF, parent form); n, number; NA, not applicable; OFC, oral food challenge; sIgE, specific IgE; SPT, skin prick testing; PedsQL™ 4.0, pediatric quality of life inventory 4.0; PPV, positive predictive value; WHOQOL-BREF, World Health Organization generic quality of life scale.

3.3 | Quality of life in patients with a suspected food allergy

In patients with a suspected food allergy who underwent an OFC with positive, negative, and inconclusive outcomes combined, food allergy-specific HRQL significantly improved after an OFC in four of eight groups in three publications: in both children and adults in one publication,¹⁹ and in parents in two publications^{18,29} (Figure 2A). The improved HRQL was only clinically relevant in parents in one publication, with a 95% CI of the mean difference (MD) exceeding the minimal clinically important difference (MCID).²⁹

Subgroup analyses were also performed for the different OFC outcomes, that is, positive, negative, and inconclusive OFC. This showed that, in patients with a positive OFC outcome (ie, food allergic patients), parent-reported food allergy-specific HRQL significantly improved after an OFC in two of three publications and this change was clinically relevant in one publication (Figure 2B).^{18,29} In patients with a negative OFC outcome (ie, non-allergic patients), food allergy-specific HRQL significantly improved after an OFC in six of eight groups in four publications: again in parents included in two publications,^{18,29} but also in adults, adolescents, and children in one publication,¹⁹ and in adolescents in another publication (Figure 2C).²⁷ The improved HRQL was only clinically relevant in one publication in which parent-reported HRQL was assessed.²⁹ In patients with an inconclusive OFC outcome, food allergy-specific HRQL did not improve after an OFC (Figure 2D).¹⁹

In two publications, HRQL after the OFC was followed up in time and was measured at 2 and 6 months after the OFC. These two publications showed that, after a negative OFC, the parent-reported HRQL further improved between 2 and 6 months, and this improvement was significant and clinically relevant (Appendix S6).^{18,29}

In addition to the inclusion of patients that underwent an OFC, one publication also included patients that did not undergo an OFC.¹⁹ All patients who underwent an OFC were suspected of having a food allergy, while the patients who did not undergo an OFC were either suspected of having a food allergy and were on the waiting list for OFC or were already diagnosed with a food allergy by a physician (Table 1). No significant difference was observed between food allergy-specific HRQL at baseline and after 7 months in children and adolescents (Appendix S7a). Furthermore, no significant difference was observed between the MD in HRQL in patients that underwent an OFC compared to the patients that did not undergo an OFC (Appendix S8).

3.4 | Domain-specific quality of life in patients with a suspected food allergy

The domain-specific parent-reported HRQL values are shown in Figure 3 and domain-specific HRQL values in children and adolescents in Appendix S9. In one publication, no domain-specific HRQL values were available.¹⁹

In parents of children with all OFC outcomes combined, parent-reported HRQL significantly improved after an OFC in all three domains in two of three publications but this change was clinically

TABLE 2 Risk of bias assessment

	Hourihane 2017	van der Valk 2016	Franxman 2015	Soller 2014	Knibb 2012	van der Velde 2012	DunnGalvin 2010	Overall risk of bias (total domain)
Study participation	L	L	H	M	M	L	L	Moderate
Study attrition	L	M	H	M	H	H	M	High
Diagnostic intervention measurement	L	L	M	L	M	L	H	Moderate
Outcome measurement	L	L	L	L	L	L	L	Low
Study confounding	M	L	L	H	M	L	M	Moderate
Statistical analysis and reporting	H	L	L	M	L	L	L	Moderate
Overall risk of bias (publication)	Moderate	Low	High	High	High	Moderate	Moderate	

relevant only in the domains of “food anxiety” and “social and dietary restriction” in one publication (Figure 3A).^{18,29} In children and adolescents with all OFC outcomes combined, food allergy-specific HRQL improved in the domain of “allergen avoidance” in children and in the domain of “emotional impact” in adolescents in one publication, although not clinically relevant (Appendix S9a).²⁷

In parents of children with a positive OFC outcome (ie, food allergic patients), parent-reported food allergy-specific HRQL significantly improved significantly after an OFC in the domain of “emotional impact” in two of three publications^{18,29} and this change was clinically relevant in one publication.¹⁸ In one of these two publications, food allergy-specific HRQL significantly improved after an OFC in the domains of “social and dietary impact” and “food anxiety”.²⁹ This change in HRQL was clinically relevant in the domain of “social and dietary impact” only. In children and adolescents with a positive OFC outcome, food allergy-specific HRQL did not improve after a positive OFC outcome (Appendix S9b).

In parents of children with a negative OFC outcome (ie, non-allergic patients), parent-reported food allergy-specific HRQL significantly improved after an OFC in all three domains in two of three publications,^{18,29} and this change was clinically relevant in all domains in one publication²⁹ and in the domain of “social and dietary impact” in the other publications¹⁸ (Figure 3C). Furthermore, HRQL significantly improved in the domains of “risk accidental exposure” and “emotional impact” in adolescents included in one publication although not clinically relevant (Appendix S9c).²⁷

3.5 | Quality of life in patients with a confirmed food allergy

In patients with a confirmed food allergy who underwent an OFC, parent-reported food allergy-specific HRQL and HRQL in children significantly improved after a single-dose OFC in one publication (Figure 4).²⁶ The standardized mean difference (SMD) was very large. The aim of the OFC in this publication was to assess the ED₀₅, which is the dose that elicits an allergic reaction in 5% of the allergic subjects (Table 1). The MD and domain-specific HRQL values were not available.

The parental burden was just significantly reduced after an OFC in patients with a confirmed food allergy included in one publication.³⁰ The SMD was small. Generic HRQL in both parents and children did not improve after an OFC (Figure 4). The domain-specific HRQL values were not available.

In addition to the inclusion of patients that underwent an OFC, one publication included patients that did not undergo an OFC.³⁰ All patients who underwent an OFC were suspected of resolution of their food allergy, while the patients who did not undergo an OFC were considered food allergic by a physician (Table 1). In parents of patients that did not undergo an OFC, no significant differences in the parental burden and generic HRQL were observed between baseline and after 3-6 months (Appendix S7b). Furthermore, no significant difference was observed between the SMD in the parental burden and generic HRQL in patients that underwent an OFC compared to patients that did not undergo an OFC (Appendix S10).

Patients with a suspected food allergy

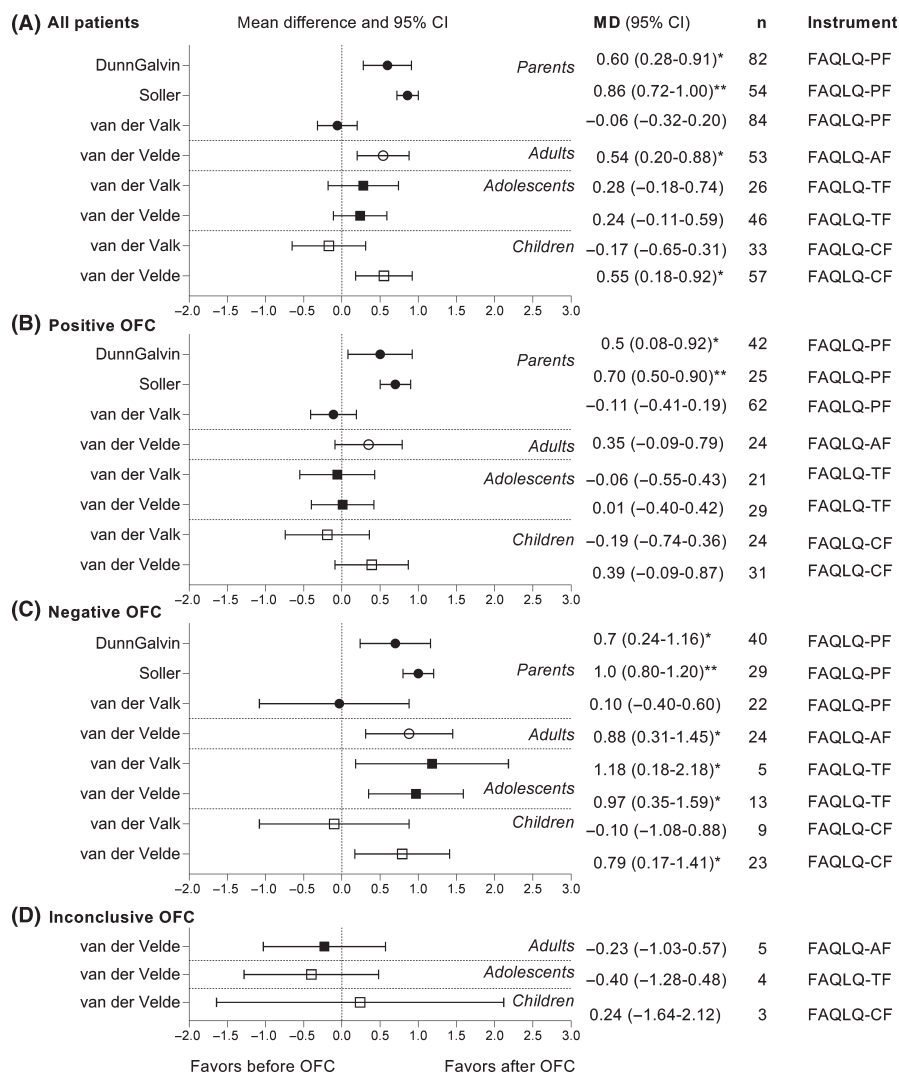


FIGURE 2 Health-related quality of life before and after an oral food challenge in patients with a suspected food allergy. Mean difference with a 95% confidence interval of food allergy-specific health-related quality of life before and after an oral food challenge (OFC) in patients with a suspected food allergy: A, all patients; B, patients with a positive OFC outcome (allergic); C, patients with a negative OFC outcome (non-allergic); D, patients with an inconclusive OFC outcome. The minimal clinically important difference of 0.5 was used to consider the mean difference as clinically relevant. **Significant and clinically relevant change in HRQL; *significant change in HRQL. CI, confidence interval; FAQLQ, food allergy quality of life questionnaire (different versions: AF, adult form; CF, child form; PF, parent form; TF, teen form); HRQL, health-related quality of life; MD, mean difference; n, number; OFC, oral food challenge

Finally, a lower parental burden (better HRQL) was observed in parents of children with a food allergy confirmed with an OFC compared to parents of children with a food allergy confirmed without an OFC in one publication (mean FAQL-PB after an OFC 1.5 (95% CI 1.37-1.62) and mean FAQL-PB without an OFC 1.88 (95% CI 1.79-1.95); $P < .0001$).²⁸

3.6 | Meta-analysis

A meta-analysis was considered inappropriate due to the limited number of publications available, the profound differences between the included populations, and the different outcome measurements (HRQL questionnaires) that were used in the included publications.

4 | DISCUSSION

We present the first systematic review that evaluates whether oral food challenges (OFC) for food allergy affect the health-related

quality of life (HRQL) in patients with a suspected or a confirmed food allergy. Our findings indicate that an OFC is associated with an improved food allergy-specific HRQL. In the majority of included publications, food allergy-specific HRQL improved after an OFC^{18,19,26,29} and not in patients that did not undergo an OFC.^{19,30} The parental burden was just significantly reduced after an OFC and did not change in patients that did not undergo an OFC. No information was available about whether other diagnostic interventions affect HRQL.

Our results show that an OFC is associated with a significantly improved parent-reported HRQL after an OFC.^{18,26,29} An OFC might have a beneficial effect because the challenge procedure clarifies the severity of the food allergy and reduces anxiety as parents and patients experience the exposure to the food allergen in a controlled environment and learn how to handle in case of severe reaction in daily practice.³¹⁻³³ In addition, an accurate food allergy diagnosis might decrease uncertainty after an OFC which is confirmed by the lack of HRQL improvement in patients after an OFC with an inconclusive outcome. Food allergy-specific HRQL continued to

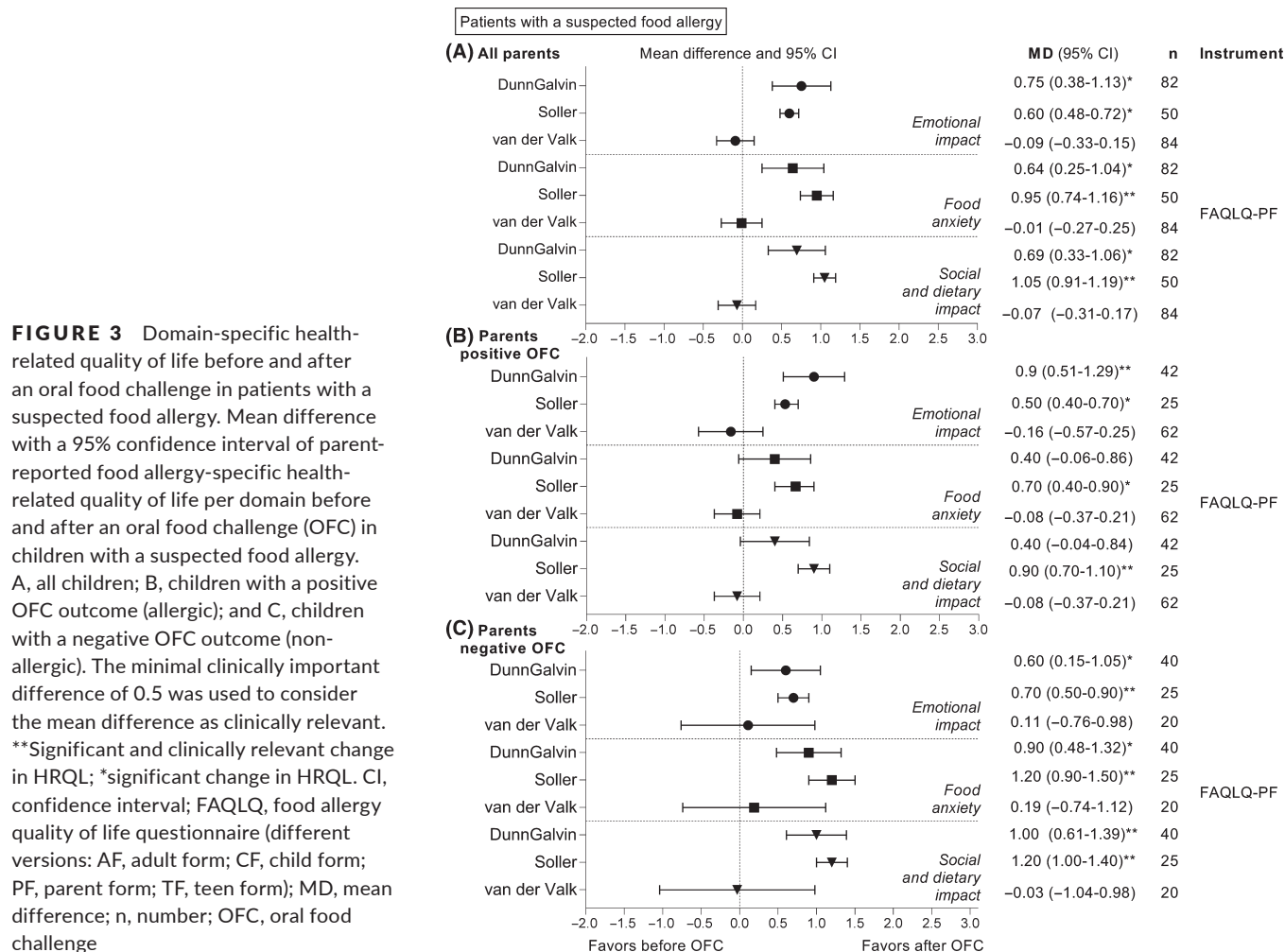


FIGURE 3 Domain-specific health-related quality of life before and after an oral food challenge in patients with a suspected food allergy. Mean difference with a 95% confidence interval of parent-reported food allergy-specific health-related quality of life per domain before and after an oral food challenge (OFC) in children with a suspected food allergy. A, all children; B, children with a positive OFC outcome (allergic); and C, children with a negative OFC outcome (non-allergic). The minimal clinically important difference of 0.5 was used to consider the mean difference as clinically relevant. **Significant and clinically relevant change in HRQL; *significant change in HRQL. CI, confidence interval; FAQLQ, food allergy quality of life questionnaire (different versions: AF, adult form; CF, child form; PF, parent form; TF, teen form); MD, mean difference; n, number; OFC, oral food challenge

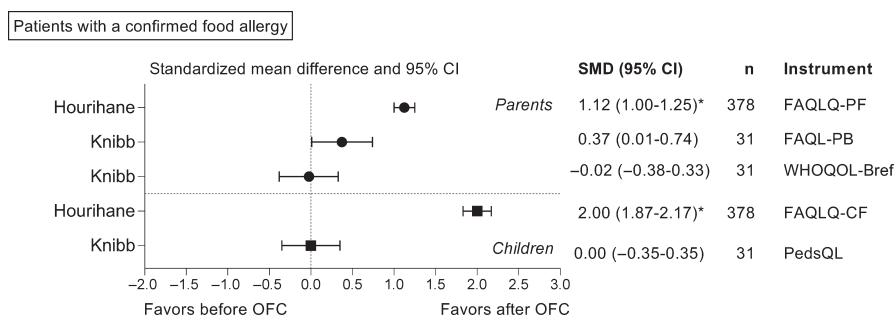


FIGURE 4 Health-related quality of life and the parental burden before and after an oral food challenge in patients with a confirmed food allergy. Standardized mean difference with a 95% confidence interval of food allergy-specific and generic health-related quality of life as well as the parental burden before and after an oral food challenge (OFC) in patients with a confirmed food allergy. The OFC was performed to evaluate the peanut eliciting dose (Houriha) or to assess resolution of food allergy (Knibb). CI, confidence interval; FAQL(Q), food allergy quality of life (Questionnaire) (different versions: PB, parental burden; PF, parent form); n, number; PedsQL™ 4.0, pediatric quality of life inventory 4.0; SMD, standardized mean difference; WHOQOL-BREF, World Health Organization generic quality of life scale

improve between 2 and 6 months after an OFC in parents included by DunnGalvin et al but not in Soller et al. This difference might be explained by several modifying factors that varied between the publications, such as the maintenance of regular clinical contact, guided food reintroduction, and other differences in management strategies after the OFC.

It must be noted that, in contrast to the publications by DunnGalvin and Soller, parent-reported food allergy-specific HRQL did not improve after an OFC in patients included by van der Valk et al.²⁷ This discrepant result might be explained by differences between the populations that were studied. The children included by van der Valk et al were all suspected of having a cashew nut allergy,

while the children included by DunnGalvin et al and Soller et al were suspected of other allergies like a peanut, cow's milk, or hen's egg allergy. Previous research has demonstrated that the type of food allergen is associated with HRQL in children and adults.^{21,34} Children with a suspected cashew nut allergy might experience no improved HRQL after an OFC because cashew nut is probably easier to avoid than other food allergens such as peanut, cow's milk, or hen's egg. This hypothesis is supported by the fact that the baseline HRQL value in patients included by van der Valk was much lower—indicating a better HRQL—compared to the baseline value in patients included by DunnGalvin et al. The baseline HRQL value in parents included by Soller et al was not reported.

The publications by van der Velde et al and Knibb et al assessed food allergy-specific HRQL in patients with and without an OFC and observed a significantly improved HRQL and reduced parental burden in patients with an OFC but not in patients without an OFC.^{19,30} However, there was no significant difference between the MD in food allergy-specific HRQL and the parental burden in patients that underwent an OFC compared to the patients that did not undergo an OFC. These results should be interpreted with caution because in both publications patients were not randomized to the OFC; thus, confounding may have biased the results as patients in who an OFC was performed were not fully comparable to those that did not undergo an OFC (Table 1). It is not surprising that HRQL did not improve in patients on the waiting list for an OFC as these patients remain uncertain regarding their food allergic status. In the publication by Knibb et al, an OFC was only performed in patients if resolution of food allergy was considered plausible by the physician, and therefore, baseline HRQL was better and the parental burden was lower in patients who underwent an OFC compared to those who did not undergo an OFC. Furthermore, the patients that underwent an OFC were significantly older which might have contributed to the improvement in HRQL in this group as an older age is associated with a better HRQL.^{35,36}

We summarized the literature on the effect of diagnostic interventions on HRQL in patients with a suspected or a confirmed food allergy. The interpretation of our review is limited as no diagnostic randomized trials have been performed, which are needed to adequately assess the true effect of a diagnostic intervention on HRQL without bias.³⁷ However, such a study design is hardly feasible as an OFC is the reference standard to diagnose a food allergy. In addition, we were unable to perform a meta-analysis to summarize the results of the included publications or to analyze subgroups of patients with different characteristics, due to the limited number of eligible publications and the differences in HRQL questionnaires that were used. Furthermore, there were a limited number of eligible publications that satisfied inclusion criteria and the majority of the included publications were at high or moderate risk of bias. Finally, our results are based on calculations using an assumed correlation coefficient (r) of .5. However, a sensitivity analysis with a range of plausible r values hardly changed our results (Appendix S11).

In conclusion, we found that an oral food challenge (OFC) is associated with an improved food allergy-specific health-related quality of life (HRQL) and a reduced parental burden of food allergy. Further

prospective HRQL research is necessary to support the findings of our review and investigate the impact of other diagnostic interventions on HRQL.

ACKNOWLEDGMENTS

We would like to thank H. van Os-Medendorp for her statistical advice.

CONFLICT OF INTEREST

None.

ORCID

Hannah M. Kansen  <http://orcid.org/0000-0003-1446-7704>

REFERENCES

- Allen KJ, Koplin JJ. The epidemiology of IgE-mediated food allergy and anaphylaxis. *Immunol Allergy Clin North Am*. 2012;32:35-50.
- Rona RJ, Keil T, Summers C, et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol*. 2007;120:638-646.
- Nwaru BI, Hickstein L, Panesar SS, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. *Allergy*. 2014;69:62-75.
- Muraro A, Dubois AE, DunnGalvin A, et al. EAACI food allergy and anaphylaxis guidelines. Food allergy health-related quality of life measures. *Allergy*. 2014;69:845-853.
- DunnGalvin A, Dubois AE, Flokstra-de Blok BM, Hourihane JO. The effects of food allergy on quality of life. *Chem Immunol Allergy*. 2015;101:235-252.
- Antolin-Amérigo D, Manso L, Caminati M, et al. Quality of life in patients with food allergy. *Clin Mol Allergy*. 2016;14:4.
- Flokstra-De Blok BMJ, Van Der Velde JL, Vlieg-Boerstra BJ, et al. Health-related quality of life of food allergic patients measured with generic and disease-specific questionnaires. *Allergy*. 2010;65:1031-1038.
- Flokstra-de Blok B, Dubois A, Vlieg-Boerstra B, et al. Health-related quality of life of food allergic patients: comparison with the general population and other diseases. *Allergy*. 2010;65:238-244.
- Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. EAACI Food Allergy and Anaphylaxis Guidelines: diagnosis and management of food allergy. *Allergy*. 2014;69:1008-1025.
- Chokshi NY, Sicherer SH, Chokshi NY, Sicherer SH. Interpreting IgE sensitization tests in food allergy. *Expert Rev Clin Immunol*. 2016;12:389-403.
- Sampson HA, Van Wijk G, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol*. 2012;130:1260-1274.
- Vlieg-Boerstra BJ, Herpertz I, Pasker L, et al. Validation of novel recipes for double-blind, placebo-controlled food challenges in children and adults. *Allergy*. 2011;66:948-954.
- Kansen H, Van Erp F, Le T, Meijer Y, Van Der Ent C. PROSPERO International prospective register of systematic reviews A systematic review of the cost-effectiveness and impact on quality of life of diagnostic testing in patients with suspected food allergy. 2017;1-6.

14. Moher D, Liberati A, Tetzlaff J, Altman D, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151:264-269.
15. Ouzzani M, Rayyan — a web and mobile app for systematic reviews. *Syst Rev*. 2016;5:210.
16. Falagas ME, Pitsouni EI, Malietzis GA, Pappas G. Comparison of PubMed, Scopus, Web of Science, and Google Scholar: strengths and weaknesses. *FASEB J*. 2017;22:338-342.
17. Hayden JA, Coté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med*. 2006;144:427-437.
18. Dunngalvin A, Cullinane C, Daly DA, Blok BMJF, Dubois AEJ, Hourihane JOB. Longitudinal validity and responsiveness of the food allergy quality of life questionnaire – parent form in children 0–12 years following positive and negative food challenges. *Clin Exp Allergy*. 2010;40:476-485.
19. Van Der Velde JL, Flokstra-De Blok BMJ, De Groot H, et al. Food allergy-related quality of life after double-blind, placebo-controlled food challenges in adults, adolescents, and children. *J Allergy Clin Immunol*. 2012;130:1136-1143.e2.
20. Cohen BL, Noone S, Muñoz-Furlong A, Sicherer SH. Development of a questionnaire to measure quality of life in families with a child with food allergy. *J Allergy Clin Immunol*. 2004;114:1159-1163.
21. Saleh-Langenberg J, Goossens NJ, Flokstra-De Blok BMJ, et al. Predictors of health-related quality of life of European food-allergic patients. *Allergy*. 2015;70:616-624.
22. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Effect sizes based on means. In: Borenstein M, Hedges LV, Higgins JPT, Rothstein HR, ed. *Introduction to Meta-Analysis*. Chichester, UK: John Wiley & Sons Ltd; 2009:21-32.
23. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. *J Clin Epidemiol*. 2008;61:102-109.
24. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. New York, NY: Academic Press; 1977.
25. Haidich A. Meta-analysis in medical research. *Hippokratia*. 2010;14(suppl 1):29-37.
26. Hourihane JOB, Allen KJ, Shreffler WG, et al. Peanut Allergen Threshold Study (PATS): novel single-dose oral food challenge study to validate eliciting doses in children with peanut allergy. *J Allergy Clin Immunol*. 2017;139:1583-1590.
27. van der Valk JPM, Gerth van Wijk R, Flokstra-de Blok BMJ, et al. No difference in health-related quality of life, after a food challenge with cashew nut in children participating in a clinical trial. *Pediatr Allergy Immunol*. 2016;27:812-817.
28. Franxman TJ, Howe L, Teich E, Greenhawt MJ. Oral food challenge and food allergy quality of life in caregivers of children with food allergy. *J Allergy Clin Immunol Pract*. 2014;3:50-56.
29. Soller L, Hourihane J, Dunngalvin A. The impact of oral food challenge tests on food allergy health-related quality of life. *Allergy*. 2014;69:1255-1257.
30. Knibb RC, Ibrahim NF, Stiefel G, et al. The psychological impact of diagnostic food challenges to confirm the resolution of peanut or tree nut allergy. *Clin Exp Allergy*. 2012;42:451-459.
31. Zijlstra WT, Flinterman AE, Soeters L, et al. Parental anxiety before and after food challenges in children with suspected peanut and hazelnut allergy. *Pediatr Allergy Immunol*. 2010;21:439-445.
32. Nguyen M, Wainstein BK, Hu W, Ziegler JB. Parental satisfaction with oral peanut food challenges; perception of outcomes and impact on management of peanut allergy. *Pediatr Allergy Immunol*. 2010;21:1119-1126.
33. Kemp AS, Allen CW, Campbell DE. Parental perceptions in egg allergy: does egg challenge make a difference? *Pediatr Allergy Immunol*. 2009;20:648-653.
34. Howe L, Franxman T, Teich E, Greenhawt M. What affects quality of life among caregivers of food-allergic children? *Ann Allergy Asthma Immunol*. 2014;113:69-74.e2.
35. Marklund B, Ahlstedt S, Nordström G. Health-related quality of life in food hypersensitive schoolchildren and their families: parents' perceptions. *Health Qual Life Outcomes*. 2006;4:48.
36. Wassenberg J, Cochard MM, Dunngalvin A, et al. Parent perceived quality of life is age-dependent in children with food allergy. *Pediatr Allergy Immunol*. 2012;23:412-419.
37. Rodger M, Ramsay T, Fergusson D. Diagnostic randomized controlled trials : the final frontier. *Trials*. 2012;13:1.

SUPPORTING INFORMATION

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

How to cite this article: Kansen HM, Le T-M, Meijer Y, et al. The impact of oral food challenges for food allergy on quality of life: A systematic review. *Pediatr Allergy Immunol*. 2018;29:527–537. <https://doi.org/10.1111/pai.12905>

1 **Appendix 1: Search strategy**

2

3 **MEDLINE**

4 Date search 6th of July 2017

5 1. foodallerg*[Title/Abstract]

6 2. "food allergy"[Title/Abstract]

7 3. "food allergies"[Title/Abstract]

8 4. "food hypersensitivity"[Title/Abstract]

9 5. "food hypersensitivities"[Title/Abstract]

10 6. peanut*[Title/Abstract]

11 7. Arachis[Title/Abstract]

12 8. milk*[Title/Abstract]

13 9. egg*[Title/Abstract]

14 10. fish*[Title/Abstract]

15 11. shellfish*[Title/Abstract]

16 12. "tree nut"[Title/Abstract]

17 13. hazelnut*[Title/Abstract]

18 14. walnut*[Title/Abstract]

19 15. macadamia*[Title/Abstract]

20 16. cashew*[Title/Abstract]

21 17. pistachio*[Title/Abstract]

22 18. wheat*[Title/Abstract]

23 19. sesame*[Title/Abstract]

24 20. soy*[Title/Abstract]

25 21. food hypersensitivity[MeSH]

26 22. Arachis[MeSH])

27 23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or

28 20 or 21 or 22

29 24. (CRD[Title/Abstract]

30	25. Component*[Title/Abstract]
31	26. Allergen*[Title/Abstract]
32	27. Ara[Title/Abstract]
33	28. Extract[Title/Abstract]
34	29. IgE[Title/Abstract]
35	30. sIgE[Title/Abstract]
36	31. "skin prick test"[Title/Abstract]
37	32. "skin prick testing"[Title/Abstract]
38	33. SPT[Title/Abstract]
39	34. challenge[Title/Abstract]
40	35. DBPCFC[Title/Abstract]
41	36. double-blind[Title/Abstract]
42	37. "double blind"[Title/Abstract]
43	38. placebo-controlled [Title/Abstract]
44	39. "placebo controlled"[Title/Abstract]
45	40. OFC[Title/Abstract]
46	41. Oral[Title/Abstract])
47	42. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or
48	41
49	43. "quality of life"[Title/Abstract]
50	44. "quality-of-life"[Title/Abstract]
51	45. QoL[Title/Abstract]
52	46. HRQL[Title/Abstract]
53	47. HRQoL[Title/Abstract]
54	48. FAQLQ*[Title/Abstract]
55	49. quality of life[MeSH]
56	50. EQ-5D[Title/Abstract]
57	51. EQ5D[Title/Abstract]

58 52. "EQ 5D"[Title/Abstract]
59 53. EuroQol-5D[Title/Abstract]
60 54. "EuroQol 5D"[Title/Abstract]
61 55. HUI[Title/Abstract]
62 56. "Health Utilities Index"[Title/Abstract]
63 57. SF-6D[Title/Abstract]
64 58. "SF 6D"[Title/Abstract]
65 59. "short form-6D"[Title/Abstract]
66 60. SF-36[Title/Abstract]
67 61. "SF 36"[Title/Abstract]
68 62. "short form 36"[Title/Abstract]
69 63. SF-12[Title/Abstract]
70 64. "SF 12"[Title/Abstract]
71 65. "short form 12"[Title/Abstract]
72 66. "short form health survey"[Title/Abstract]
73 67. "State-Trait Anxiety Inventory"[Title/Abstract]
74 68. STAI[Title/Abstract])
75 69. 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or
76 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68
77 70. 23 and 42 and 69
78

79 EMBASE

80 Date search 6th of July 2017

- 81 1. foodallerg*:ab,ti
- 82 2. 'food allergy':ab,ti
- 83 3. 'food allergies':ab,ti
- 84 4. 'food hypersensitivity':ab,ti
- 85 5. 'food hypersensitivities':ab,ti

86	6. peanut*:ab,ti
87	7. Arachis:ab,ti
88	8. milk:ab,ti
89	9. egg*:ab,ti
90	10. fish*:ab,ti
91	11. shellfish*:ab,ti
92	12. 'tree nut':ab,ti
93	13. hazelnut*:ab,ti
94	14. walnut*:ab,ti
95	15. macadamia*:ab,ti
96	16. cashew*:ab,ti
97	17. pistachio*:ab,ti
98	18. wheat*:ab,ti
99	19. sesame*:ab,ti
100	20. soy*:ab,ti
101	21. 'food allergy'/exp
102	22. 'arachis'/exp)
103	23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
104	or 20 or 21 or 22
105	24. crd:ab,ti
106	25. component*:ab,ti
107	26. allergen*:ab,ti
108	27. ara:ab,ti
109	28. extract:ab,ti
110	29. ige:ab,ti
111	30. sige:ab,ti
112	31. 'skin prick test':ab,ti
113	32. 'skin prick testing':ab,ti

114	33. spt:ab,ti
115	34. challenge:ab,ti
116	35. dbpcfc:ab,ti
117	36. 'double-blind':ab,ti
118	37. 'double blind':ab,ti
119	38. 'placebo-controlled':ab,ti
120	39. 'placebo controlled':ab,ti
121	40. ofc:ab,ti
122	41. oral:ab,ti
123	42. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or
124	41
125	43. 'quality of life':ab,ti
126	44. 'quality-of-life':ab,ti
127	45. qol:ab,ti
128	46. hrql:ab,ti
129	47. hrqol:ab,ti
130	48. faqlq*:ab,ti
131	49. 'quality of life'/exp
132	50. 'quality of life':ab,ti
133	51. EQ-5D:ab,ti
134	52. EQ5D:ab,ti
135	53. 'EQ 5D':ab,ti
136	54. EuroQol-5D:ab,ti
137	55. 'EuroQol 5D':ab,ti
138	56. HUI:ab,ti
139	57. 'Health Utilities Index':ab,ti
140	58. SF-6D:ab,ti
141	59. 'SF 6D':ab,ti

- 142 60. 'short form-6D':ab,ti
143 61. SF-36:ab,ti
144 62. 'SF 36':ab,ti
145 63. 'short form 36':ab,ti
146 64. SF-12:ab,ti
147 65. 'SF 12':ab,ti
148 66. 'short form 12':ab,ti
149 67. 'short form health survey':ab,ti
150 68. 'State-Trait Anxiety Inventory':ab,ti
151 69. STAI:ab,ti
152 70. 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or
153 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69
154 71. 23 and 42 and 70 and [embase]/lim not [medline]/lim
155

156 **Cochrane Library**

157 Date search 6th of July 2017

- 158 1. foodallerg*:ab,ti,kw
159 2. "food allergy":ab,ti,kw
160 3. "food allergies":ab,ti,kw
161 4. "food hypersensitivity":ab,ti,kw
162 5. "food hypersensitivities":ab,ti,kw
163 6. peanut*:ab,ti,kw
164 7. Arachis:ab,ti,kw
165 8. milk:ab,ti,kw
166 9. egg*:ab,ti,kw
167 10. fish*:ab,ti,kw
168 11. shellfish*:ab,ti,kw
169 12. "tree nut":ab,ti,kw

170	13. hazelnut*:ab,ti,kw
171	14. walnut*:ab,ti,kw
172	15. macadamia*:ab,ti,kw
173	16. cashew*:ab,ti,kw
174	17. pistachio*:ab,ti,kw
175	18. wheat*:ab,ti,kw
176	19. sesame*:ab,ti,kw
177	20. soy*:ab,ti,kw)
178	21. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
179	or 20
180	22. CRD:ab,ti,kw
181	23. Component*:ab,ti,kw
182	24. Allergen*:ab,ti,kw
183	25. Ara:ab,ti,kw
184	26. Extract:ab,ti,kw
185	27. ige:ab,ti,kw
186	28. sige:ab,ti,kw
187	29. "skin prick test":ab,ti,kw
188	30. "skin prick testing":ab,ti,kw
189	31. spt:ab,ti,kw
190	32. challenge:ab,ti,kw
191	33. dbpcfc:ab,ti,kw
192	34. "double-blind":ab,ti,kw
193	35. 'double blind':ab,ti,kw
194	36. "placebo-controlled":ab,ti,kw
195	37. "placebo controlled":ab,ti,kw
196	38. ofc:ab,ti,kw
197	39. oral:ab,ti,kw

198 40. 22 or 23 or 24 or 25 or 27 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or
199 39
200 41. "quality of life":ti,ab,kw
201 42. "quality-of-life":ti,ab,kw
202 43. QoL:ti,ab,kw
203 44. HRQL:ti,ab,kw
204 45. HRQoL:ti,ab,kw
205 46. FAQLQ*:ti,ab,kw
206 47. EQ-5D:ti,ab,kw
207 48. EQ5D:ti,ab,kw
208 49. "EQ 5D" :ti,ab,kw
209 50. EuroQol-5D:ti,ab,kw
210 51. "EuroQol 5D" :ti,ab,kw
211 52. HUI:ti,ab,kw
212 53. "Health Utilities Index" :ti,ab,kw
213 54. SF-6D:ti,ab,kw
214 55. "SF 6D" :ti,ab,kw
215 56. "short form-6D" :ti,ab,kw
216 57. SF-36:ti,ab,kw
217 58. "SF 36" :ti,ab,kw
218 59. "short form 36" :ti,ab,kw
219 60. SF-12:ti,ab,kw
220 61. "SF 12" :ti,ab,kw
221 62. "short form 12" :ti,ab,kw
222 63. "short form health survey" :ti,ab,kw
223 64. "State-Trait Anxiety Inventory":ti,ab,kw
224 65. STAI:ti,ab,kw

225 66. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or
226 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65
227 67. 21 and 40 and 66
228 **CINAHL**
229 Date search 6th of July 2017
230 1. foodallergy
231 2. foodallergies
232 3. foodallergen
233 4. "food allergy"
234 5. "food allergies"
235 6. peanut
236 7. milk
237 8. egg
238 9. fish
239 10. shellfish
240 11. "tree nut"
241 12. hazelnut
242 13. walnut
243 14. macadamia
244 15. cashew
245 16. pistachio
246 17. wheat
247 18. sesame
248 19. soy
249 20. "food hypersensitivity"
250 21. Arachis
251 22. (MH "Food Hypersensitivity")

252	23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
253	or 20 or 21 or 22
254	24. CRD
255	25. Component
256	26. Allergen
257	27. Ara
258	28. Extract
259	29. IgE
260	30. slgE
261	31. "skin prick test"
262	32. "skin prick testing"
263	33. SPT
264	34. challenge
265	35. DBPCFC
266	36. double-blind
267	37. "double blind"
268	38. placebo-controlled
269	39. "placebo controlled"
270	40. OFC
271	41. Oral
272	42. 24 or 24 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or
273	41
274	43. "quality of life"
275	44. "quality-of-life"
276	45. QoL OR HRQL
277	46. HRQoL
278	47. FAQLQ
279	48. (MH "Quality of Life+")

280	49. EQ-5D
281	50. EQ5D
282	51. "EQ 5D"
283	52. EuroQol-5D
284	53. "EuroQol 5D"
285	54. HUI
286	55. "Health Utilities Index"
287	56. SF-6D
288	57. "SF 6D"
289	58. "short form-6D"
290	59. SF-36
291	60. "SF 36"
292	61. "short form 36"
293	62. SF-12
294	63. "SF 12"
295	64. "short form 12"
296	65. "short form health survey"
297	66. "State-Trait Anxiety Inventory"
298	67. STAI
299	68. 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or
300	60 or 61 or 62 or 63 or 64 or 65 or 66 or 67
301	69. 23 and 42 and 68
302	
303	

Reasons for exclusion of publications identified through database searching (until 06-07-2017)					
First author	Year	n	Full text available	Category of exclusion	Reason for exclusion
Soller(1)	2017	1	No	Intervention	No diagnostic intervention investigated
Westwood(2)	2016	1	Yes	Study design	Review
Uehara(3)	2016	1	No	Outcome	Quality of life questionnaire not validated
Danchin(4)	2016	1	Yes	Intervention	No diagnostic intervention investigated
Greenhawt(5)	2016	1	No	Outcome	Quality of life questionnaire not validated
Kajornrattana(6)	2016	1	No	Intervention	No diagnostic intervention investigated
Couch(7)	2016	1	Yes	Outcome	Timing of questionnaire (not before and after intervention)
Protudjer(8)	2015	1	Yes	Intervention	No diagnostic intervention investigated
Venter(9)	2015	1	Yes	Intervention	No diagnostic intervention investigated
Soller(1)	2014	1	No	Intervention	No diagnostic intervention investigated
Howe(10)	2014	1	Yes	Intervention	No diagnostic intervention investigated
Le(11)	2013	1	Yes	Intervention	No diagnostic intervention investigated
Zurzolo(12)	2013	4	Yes	Study design	Study protocol
Knibb(13)	2013	2	Yes	Intervention	No diagnostic intervention investigated
Brown(14)	2012	1	No	Population	Tolerant patients (after negative oral food challenge)
Finger(15)	2012	1	No	Outcome	Timing of questionnaire (not before and after intervention)
Kirste(16)	2012	1	No	Study design	Conference abstract, no further details could be retrieved either as full text publication or after contacting study authors
Dubois(17)	2011	1	No	Study design	Invited speaker presentation
Rotiroti(18)	2011	1	No	Outcome	Quality of life questionnaire not validated
Paterakis(19)	2011	1		Outcome	No quality of life questionnaire (State-Trait Anxiety Inventory)
Velde, van der(20)	2010	2		Outcome	Quality of life questionnaire used with informed and blind administration
Flammarion(21)	2009	1	No	Population	Tolerant patients (after negative oral food challenge)
Sohi(22)	2009	1		Population	Tolerant patients (after negative oral food challenge)
Zijlstra(23)	2009	1		Outcome	No quality of life questionnaire (State-Trait Anxiety Inventory)
Ostblom(24)	2008	1		Intervention	No diagnostic intervention investigated
Reasons for exclusion of publications identified through citations analysis of all full text screened publications (06-07-2017)					
First author	Year	n	Full text available	Category of exclusion	Reason for exclusion
Polloni(25)	2017	1		Outcome	No quality of life questionnaire (State-Trait Anxiety Inventory)
Valk, van der(26)	2016	1		Duplicate	Already included in systematic review
Danchin(4)	2016	1		Duplicate	Excluded during full text screening of database search
Davis(27)	2015	1		Outcome	Quality of life questionnaire not validated
Venter(9)	2015	1		Duplicate	Excluded during data analysis
Franxman(28)	2015	1		Duplicate	Already included in systematic review
Protudjer(8)	2015	1		Duplicate	Excluded during full text screening of database search
Venter(9)	2015	1		Duplicate	Already included in systematic review
Soller(29)	2014	1		Duplicate	Already included in systematic review
Reese	2013	1		Study design	Editorial
Herbert(30)	2013	1		Outcome	No quality of life questionnaire (multiple anxiety questionnaires)

Knibb(31)	2013	1		Outcome	No quality of life questionnaire (Hospital Anxiety and Depression Scale)
Velde, van der(32)	2012	2		Duplicate	Already included in systematic review
Knibb(33)	2012	2		Duplicate	Already included in systematic review
Flammarion(21)	2010	1		Duplicate	Excluded during full text screening of database search
Kemp(34)	2009	1		Outcome	Quality of life questionnaire not validated

	Inclusion criteria	Exclusion criteria
Study design	Studies in Dutch, English, German, French or Spanish	- Systematic reviews - Meta-analysis - Research protocols - Editorials
Population	- All age - Suspected or confirmed food allergy - Any setting (primary, secondary and tertiary care)	- Animal studies - Only non-allergic patients included
Intervention	- Specific IgE using allergen extract - Skin prick testing - Oral food challenges (double blind placebo controlled food challenges and open food challenges) - Component resolved diagnostics	
Outcome	- Changes in disease specific or generic quality of life using a validated instrument before and after diagnostic intervention. - Difference in disease specific or generic quality of life using a validated instrument in patients with or without diagnostic intervention	No validated disease specific or generic quality of life instrument used

Appendix 4: Criteria for quality assessment
Modified version of the Quality in Prognostic Studies (QUIPS) tool(35)

Domains	Prompting items to consider
Study participation	A. Adequate participation in the study by eligible persons ($\geq 80\%$)
	B. Adequate methods used to identify and recruit the study population (if applicable, this is graded for both cases and controls)
	C. Adequate description of inclusion and exclusion criteria (if applicable, this is graded for both cases and controls)
Study attrition	D. Adequate response rate for study participants ($\geq 80\%$)
	E. There are no important differences between participants and non-participants on key characteristics (age, criteria for suspected or confirmed food allergy, number of food allergies)
Diagnostic intervention measurement	F. A clear definition or description of the diagnostic intervention is provided If applicable, including a food challenge protocol.
	G. The method and setting of the diagnostic intervention is the same for all study participants
	H. The diagnostic intervention of interest is not performed in the control population (if applicable)
Outcome measurement	I. Adequate description of the timing of the HRQL measurement
	J. The method and setting of the HRQL measurement is the same for all study participants
Study confounding	K. All important confounders (age, number of food allergies, history of anaphylaxis and baseline HRQL scores) are measured
	L. Important potential confounders are accounted for in the analysis
Statistical analysis and reporting	M. The statistical analysis is conducted according to a conceptual framework
	N. There is no selective reporting of results

Grading of quality assessment

	High risk of bias	Moderate risk of bias	Low risk of bias
Total risk of bias per domain in one publication	$\geq 50\%$ of items 'no' or 'unsure', 0% 'yes', and $\leq 50\%$ of items 'partial'		$\geq 50\%$ of items 'yes', 0% 'no' or 'unsure', and $\leq 50\%$ of items 'partial'
Total risk of bias in one publication	$\geq 25\%$ of domains at high risk of bias or $\geq 66\%$ of domains at moderate or high risk	No low or high risk of bias	$\geq 66\%$ of domains considered at low risk of bias and 0% high
Total risk of bias per domain in all publications	$\geq 25\%$ of publications at high risk of bias for this domain or $\geq 66\%$ of publications at moderate or high risk		$\geq 66\%$ of publications at low risk of bias and 0% high

HRQL, health-related quality of life;

Houri hane 2017(36)		
Study participation		L
Method used to identify population (cases)	Consecutive enrollment	yes
Method used to identify population (controls)	NA	
In- and exclusion criteria are adequately described (cases)	Inclusion and exclusion criteria are described.	yes
In- and exclusion criteria are adequately described (controls)	NA	
Adequate participation by eligible individuals (≥80%)	The participation rate 74%.	partial
Study attrition		L
Adequate response rate (≥80%)	The response rate is 99%.	yes
Differences between participants and non-participants	There were no significant differences between participants and non-participants concerning age (p=0.62) and inclusion criteria for diagnosing peanut allergy (p=0.17). Single or multiple food allergies were not compared.	partial
Diagnostic intervention measurement		L
Clear definition of diagnostic intervention	A single dose peanut food challenge is performed in all cases, according to a clear described protocol. Criteria for a positive food challenge are reported.	yes
Methods the same for all study participants	Yes, the same recipe and food challenge protocol is used for all participants.	yes
Diagnostic intervention not performed in control population	NA	
Outcome measurement		L
Timing of quality of life measurement	The time point of the HRQL questionnaire before the OFC was not described. The follow-up questionnaire is one month after the OFC.	partial
Methods the same for all study participants	Questionnaires were self-administered by parents (FAQLQ-PF 0-12 years) or children (FAQLQ-CF 8-17 years). It was not described which parent should fill out the questionnaire.	yes
Study confounding		M
All important confounders are measured	Yes: age. No: number of food allergies, history of anaphylaxis and baseline quality of life scores.	partial
All important confounders are accounted for in the analyses	Yes: age. No: number of food allergies, history of anaphylaxis and baseline quality of life scores.	partial
Statistical analysis and reporting		H
Analysis conducted according to a conceptual framework	Statistical analysis is appropriate and based on a conceptual framework. The methods for model building are unclear.	partial
Full outcome data are available	No full outcome data are reported. Mean quality of life scores before and after the diagnostic interventions or mean differences are not reported, only an effect size.	no
Overall risk of bias (publication)	moderate	

van der Valk 2016(26)		
Study participation		L
Method used to identify population (cases)	Consecutive enrollment.	yes
Method used to identify population (controls)	NA	
In- and exclusion criteria are adequately described (cases)	Inclusion and exclusion criteria are described.	yes
In- and exclusion criteria are adequately described (controls)	NA	
Adequate participation by eligible individuals ($\geq 80\%$)	The participation rate of the initial study is around 40%.	partial
Study attrition		M
Adequate response rate ($\geq 80\%$)	The response rate is 63%.	partial
Differences between participants and non-participants	There was no significant difference in gender ($p=0.92$), age ($p=0.74$) and history of cashew nut allergy ($p=0.12$), among others. Differences in number of other food allergies were not reported.	partial
Diagnostic intervention measurement		L
Clear definition of diagnostic intervention	A DBPCFC is performed in all cases, according to a clear described protocol.	yes
Methods the same for all study participants	Yes, all study participants were challenged according to the same DBPCFC protocol.	yes
Diagnostic intervention not performed in control population	NA	
Outcome measurement		L
Timing of quality of life measurement	The time point of the HRQL questionnaire before the OFC was not described. The follow-up questionnaire is six months after the OFC.	partial
Methods the same for all study participants	Yes, age appropriate questionnaires were used in all patients. No details on methods of administration or which parent should fill out the questionnaire.	yes
Study confounding		L
All important confounders are measured	Yes: age, single or multiple food allergies and baseline quality of life scores. No: history of anaphylaxis.	partial
All important confounders are accounted for in the analyses	Yes: age, single or multiple food allergies and baseline quality of life scores. No: history of anaphylaxis.	yes
Statistical analysis and reporting		L
Analysis conducted according to a conceptual framework	Statistical analysis, including model building, is appropriate and based on a conceptual framework.	yes
Full outcome data are available	Full outcome data are reported.	yes
Overall risk of bias (publication)	low	

Franxman 2015(28)		
Study participation		H
Method used to identify population (cases)	No consecutive enrollment. Patients who had undergone an OFC were identified from a divisional database, with additional cases identified by review of International Classification of Disease coding, Current Procedural Terminology coding for an OFC, and chart review of the clinic schedules.	partial
Method used to identify population (controls)	Sampling and recruitment of the control cohort is not described.	no
In- and exclusion criteria are adequately described (cases)	Inclusion criteria are not adequately described, while exclusion criteria are.	partial
In- and exclusion criteria are adequately described (controls)	Inclusion and exclusion criteria of the control population are not described.	no
Adequate participation by eligible individuals (≥80%)	The participation rate is 34%. For the control group, the participation rate is unknown.	no
Study attrition		H
Adequate response rate (≥80%)	The response rate for cases is less than 50%. The response rate for controls is unknown.	no
Differences between participants and non-participants	Not described.	unsure
Diagnostic intervention measurement		M
Clear definition of diagnostic intervention	It is not described whether open or double blind challenges were performed and no food challenge protocol was provided.	no
Methods the same for all study participants	Not described.	unsure
Diagnostic intervention not performed in control population	Yes, the control population did not undergo an OFC.	yes
Outcome measurement		L
Timing of quality of life measurement	Patients participated at a random time point ≤ 11 years after an OFC (median duration in months given), or ≤11 years after a food allergy diagnosis without an OFC.	partial
Methods the same for all study participants	Caregivers were contacted via mail, and via follow-up telephone calls. The surveys were administered to the control group within the same time frame as for the OFC group with the same contact methodology.	yes
Study confounding		L
All important confounders are measured	Yes: age, number of food allergies and history of anaphylaxis. No: baseline quality of life scores.	partial
All important confounders are accounted for in the analyses	Yes: age, history of anaphylaxis. No: number of food allergies and baseline quality of life scores.	yes
Statistical analysis and reporting		L
Analysis conducted according to a conceptual framework	Statistical analysis, including model building, is appropriate and based on a conceptual framework.	yes
Full outcome data are available	Full outcome data are reported.	yes
Overall risk of bias (publication)	high	

Soller 2014(29)		
Study participation		M
Method used to identify population (cases)	No consecutive enrollment. Participants were randomly selected from the food challenge waiting list.	partial
Method used to identify population (controls)	NA	
In- and exclusion criteria are adequately described (cases)	Inclusion and exclusion are not described.	no
In- and exclusion criteria are adequately described (controls)	NA	
Adequate participation by eligible individuals (≥80%)	The response rate on questionnaires at all time-points is 92% of all eligible patients. Therefor also initial study participation can be considered adequate.	yes
Study attrition		M
Adequate response rate (≥80%)	The response rate is 92%.	yes
Differences between participants and non-participants	Not described.	unsure
Diagnostic intervention measurement		L
Clear definition of diagnostic intervention	An open OFC is performed, without a clear described protocol. Criteria for a positive or negative food challenge are described.	partial
Methods the same for all study participants	All food challenges were open and performed in the same allergy center.	yes
Diagnostic intervention not performed in control population	NA	
Outcome measurement		L
Timing of quality of life measurement	2 months before the OFC, on the day of the OFC, and 2 months and 6 months after the OFC.	yes
Methods the same for all study participants	The methods and setting of outcome measurement (quality of life questionnaires administered) was not described.	partial
Study confounding		H
All important confounders are measured	Yes: age, baseline quality of life scores. No: number of food allergies, history of anaphylaxis.	partial
All important confounders are accounted for in the analyses	No (important) confounders were considered in the final analysis.	no
Statistical analysis and reporting		M
Analysis conducted according to a conceptual framework	Statistical analysis is appropriate and based on a conceptual framework. The methods for model building are unclear.	partial
Full outcome data are available	No full outcome data are reported, only differences in quality of life scores.	partial
Overall risk of bias (publication)	high	

Knibb 2012(33)		
Study participation		M
Method used to identify population (cases)	No details described on the recruitment of the study participants.	no
Method used to identify population (controls)	No details described on the recruitment of the study participants.	no
In- and exclusion criteria are adequately described (cases)	Inclusion and exclusion criteria are described.	yes
In- and exclusion criteria are adequately described (controls)	Inclusion and exclusion criteria are described.	yes
Adequate participation by eligible individuals ($\geq 80\%$)	The participation rate of eligible patients is 59%.	partial
Study attrition		H
Adequate response rate ($\geq 80\%$)	The response rate is 79%.	partial
Differences between participants and non-participants	Not described.	unsure
Diagnostic intervention measurement		M
Clear definition of diagnostic intervention	An open OFC was performed, without a clear described protocol. No criteria for positive or negative OFCs were described.	partial
Methods the same for all study participants	All challenges were open OFCs. No further details were provided.	unsure
Diagnostic intervention not performed in control population	Yes, the control population did not undergo an oral food chall.	yes
Outcome measurement		L
Timing of quality of life measurement	Baseline (following a clinic appointment) and follow-up (3-6 months following OFC, or in the case of non-challenged families, 3-6 months following the return of baseline questionnaire)	yes
Methods the same for all study participants	Children and mothers completed baseline and 3-6 months follow-up questionnaires at home. Questionnaires during oral food challenge were completed in the clinical setting.	yes
Study confounding		M
All important confounders are measured	Yes, all important confounder data are available at baseline.	yes
All important confounders are accounted for in the analyses	No (important) confounders were considered in the final analysis.	no
Statistical analysis and reporting		L
Analysis conducted according to a conceptual framework	Statistical analysis is appropriate and based on a conceptual framework. No model is built.	yes
Full outcome data are available	Full outcome data are reported.	yes
Overall risk of bias (publication)	high	

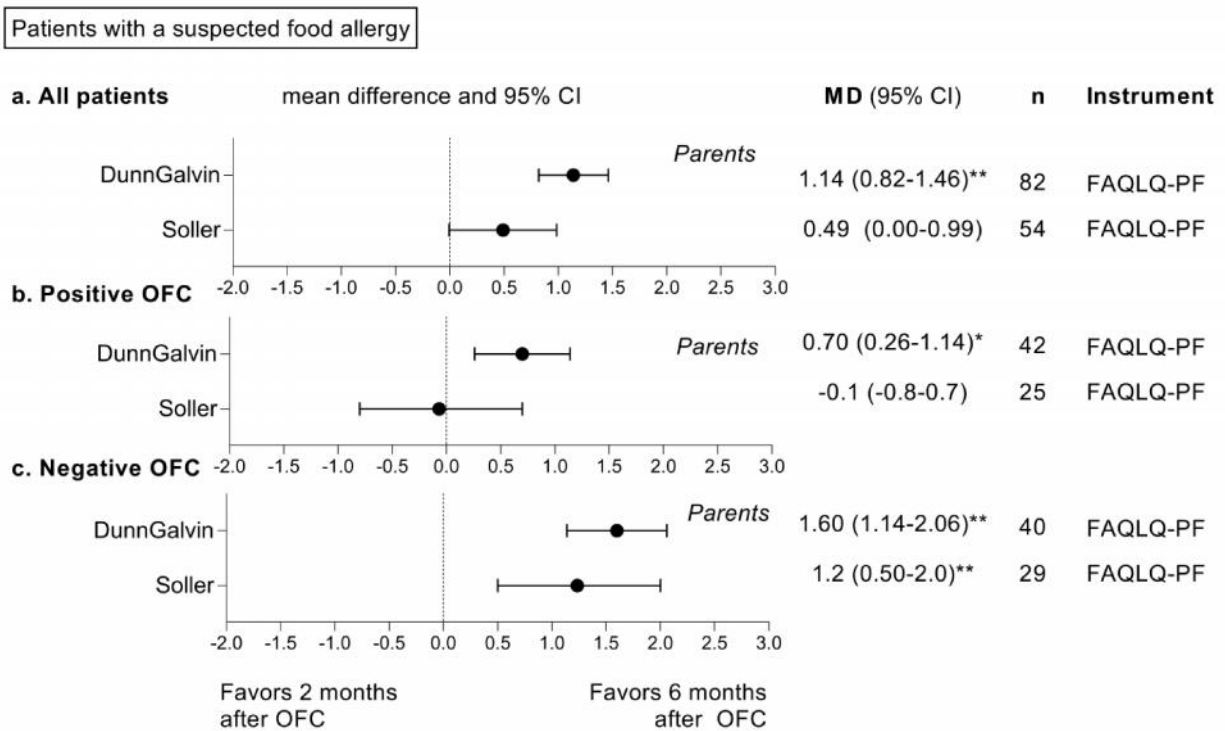
van der Velde 2012(32)		
Study participation		L
Method used to identify population (cases)	All patients visiting the clinic with suspected food allergy were placed on the waiting list for a DBPCFC on a first-come, first-served basis. Participants who were expected to have a DBPCFC within 6 months were included in the experimental group (cases).	yes
Method used to identify population (controls)	Participants on the waiting list who were not expected to have a DBPCFC within 6 months were included in the control group. Additionally, participants recruited through Dutch food allergy support organizations were included in the control group when they reported a physician-diagnosed food allergy (skin prick test, sIgE). Methods for recruitment through the support organization are unclear.	partial
In- and exclusion criteria are adequately described (cases)	Inclusion and exclusion criteria are described.	yes
In- and exclusion criteria are adequately described (controls)	Inclusion and exclusion criteria are described.	yes
Adequate participation by eligible individuals ($\geq 80\%$)	The participation rate is 76%.	partial
Study attrition		H
Adequate response rate ($\geq 80\%$)	The response rate is 74%.	partial
Differences between participants and non-participants	Not described.	unsure
Diagnostic intervention measurement		L
Clear definition of diagnostic intervention	A DBPCFC is performed in all cases according to a clear described protocol.	yes
Methods the same for all study participants	The two centers collaborate on uniform methodology of DBPCFC procedures.	yes
Diagnostic intervention not performed in control population	Yes, the control population did not undergo an OFC.	yes
Outcome measurement		L
Timing of quality of life measurement	Challenged cases: 1 month before (baseline) and 6 months after (follow-up) a DBPCFC. Unchallenged cases: twice with a 7-month interval without undergoing a DBPCFC.	yes
Methods the same for all study participants	All questionnaires were sent home and the same questionnaires were used in all study participants.	yes
Study confounding		L
All important confounders are measured	Yes, all important confounder data are available.	yes
All important confounders are accounted for in the analyses	Yes: age, number of food allergies and baseline quality of life scores. No: history of anaphylaxis.	yes
Statistical analysis and reporting		L
Analysis conducted according to a conceptual framework	Statistical analysis, including model building, is appropriate and based on a conceptual framework.	yes
Full outcome data are available	Full outcome data are reported.	yes
Overall risk of bias (publication)	moderate	

Dunn Galvin 2010(37)		
Study participation		L
Method used to identify population (cases)	No consecutive enrollment, but a random sample of participants recruited during specialist pediatric allergy clinic. No recruitment details are reported.	no
Method used to identify population (controls)	NA	
In- and exclusion criteria are adequately described (cases)	Inclusion and exclusion criteria are described.	yes
In- and exclusion criteria are adequately described (controls)	NA	
Adequate participation by eligible individuals (≥80%)	The participation rate is 94%.	yes
Study attrition		M
Adequate response rate (≥80%)	The response rate is 96%.	yes
Differences between participants and non-participants	Not described.	unsure
Diagnostic intervention measurement		H
Clear definition of diagnostic intervention	Not described.	no
Methods the same for all study participants	Not described.	no
Diagnostic intervention not performed in control population	NA	
Outcome measurement		L
Timing of quality of life measurement	Before the OFC (morning of the OFC) and at 2 and 6 months after the OFC.	yes
Methods the same for all study participants	Mothers were asked to fill-out the questionnaire in the Children's Day Unit on the morning of the OFC. Questionnaires were again completed at home 2 months and 6 months after the OFC.	yes
Study confounding		M
All important confounders are measured	Yes: age, number of food allergies, history of anaphylaxis and baseline quality of life scores.	yes
All important confounders are accounted for in the analyses	No (important) confounders were considered in the final analysis.	no
Statistical analysis and reporting		L
Analysis conducted according to a conceptual framework	It is unclear what variables were taken into account in the final analysis.	partial
Full outcome data are available	Full outcome data are reported.	yes
Overall risk of bias (publication)	moderate	

324
325 DBPCFC, double-blind placebo-controlled food challenge; H, high; L, low; M, moderate; NA, not
326 applicable; OFC, oral food challenge;

Appendix 6: Health-related quality of life after an oral food challenge in patients with a suspected food allergy two and six months after an OFC

Mean difference with 95% confidence interval of food allergy specific health-related quality of life between two and six months after an oral food challenge (OFC) in patients with a suspected food allergy: a) all patients; b) patients with a positive OFC outcome (allergic); c) patients with a negative OFC outcome (non-allergic). The minimal clinically important difference of 0.5 was used to consider the mean difference as clinically relevant.



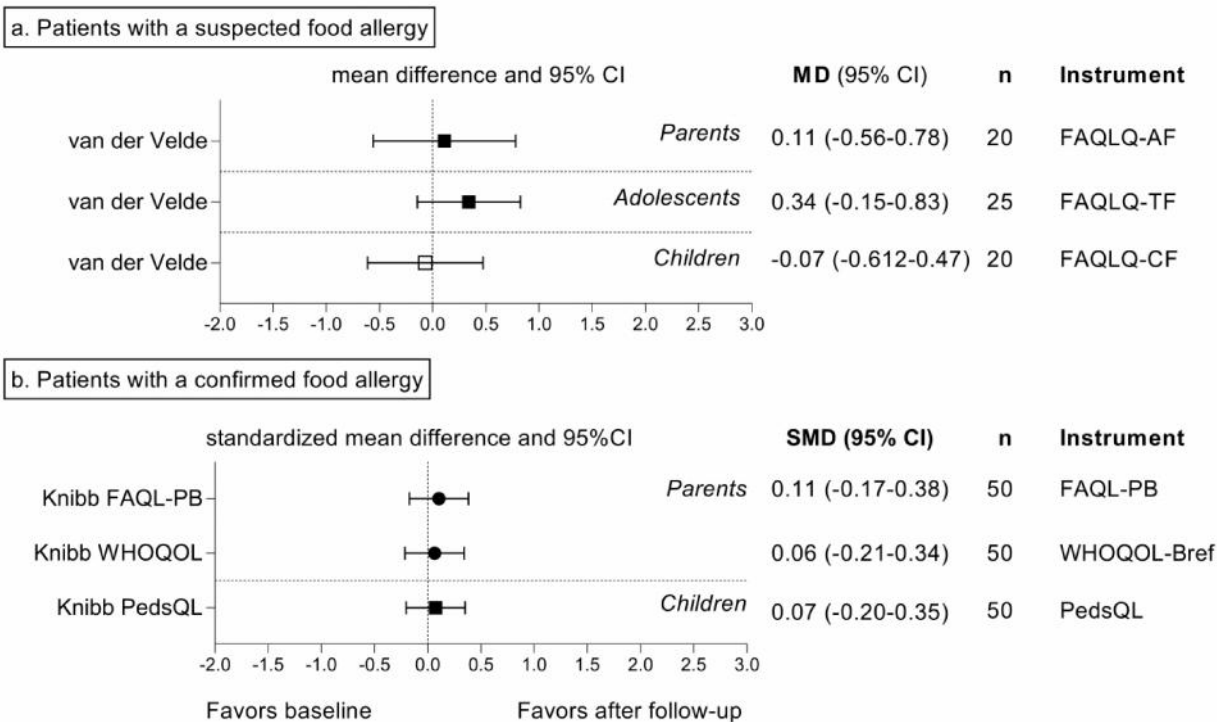
** significant and clinically relevant change in HRQL; * significant change in HRQL

CI, confidence interval; FAQLQ-PF, Food Allergy Quality of Life Questionnaire-Parent Form; MD, mean difference; n, number; OFC, oral food challenge.

Appendix 7: Health related quality of life and parental burden in patients without an OFC

a. Mean difference with 95% confidence interval of food allergy specific health-related quality of life in patients with a suspected food allergy who did not undergo an oral food challenge.

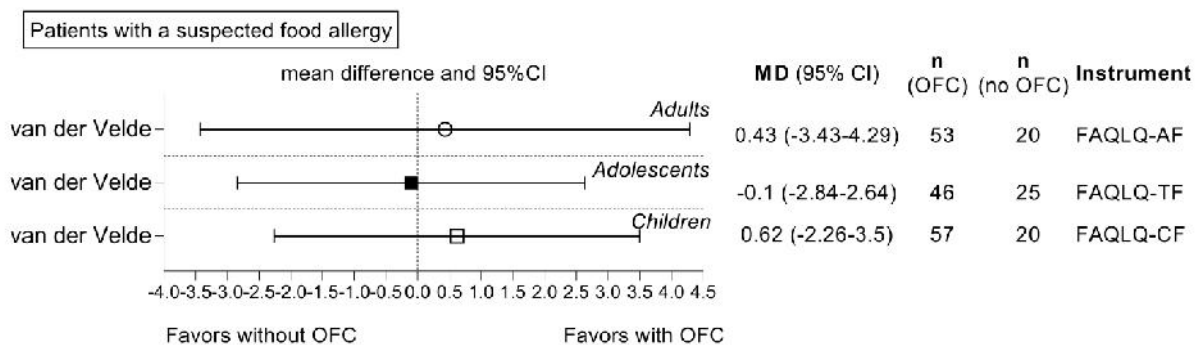
b. Standardized mean difference with 95% CI of the parental burden (FAQL-PB) and generic HRQL (WHOQOL-Bref, PedsQL) in patients with a confirmed food allergy who did not undergo an oral food challenge.



CI, confidence interval; FAQL(Q), Food Allergy Quality of Life (Questionnaire) (different versions: AF, Adult Form; CF, Child Form; PB, Parental Burden; TF, Teen Form); MD, mean difference; n, number.

Appendix 8: Health-related quality of life with or without an oral food challenge in patients with a suspected food allergy

Mean difference with 95% confidence interval between the mean difference in health-related quality of life in patients that underwent an oral food challenge (OFC) and those that did not undergo an OFC. An OFC was performed in patients with a suspected food allergy. An OFC was not performed in patients with a suspected food allergy on the waiting list for an OFC, or in patients considered food allergic by a physician.



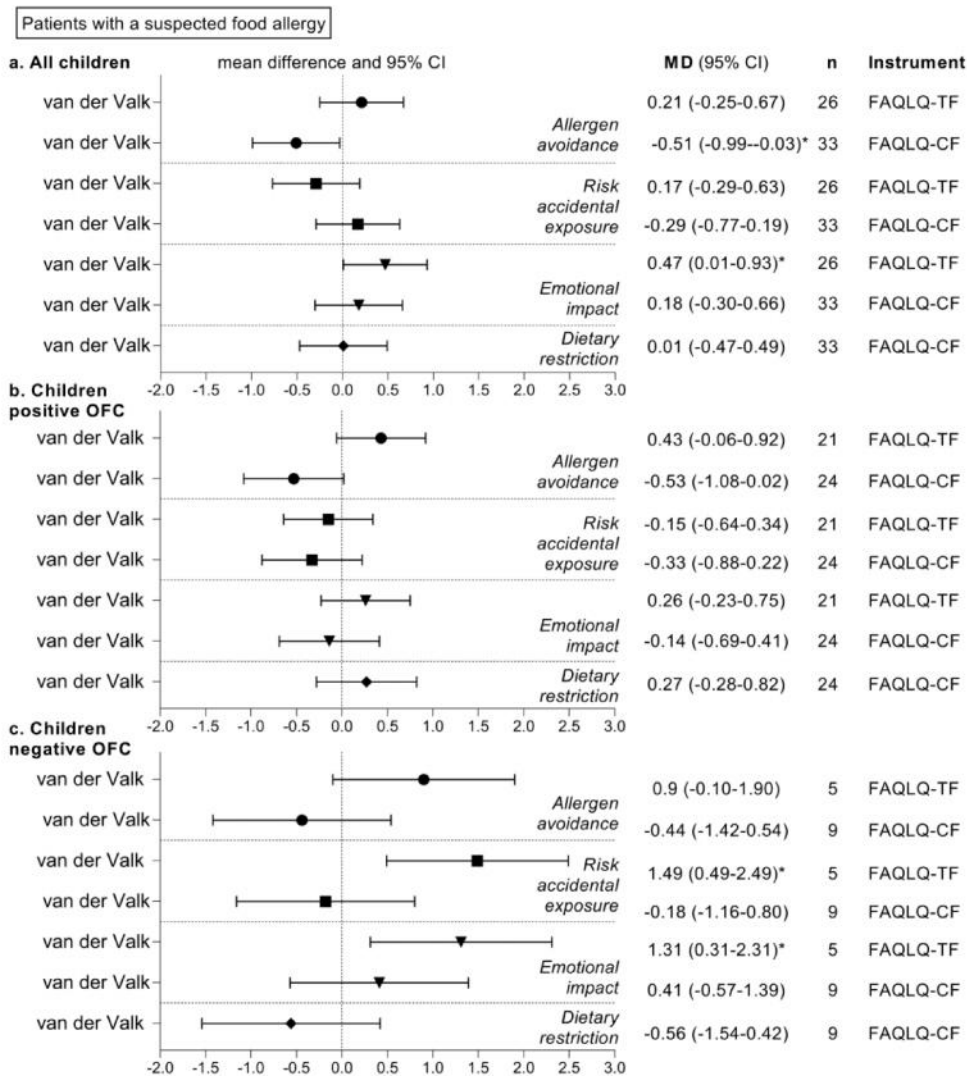
* significant change in HRQL

CI, CI, confidence interval; FAQLQ, Food Allergy Quality of Life Questionnaire (different versions: AF, Adult Form; CF, Child Form; TF, Teen Form); MD, mean difference; n, number; OFC, oral food challenge.

Appendix 9: Domain specific health-related quality of life before and after an oral food challenge in children and adolescents with a suspected food allergy

Mean difference with 95% confidence interval of food allergy specific health related quality of life per domain before and after an oral food challenge in children and adolescents with a suspected food allergy:

a) all children and adolescents; b) children and adolescents with a positive OFC outcome (allergic); c) children and adolescents with a negative OFC outcome (non-allergic).

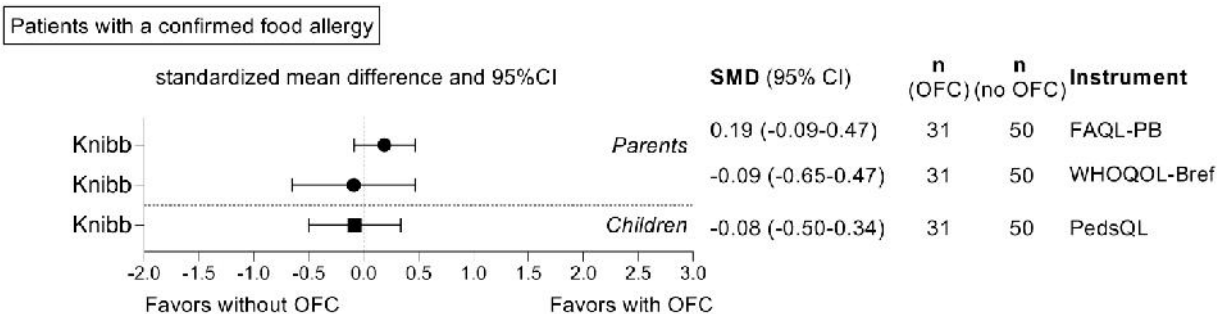


* significant change in HRQL

368 CI, CI, confidence interval; FAQLQ, Food Allergy Quality of Life Questionnaire (different versions: CF,
369 Child Form; TF, Teen Form); HRQL, health-related quality of life; MD, mean difference; n, number; OFC,
370 oral food challenge.

Appendix 10: Health-related quality of life and the parental burden with or without an oral food challenge in patients with a confirmed food allergy

Standardized mean difference with 95% confidence interval of generic health-related quality of life and the parental burden in patients that underwent an oral food challenge and those that did not undergo an OFC. An OFC was performed in patients with a confirmed food allergy to evaluate resolution of food allergy. An OFC was not performed in patients considered food allergic by a physician.



CI, confidence interval; FAQL-PB, Food Allergy Quality of Life-Parental Burden; MD, mean difference; n, number; PedsQL™ 4.0, Paediatric Quality of Life Inventory 4.0; SMD, standardized mean difference; WHOQOL-BREF, World Health Organization generic Quality of Life scale.

Appendix 11a: Sensitivity analysis (suspected food allergy)

Sensitivity analysis with a different correlation coefficient to calculate the 95% confidence interval of the mean difference in health-related quality of life (HRQL) in patients with a suspected food allergy before and after an oral food challenge. The minimal clinically important difference of 0.5 was used to consider the MD as clinically relevant.

DunnGalvin	r=0.5			r=0.2			r=0.8		
	MD	95% CI		MD	95% CI		MD	95% CI	
FAQLQ-PF (0-2M)									
Total	0.60*	0.28	0.91	0.60*	0.20	0.99	0.60*	0.40	0.8
Positive patients	0.50*	0.08	0.92	0.50	-0.04	1.04	0.50*	0.23	0.77
Negative patients	0.70*	0.24	1.16	0.70*	0.11	1.29	0.70*	0.41	0.99
All patients (EI)	0.75*	0.46	1.05	0.75*	0.38	1.13	0.75**	0.57	0.94
All patients (FA)	0.64*	0.33	0.95	0.64*	0.25	1.04	0.64*	0.45	0.84
All patients (SDI)	0.69*	0.40	0.98	0.69*	0.33	1.06	0.69**	0.50	0.88
Positive patients (EI)	0.90**	0.51	1.29	0.90*	0.4	1.4	0.90**	0.65	1.15
Positive patients (FA)	0.40	-0.06	0.86	0.40	-0.18	0.98	0.40*	0.11	0.69
Positive patients (SDI)	0.40	-0.04	0.84	0.40	-0.14	0.94	0.40*	0.11	0.69
Negative patients (EI)	0.60*	0.15	1.05	0.60*	0.03	1.17	0.60*	0.31	0.89
Negative patients (FA)	0.90*	0.48	1.32	0.90*	0.37	1.43	0.90**	0.63	1.17
Negative patients (SDI)	1.00**	0.62	1.38	1.00**	0.52	1.48	1.00**	0.76	1.24
FAQLQ-PF (2-6M)									
Total	1.14**	0.82	1.46	1.14**	0.74	1.54	1.14**	0.94	1.34
Positive patients	0.70*	0.26	1.14	0.70*	0.14	1.26	0.70*	0.42	0.98
Negative patients	1.60**	1.14	2.06	1.60**	1.01	2.19	1.60**	1.31	1.89
All patients (EI)	1.19**	0.89	1.419	1.19**	0.81	1.57	1.19**	1.00	1.38
All patients (FA)	0.99**	0.67	1.31	0.99**	0.58	1.40	0.99**	0.78	1.19
All patients (SDI)	1.14**	0.87	1.41	1.14**	0.79	1.48	1.14**	0.96	1.31
Positive patients (EI)	0.80*	0.42	1.18	0.80*	0.32	1.28	0.80**	0.56	1.04
Positive patients (FA)	0.50*	0.02	0.98	0.50	-0.11	1.11	0.50*	0.19	0.81
Positive patients (SDI)	0.60*	0.22	0.98	0.60*	0.12	1.08	0.60*	0.36	0.84
Negative patients (EI)	1.60**	1.18	2.02	1.60**	1.07	2.13	1.60**	1.33	1.87
Negative patients (FA)	1.50**	1.03	1.92	1.50**	0.97	2.03	1.50**	1.23	1.77
Negative patients (SDI)	1.70**	1.33	2.07	1.70**	1.23	2.17	1.70**	1.46	1.94
Soller	r=0.5			r=0.2			r=0.8		
	MD	95% CI		MD	95% CI		MD	95% CI	
FAQLQ-PF (0-2M)									
Total	0.86**	0.719	1.003	0.86**	0.68	1.04	0.86**	0.77	0.95
All patients (EI)	0.60*	0.48	0.72	0.60*	0.46	0.75	0.60**	0.51	0.70
All patients (FA)	0.95**	0.74	1.16	0.95**	0.68	1.22	0.95**	0.82	1.08
All patients (SDI)	1.05**	0.91	1.19	1.05**	0.87	1.23	1.05**	0.96	1.14
FAQLQ-PF (2-6M)									
Total	0.49	-0.01	0.99	0.49	-0.14	1.17	0.49*	0.178	0.81
All patients (EI)	0.50*	0.08	0.92	0.50	-0.04	1.04	0.50*	0.23	0.77
All patients (FA)	0.70*	0.12	1.28	0.70	-0.02	1.42	0.70*	0.32	1.08
All patients (SDI)	0.55*	0.02	1.08	0.55	-0.12	1.22	0.55*	0.21	0.89

van der Valk	r=0.5			r=0.2			r=0.8		
	MD	95% CI		MD	95% CI		MD	95% CI	
FAQLQ-PF (0-6M)									
Total	-0.06	-0.32	0.2	-0.06	-0.38	0.26	-0.06	-0.22	0.1
Positive patients	-0.11	-0.41	0.19	-0.11	-0.48	0.26	-0.11	-0.31	0.09
Negative patients	0.1	-0.4	0.6	0.1	-0.52	0.72	0.1	-0.24	0.44
All patients (EI)	-0.09	-0.33	0.15	-0.09	-0.39	0.21	-0.09	-0.24	0.06
All patients (FA)	-0.01	-0.27	0.25	-0.01	-0.34	0.32	-0.01	-0.18	0.16
All patients (SDI)	-0.07	-0.31	0.17	-0.07	-0.37	0.23	-0.07	-0.22	0.08
Positive patients (EI)	-0.16	-0.57	0.25	-0.16	-0.59	0.27	-0.16	-0.54	0.22
Positive patients (FA)	-0.08	-0.37	0.21	-0.08	-0.39	0.23	-0.08	-0.34	0.18
Positive patients (SDI)	-0.08	-0.37	0.21	-0.08	-0.39	0.23	-0.08	-0.34	0.18
Negative patients (EI)	0.11	-0.76	0.98	0.11	-0.79	1.01	0.11	-0.71	0.93
Negative patients (FA)	0.19	-0.74	1.12	0.19	-0.77	1.15	0.19	-0.69	1.07
Negative patients (SDI)	-0.03	-1.04	0.98	-0.03	-1.07	1.01	-0.03	-0.99	0.93
FAQLQ-TF (0-6M)									
Total	0.28	-0.18	0.74	0.28	-0.3	0.86	0.28	-0.02	0.58
Positive patients	-0.06	-0.55	0.43	-0.06	-0.67	0.55	-0.06	-0.37	0.25
Negative patients	1.18*	0.18	2.18	1.18	-0.06	2.42	1.18*	0.49	1.87
All patients (AA)	0.21	-0.25	0.67	0.21	-0.37	0.79	0.21	-0.09	0.51
All patients (RAE)	0.17	-0.29	0.63	0.17	-0.41	0.75	0.17	-0.13	0.47
All patients (EI)	0.47*	0.01	0.93	0.47	-0.11	1.05	0.47*	0.17	0.77
Positive patients (AA)	0.43	-0.06	0.92	0.43	-0.18	1.04	0.43*	0.12	0.74
Positive patients (RAE)	-0.15	-0.64	0.34	-0.15	-0.76	0.46	-0.15	-0.46	0.16
Positive patients (EI)	0.26	-0.23	0.75	0.26	-0.35	0.87	0.26	-0.05	0.57
Negative patients (AA)	0.9	-0.1	1.9	0.9	-0.34	2.14	0.9*	0.21	1.59
Negative patients RAE)	1.49*	0.49	2.49	1.49*	0.25	2.73	1.49**	0.8	2.18
Negative patients RAE)	1.31*	0.31	2.31	1.31*	0.07	2.55	1.31**	0.62	2
FAQLQ-CF (0-6M)									
Total	-0.17	-0.65	0.31	-0.17	-0.78	0.44	-0.17	-0.48	0.14
Positive patients	-0.19	-0.74	0.36	-0.19	-0.88	0.5	-0.19	-0.54	0.16
Negative patients	-0.1	-1.08	0.88	-0.1	-1.34	1.14	-0.1	-0.72	0.52
All patients (AA)	-0.51	-0.99	-0.03	-0.51	-1.12	0.1	-0.51	-0.82	-0.2
All patients (RAE)	-0.29	-0.77	0.19	-0.29	-0.9	0.32	-0.29	-0.6	0.02
All patients (EI)	0.18	-0.3	0.66	0.18	-0.43	0.79	0.18	-0.13	0.49
All patients (DR)	0.01	-0.47	0.49	0.01	-0.6	0.62	0.01	-0.3	0.32
Positive patients (AA)	-0.53	-1.08	0.02	-0.53	-1.22	0.16	-0.53	-0.88	-0.18
Positive patients (RAE)	-0.33	-0.88	0.22	-0.33	-1.02	0.36	-0.33	-0.68	0.02
Positive patients (EI)	-0.14	-0.69	0.41	-0.14	-0.83	0.55	-0.14	-0.49	0.21
Positive patients(DR)	0.27	-0.28	0.82	0.27	-0.42	0.96	0.27	-0.08	0.62
Negative patients (AA)	-0.44	-1.42	0.54	-0.44	-1.68	0.8	-0.44	-1.06	0.18
Negative patients RAE)	-0.18	-1.16	0.8	-0.18	-1.42	1.06	-0.18	-0.8	0.44
Negative patients (EI)	0.41	-0.57	1.39	0.41	-0.83	1.65	0.41	-0.21	1.03
Negative patients (DR)	-0.56	-1.54	0.42	-0.56	-1.8	0.68	-0.56	-1.18	0.06
Van der Velde	r=0.5			r=0.2			r=0.8		
	MD	95% CI		MD	95% CI		MD	95% CI	
FAQLQ-CF (0-6M)									
Total (with OFC)	0.55*	0.18	0.92	0.55*	0.08	1.02	0.55*	0.32	0.78
Positive (with OFC)	0.39	-0.09	0.87	0.39	-0.22	1.00	0.39*	0.08	0.70
Negative (with OFC)	0.79*	0.17	1.41	0.79*	0.01	1.57	0.79*	0.40	1.18
Inconclusive (with OFC)	0.24	-1.64	2.12	0.24	-2.14	2.62	0.24	-0.95	1.43
Total (without OFC)	-0.07	-0.61	0.47	-0.07	-0.76	0.62	-0.07	-0.41	0.27
Total (with vs. without OFC)	0.62	-2.26	3.50	0.62	-2.26	3.50	0.62	-2.26	3.50

FAQLQ-TF (0-6M)									
Total (with OFC)	0.24	-0.11	0.59	0.24	-0.19	0.67	0.24*	0.01	0.47
Positive (with OFC)	0.01	-0.40	0.42	0.01	-0.51	0.53	0.01	-0.25	0.27
Negative (with OFC)	0.97*	0.35	1.59	0.97*	0.20	1.74	0.97**	0.54	1.40
Inconclusive (with OFC)	-0.4	-1.28	0.48	-0.40	-1.49	0.69	-0.40	-1.01	0.21
Total (without OFC)	0.34	-0.15	0.83	0.34	-0.27	0.95	0.34*	0.03	0.65
Total (with vs. without OFC)	-0.1	-2.84	2.64	-0.10	-2.87	2.67	-0.10	-2.74	2.54
FAQLQ-AF (0-6M)									
Total (with OFC)	0.54*	0.20	0.88	0.54*	0.11	0.97	0.54*	0.32	0.76
Positive (with OFC)	0.35	-0.09	0.79	0.35	-0.20	0.90	0.35*	0.06	0.64
Negative (with OFC)	0.88*	0.31	1.45	0.88*	0.16	1.60	0.88**	0.52	1.24
Inconclusive (with OFC)	-0.23	-1.03	0.57	-0.23	-1.23	0.77	-0.23	-0.76	0.30
Total (without OFC)	0.11	-0.56	0.78	0.11	-0.74	0.96	0.11	-0.31	0.53
Total (with vs. without OFC)	0.43	-3.43	4.29	0.43	-3.44	4.30	0.43	-3.36	4.22

** significant and clinically relevant change in HRQL; * significant change in HRQL

CI, confidence interval; FAQLQ, Food Allergy Quality of Life Questionnaire (*different versions*: AF, Adult

Form; CF, Child Form; TF, Teen Form; PF, Parent Form and *different domains*: AA, Allergen Avoidance;

DR, Dietary Restrictions; EI, Emotional Impact; FA, Food Anxiety; RAE, Risk of Accidental Exposure; SDI,

Social and Dietary Impact); HRQL, health-related quality of life; M, months; MD, mean difference; OFC,

oral food challenge; r, correlation coefficient.

395 **Appendix 11b:** Sensitivity analysis (confirmed food allergy)

396 *Sensitivity analysis with a different correlation coefficient to calculate the 95% confidence interval of the*
 397 *standardized mean difference in health-related quality of life in patients with a confirmed food allergy*
 398 *before and after an oral food challenge.*

Hourihane	r=0.5			r=0.2			r=0.8		
	SMD	95% CI		SMD	95% CI		SMD	95% CI	
FAQLQ-PF (0-1M)									
Total	1.12*	1.00	1.25	1.12*	0.96	1.29	1.12*	1.04	1.21
FAQLQ-CF (0-1M)									
Total	2.00*	1.83	2.17	2.00*	1.78	2.22	2.00*	1.89	2.11
Knibb	r=0.5			r=0.2			r=0.8		
	SMD	95% CI		SMD	95% CI		SMD	95% CI	
FAQL-PB (0-3 to 6M)									
Total (with OFC)	0.37	0.01	0.37	-0.09	-0.09	0.83	0.37	0.14	0.60
Total (without OFC)	0.11	-0.17	0.11	-0.25	-0.25	0.46	0.11	-0.07	0.28
Total (with vs. without OFC)	0.19	-0.09	0.19	-0.16	-0.16	0.54	0.19	0.01	0.37
PedsQL™ 4.0 (0-3 to 6M)									
Total (with OFC)	0.00	-0.35	0.00	-0.45	-0.45	0.45	0.00	-0.22	0.22
Total (without OFC)	0.07	-0.20	0.07	-0.28	-0.28	0.43	0.07	-0.10	0.25
Total (with vs. without OFC)	-0.08	-0.50	-0.08	-0.61	-0.61	0.45	-0.08	-0.34	0.19
WHOQOL-BREF (0-3 to 6M)									
Total (with OFC)	-0.02	-0.38	-0.02	-0.47	-0.47	0.42	-0.02	-0.25	0.20
Total (without OFC)	0.06	-0.21	0.06	-0.29	-0.29	0.42	0.06	-0.12	0.24
Total (with vs. without OFC)	-0.09	-0.65	-0.09	-0.80	-0.80	0.62	-0.09	-0.44	0.27

399 * significant change in HRQL

400 FAQLQ, Food Allergy Quality of Life Questionnaire; PB, Parental Burden; PF, Parent Form; CF, Child

401 Form; M, months; OFC, oral food challenge; PedsQL™ 4.0, Paediatric Quality of Life Inventory 4.0;

402 WHOQOL-BREF, World Health Organization generic Quality of Life scale.

403 CI, confidence interval; HRQL, health-related quality of life; SMD, standardized mean difference.

References

1. Soller L, Mill C, Wong T, et al. Determinants of Quality of life (QOL) Among Children Undergoing Oral Food Challenge (OFC) in Canada. *J Allergy Clin Immunol.* 2017;139(2):AB57.
2. Westwood M, Ramaekers B, Lang S, et al. ImmunoCAP ISAC and microtest for multiplex allergen testing in people with difficult to manage allergic disease: A systematic review and cost analysis. *Health Technology Assessment.* 2016. p. 1–178.
3. Uehara H, Fujii Y, Sekimoto K, et al. Concerns and expectations of pediatric patients and parents with regards to oral food challenges. *Allergy.* 2016;71:118–272.
4. Danchin M, De Bono N, Allen K, Tang M, Hiscock H. Managing simple food allergy in community settings: A pilot study investigating a new model of care. *J Paediatr Child Health.* 2016;52(3):315–20.
5. Greenhawt MJ, Couch CE, Franxman TJ, Galvin AD. The relationship between self-efficacy, quality of life, and oral food challenge. *J Allergy Clin Immunol.* 2016;137(2):AB135.
6. Kajornrattana T, Sangsupawanich P, Yuenyongviwat A. Impact of parent-reported food allergies on children's growth and quality of life of the caregivers. *J Allergy Clin Immunol.* 2016;137(2):AB255.
7. Couch C, Franxman T, Greenhawt M. The economic effect and outcome of delaying oral food challenges. *Ann Allergy Asthma Immunol.* 2016;116(5):420–4.
8. Protudjer JLP, Jansson S a., Ostblom E, et al. Health-related quality of life in children with objectively diagnosed staple food allergy assessed with a disease-specific questionnaire. *Acta Paediatr Int J Paediatr.* 2015;104(10):1047–54.
9. Venter C, Sommer I, Moonesinghe H, et al. Health-Related Quality of Life in children with perceived and diagnosed food hypersensitivity. *Pediatr Allergy Immunol.* 2015;26(2):126–32.
10. Howe L, Franxman T, Teich E, Greenhawt M. What affects quality of life among caregivers of food-allergic children? *Ann Allergy Asthma Immunol.* 2014;113(1):69–74.e2.
11. Le T-M, Flokstra-De Blok BMJ, Van Hoffen E, et al. Quality of life is more impaired in patients seeking medical care for food allergy. *Int Arch Allergy Immunol.* Switzerland; 2013;162(4):335–9.
12. Zurzolo GA, Allen KJ, Taylor SL, et al. Peanut Allergen Threshold Study (PATs): validation of

- 432 eliciting doses using a novel single-dose challenge protocol. *Allergy Asthma Clin Immunol.*
433 2013;9(1):35.
- 434 13. Knibb RC, Ibrahim NF, Petley R, Cummings AJ, King RM, Roberts G, et al. Validation of the
435 Paediatric Food Allergy Quality of Life Questionnaire (PFA-QL). *Pediatr Allergy Immunol.*
436 2013;24(3):288–92.
- 437 14. Brown T, Boyle R, Gore C, Warner J, Cox H. Effects of oral food challenges to selected nut(s) on
438 quality of life and risk. *Clin Exp Allergy.* 2012;42:1815–62.
- 439 15. Finger A, Pfannenstiel C, Schonfelder A, Frank F, Buderus S, Lange L. Improvement of quality of
440 life in children with milk and egg allergy after proof of tolerance to baked products. *Allergy.*
441 2012;96:1–97.
- 442 16. Kirste L, Takaro TK, Kuzeljevic B, Wong T, Chan ES. Outcome Rather Than the Type of
443 Diagnostic Intervention Predicts Improvement in Health-Related Quality of Life Score Among
444 Children With Food Allergy Between 0-12 Years. *J Allergy Clin Immunol.* 2012;129(2):AB132.
- 445 17. Dubois AT. Benefits of effective diagnosis on impact of quality of life. *Clin Transl Allergy.*
446 2011;1(Suppl 1):2011.
- 447 18. Rotiroti G, Gardner J, Coppens K, Parker J. Usefulness of peanut and hazelnut molecular
448 components for the diagnosis of nut allergy. Our experience in clinical practice. *Clin Transl Allergy.*
449 2011;1.
- 450 19. Paterakis M, Mudd K, Holbrook T, Page G, Gross D, Wood R. Do Peanut Oral Food Challenges
451 Produce More Stress? Self-reported Anxiety Measurement Of Food Allergic Children And Their
452 Parents Prior To Oral Food Challenges. *J Allergy Clin Immunol.* 2011;127(2):AB76.
- 453 20. van der Velde J, Flokstra-de Blok B, Vlieg-Boerstra J, Oude Elberink J, Duiveman E DA. Should
454 Previous Responses Be Shown to Study Objects; A Comparison of Informed versus Blind
455 Administration of the Food Allergy Quality of Life Questionnaire-Adult Form (FAQLQ-AF). *J Allergy*
456 *Clin Immunol.* 2015;123(2):S25.
- 457 21. Flammarion S, Santos C, Romero D. Changes in diet and life of children with food allergies after a
458 negative food challenge. *Allergy.* 2010;65:791–804.
- 459 22. Sohi D, Mkandawire C, James A, et al. Outcome of food challenges in children. *Clin Exp Allergy.*

2009;39(12):1937–58.

23. Zijlstra WT, Flinterman AE, Soeters L, et al. Parental anxiety before and after food challenges in children with suspected peanut and hazelnut allergy. *Pediatr Allergy Immunol.* 2010;21:439–45.

24. Ostblom E, Egmar A-C, Gardulf A, Lilja G, Wickman M. The impact of food hypersensitivity reported in 9-year-old children by their parents on health-related quality of life. *Allergy.* 2008;63(2):211–8.

25. Polloni L, Ferruzza E, Ronconi L, et al. Assessment of children's nutritional attitudes before oral food challenges to identify patients at risk of food reintroduction failure: a prospective study. *Allergy.* 2017;72(5):731–6.

26. van der Valk JPM, Gerth van Wijk R, Flokstra-de Blok BMJ, et al. No difference in health-related quality of life, after a food challenge with cashew nut in children participating in a clinical trial. *Pediatr Allergy Immunol.* 2016;27(8):812–7.

27. Davis N, Egan M, Sicherer SH. Factors resulting in deferral of diagnostic oral food challenges. *J Allergy Clin Immunol Pract. American Academy of Allergy, Asthma & Immunology;* 2015;3(5):811–812.e1.

28. Franxman TJ, Howe L, Teich E, Greenhawt MJ. Oral Food Challenge and Food Allergy Quality of Life in Caregivers of Children with Food Allergy. *J Allergy Clin Immunol Pract.* 2014;3(1):50–6.

29. Soller L, Hourihane J, Dunngalvin A. The impact of oral food challenge tests on food allergy health-related quality of life. *Allergy.* 2014;69(9):1255–7.

30. Herbert LJ, Dahlquist LM, Bollinger ME. Maternal intolerance of uncertainty, anxiety, and adherence with food challenge referrals. *J Health Psychol.* 2013;18(9):1209–19.

31. Knibb RC, Semper H. Impact of suspected food allergy on emotional distress and family life of parents prior to allergy diagnosis. *Pediatr Allergy Immunol.* 2013;24(8):798–803.

32. Van Der Velde JL, Flokstra-De Blok BMJ, De Groot H, et al. Food allergy-related quality of life after double-blind, placebo-controlled food challenges in adults, adolescents, and children. *J Allergy Clin Immunol.* 2012;130(5):1136–1143.e2.

33. Knibb RC, Ibrahim NF, Stiefel G, et al. The psychological impact of diagnostic food challenges to confirm the resolution of peanut or tree nut allergy. *Clin Exp Allergy.* 2012;42(3):451–9.

- 488 34. Kemp AS, Allen CW, Campbell DE. Parental perceptions in egg allergy: Does egg challenge make
489 a difference? *Pediatr Allergy Immunol.* 2009;20(7):648–53.
- 490 35. Hayden JA, Coté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic
491 reviews. *Ann Intern Med.* 2006;144(6):427–37.
- 492 36. Hourihane JOB, Allen KJ, Shreffler WG, et al. Peanut Allergen Threshold Study (PATs): Novel
493 single-dose oral food challenge study to validate eliciting doses in children with peanut allergy. *J*
494 *Allergy Clin Immunol.* 2017;139(5):1583–90.
- 495 37. Dunngalvin A, Cullinane C, Daly DA, Blok BMJF, Dubois AEJ, Hourihane JOB. Longitudinal
496 validity and responsiveness of the Food Allergy Quality of Life Questionnaire – Parent Form in
497 children 0 – 12 years following positive and negative food challenges *Clinical & Experimental*
498 *Allergy.* 2010;476–85.
- 499