The impact of oral food challenges for food allergy on quality of life

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Published in:
Pediatric Allergy and Immunology

DOI:
10.1111/pai.12905

Publication date:
2018

Title page

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

Short title: Oral food challenges and quality of life

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Tel: +31 (0) 88 75 75 2 84

Funding received: none.

Conflicts of interest regarding this manuscript: none.

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-TF	Food Allergy Quality of Life Questionnaire-Teen Form
FAQLQ-PF	Food Allergy Quality of Life Questionnaire-Parent Form
HRQL	health-related quality of life, HRQL
MD	mean difference
MCID	minimal clinically important difference
OFC	oral food challenge
PedsQL^{TM} 4.0	Paediatric 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

Abstract page

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Journal: Pediatr Allergy Immunol

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 (i.e. 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.

Offprint request

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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 is to provide a systematic synthesis of the current evidence on the impact of diagnostic interventions for food allergy on HRQL.

Methods

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 supplemental material (Appendix 1). Four databases were searched from inception until July 6th 2017: MEDLINE, EMBASE, the Cochrane Library and CINAHL. All identified citations were imported into Rayyan for de-duplication and title and abstract screening.(15) All identified publications were screened by two authors (HK, 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 supplemental material (Appendix 2). Any discrepancies between two authors were resolved by discussion and consensus, or by consulting a third reviewer (TL) if necessary.

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 supplemental material (Appendix 3).

Quality of paper assessment

The included publications were assessed for risk of bias in duplicate (HK, FE) according to a modified version of the Quality in Prognostic Studies (QUIPS) tool (Appendix 4).(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 last, 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.

Outcome assessment

HRQL 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 to 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 to 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, Dietary restrictions), the FAQLQ-TF

contains 23 items and 3 domains (Allergen Avoidance, Risk of Accidental Exposure, Emotional Impact), the FAQLQ-AF contains 29 items and 4 domains (Allergen Avoidance, Risk of Accidental Exposure, Emotional Impact, Food Allergy-related Health), and the FAQLQ-PF contains 30 items and 3 domains (Emotional Impact, Food Anxiety, Social Dietary Limitations). The FAQLQ-items are scored on a seven-point scale. The longitudinal validity and responsiveness of the FAQLQ has 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 Paediatric Quality of Life Inventory 4.0 (PedsQL^{TM} 4.0) in children and the World Health Organization generic Quality of Life scale (WHOQOL-BREF) in parents. The PedsQL^{TM} 4.0 is a validated generic HRQL questionnaire for children 8 to 12 years of age which contains 23 items and 4 domains (Physical, Emotional, Social, School).). The WHOQOL-BREF is a validated generic HRQL questionnaire for adults which contains 26 items and 4 domains (Physical, Psychological, Social, Environmental).

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 is to confirm or exclude the diagnosis of a food allergy while the aim of an OFC in patients with a confirmed food allergy is 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 = 0.5, and performed a sensitivity

analysis to evaluate the impact of this assumption using a range of plausible correlation (r=0.2 and r=0.8). 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)

Results

Selection of eligible publications

The search results are summarized in a flowchart in Fig. 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: 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.

Characteristics of included publications

The characteristics of the seven included publications are summarized in Table I. 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 dose(26) 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 publication(27) (Table II). The complete results of the risk of bias assessment are published in the supplemental material (Appendix 5).

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) (Fig. 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, i.e. positive, negative and inconclusive OFC. This showed that in patients with a positive OFC outcome (i.e. 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 (Fig. 2b).(18,29) In patients with a negative OFC outcome (i.e. 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 (Fig. 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 (Fig. 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 two and six months and this improvement was significant and clinically relevant (Appendix 6).(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 I). No significant difference was observed between food allergy specific HRQL at baseline and after 7 months in children, and adolescents (Appendix 7a). 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 8).

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

The domain specific parent-reported HRQL values are shown in Fig. 3, and domain-specific HRQL values in children and adolescents in Appendix 9. 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 relevant only in the domains of 'food anxiety' and 'social and dietary restriction' in one publication (Fig. 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 9a).(27)

In parents of children with a positive OFC outcome (i.e. 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 9b).

In parents of children with a negative OFC outcome (i.e. 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 publication(29) and in the domain of 'social and dietary impact' in the other publication(18) (Fig. 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 9c).(27)

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 (Fig. 4).(26) The standardized mean difference (SMD) was very large. The aim of the OFC in this publication was to assess the ED_{05}, which is the dose that elicits an allergic reaction in 5% of the allergic subjects (Table I). 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 effect size was small. Generic HRQL in both parents and children did not improve after an OFC (Fig. 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 I). 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 7b). 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 10).

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); $p<0.0001$).(28)

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.

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, 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 improve between two and six 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 or 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 I). 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 0.5. However, a sensitivity analysis with a range of plausible r values hardly changed our results (Appendix 11).

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.

Figure legends

Figure 1: PRISMA flowchart of study selection.

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.

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); 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 (Hourihane), 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^{TM} 4.0, Paediatric Quality of Life Inventory 4.0; SMD, standardized mean difference; WHOQOL-BREF, World Health Organization generic Quality of Life scale.

Table 1: Characteristics of included publications

Suspected food allergy						
Publication	**Study design, geographical area**	**Participants**	**Food allergen** (n)	**Intervention**	**Control**	**Outcome**
DunnGalvin 2010(18)	Prospective cohort study in Europe (Ireland)	82 children (≤12 year) 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 months after OFC 3 6 months after OFC
Soller 2014(29)	Prospective cohort study in Europe (Ireland)	54 children (≤12 year) 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 months before OFC 2 Day OFC 3 2 months after OFC 4 6 months after OFC
van der Valk 2016(27)	Prospective cohort study in Europe (Netherlands)	112 children (≤17 year) with a suspected cashew nut allergy and their parents. A suspected cashew nut allergy was based on 1) sensitization (positive skin prick test or sIgE) and a clinical history of previous positive reaction to cashew nut, or 2) unknown exposure.	Cashew nut (112)	DBPCFC	NA	FAQLQ-PF, FAQLQ-TF and FAQLQ-CF at: 1 Before OFC 2 6 months after OFC

Publication	Study design, geographical area	Participants	Food allergen	Intervention	Control	Outcome
van der Velde, 2012(19)	Prospective cohort study in Europe (Netherlands)	57 children (8-12 year), 46 adolescents (13-17 year) and 53 adult (≥18 year) with a suspected food allergy on the waiting list for an OFC (expected waiting time < 6 months) 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 months) 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 month before OFC (or baseline) 2. 6 months after OFC (or 7 months after baseline)
Confirmed food allergy						

Hourihane 2017(26)	Prospective cohort study in Europe (Ireland), the United States (Boston) and Australia (Melbourne)	378 children (≤18 year) with a confirmed peanut allergy. A confirmed peanut allergy was based on 1) a convincing clinical history within 2 years and sensitization (SPT or sIgE), or 2) a positive OFC (either an open OFC or a DBPCFC) within 2 years, or 3) no previous ingestion of peanut with sensitization to peanut > 95% PPV (sIgE ≥15 kU/L and/or peanut SPT ≥8mm within 2 months).	Peanut (378)	Single dose OFC to assess the predicted peanut eliciting dose	NA	FAQLQ-PF and FAQLQ-CF at: Before OFC 1. 1 month after OFC

Publication	**Study design, geographical area**	**Participants**	**Food allergen**	**Intervention**	**Control**	**Outcome**
Franxman 2015(28)	Cross-sectional study in the United States (Michigan)	115 children (≤18 year) with a positive OFC during the past 11 years 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 year after OFC (or after diagnosis without OFC)

Knibb 2012(30)	Prospective cohort in Europe (United Kingdom)	40 children (6-16 year) 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 years) 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, WHOQOL-BREF at: 1. Before OFC (or post clinic) 3-6 months after OFC (or 3-6 months 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, Paediatric Quality of Life Inventory 4.0; PPV, positive predictive value; WHOQOL-BREF, World Health Organization generic Quality of Life scale.

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	

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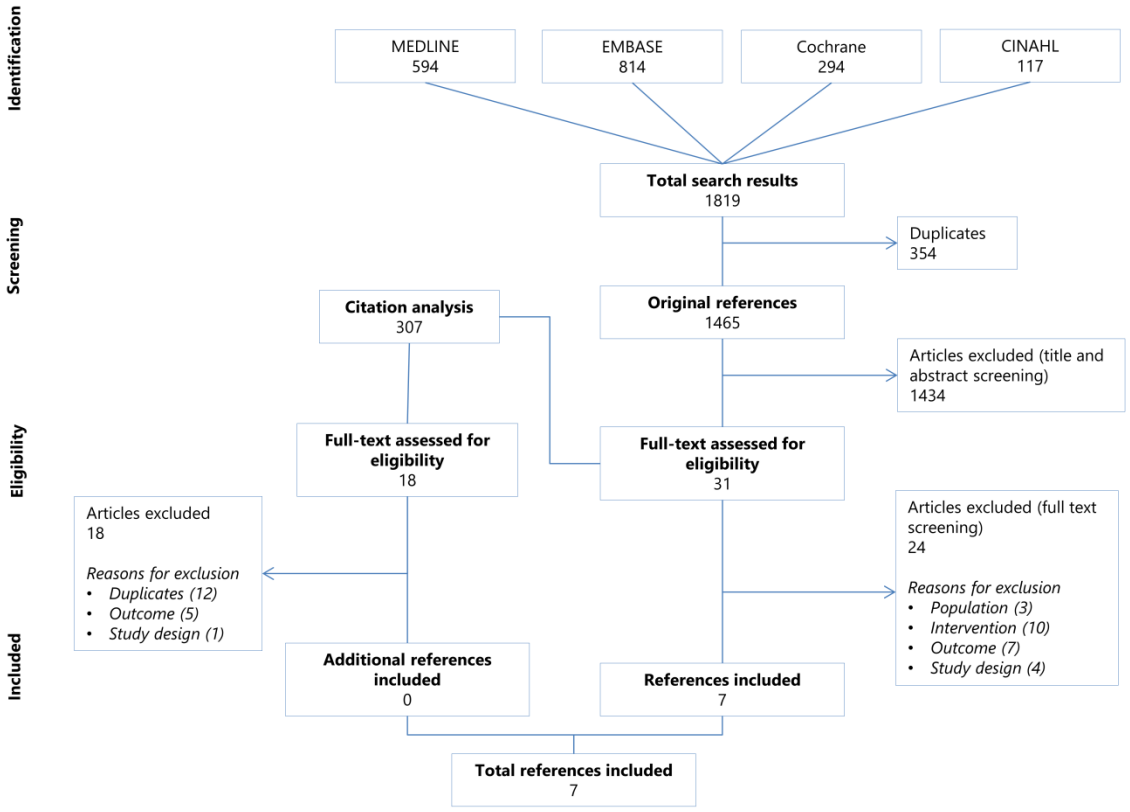
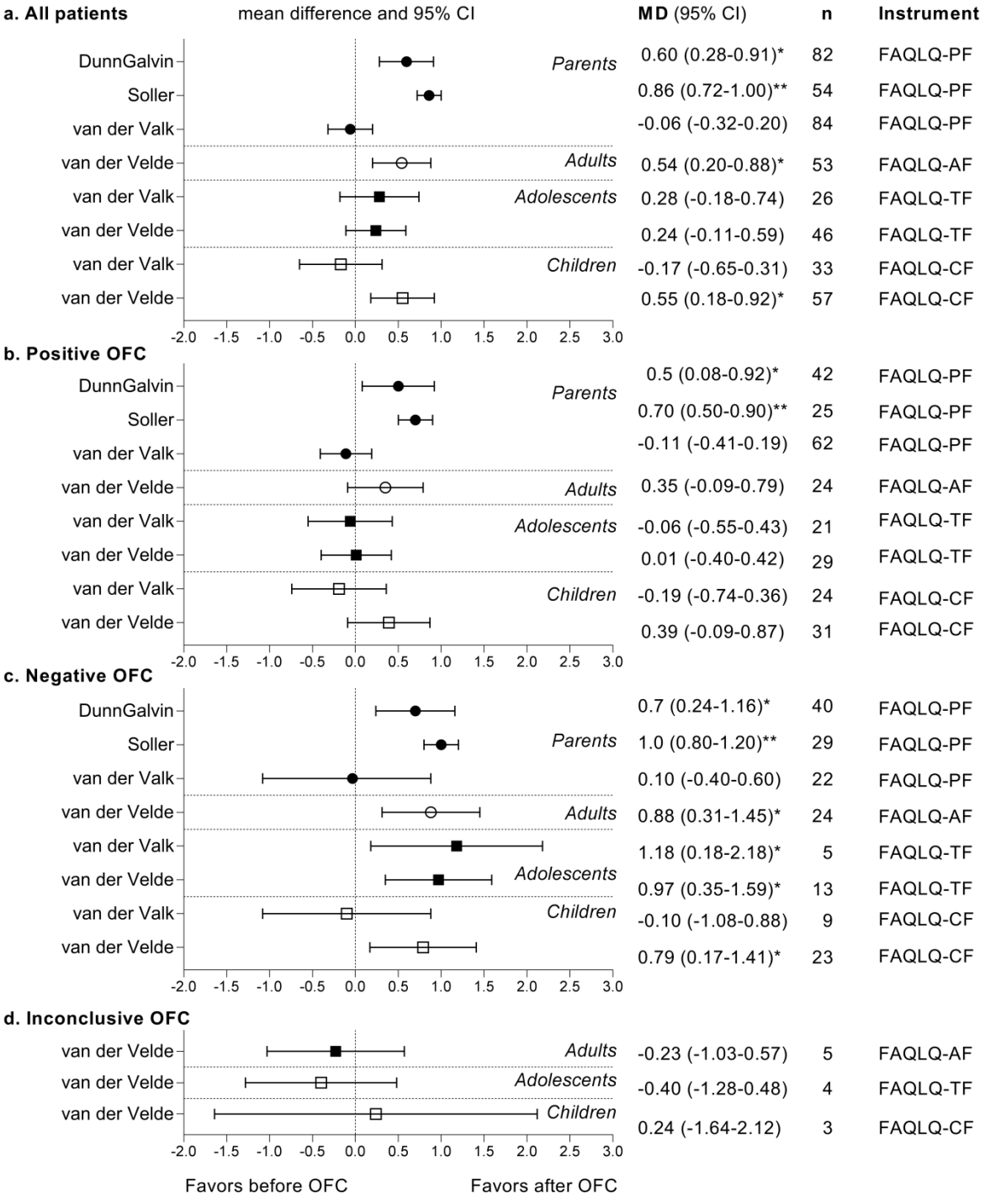
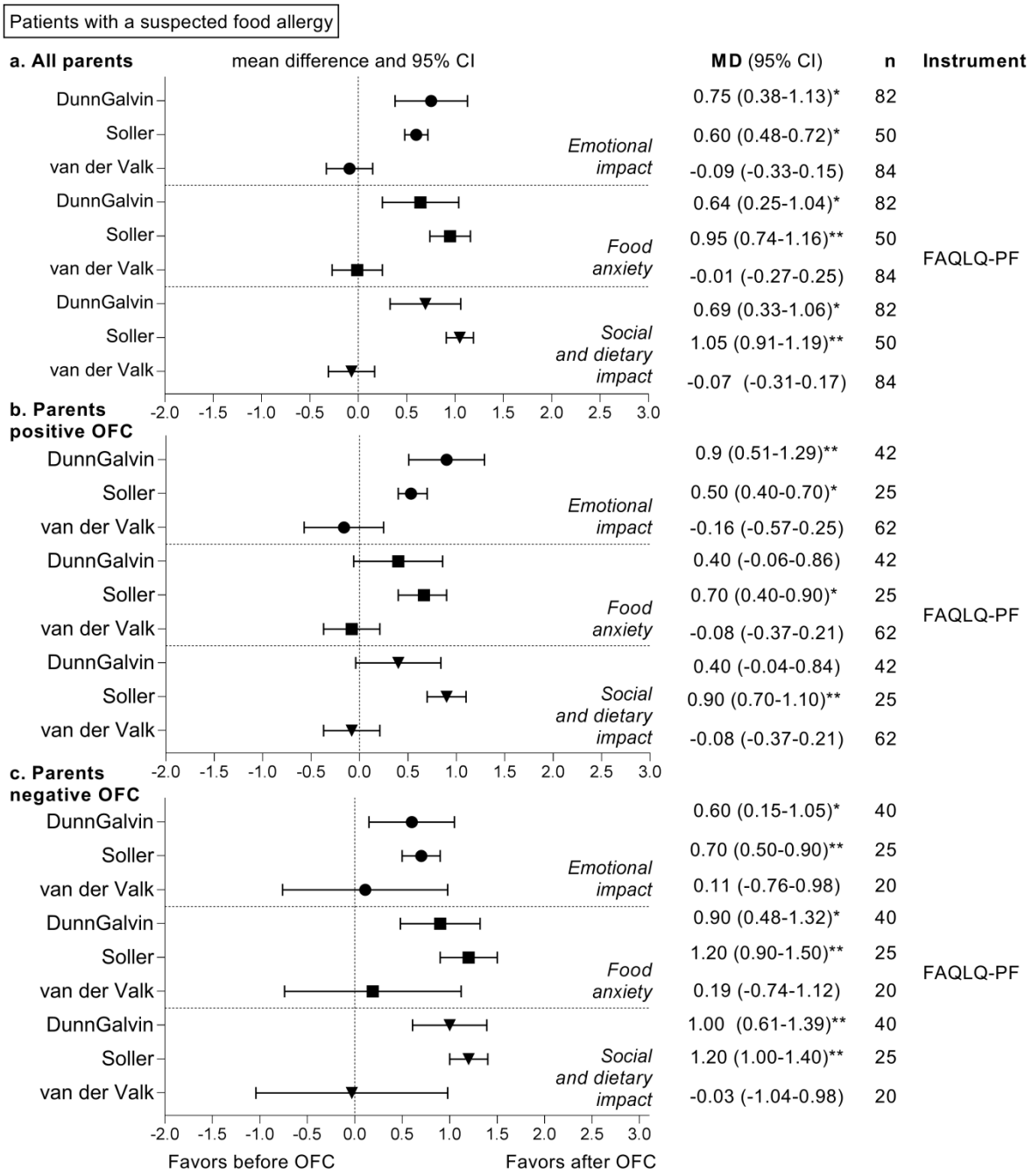
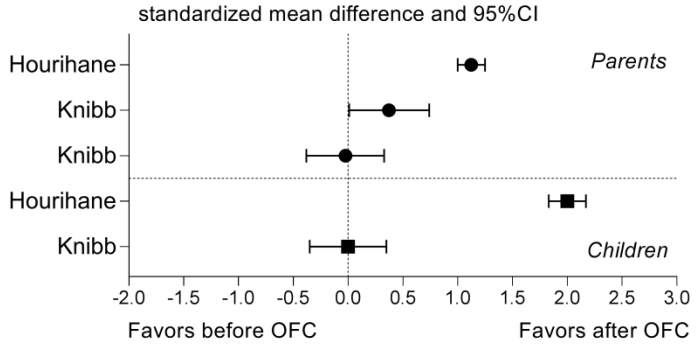


Patients with a suspected food allergy





Patients with a confirmed food allergy



	SMD (95% CI)	n	Instrument
Hourihane	1.12 (1.00-1.25)*	378	FAQLQ-PF
Knibb	0.37 (0.01-0.74)	31	FAQL-PB
Knibb	-0.02 (-0.38-0.33)	31	WHOQOL-Bref
Hourihane	2.00 (1.87-2.17)*	378	FAQLQ-CF
Knibb	0.00 (-0.35-0.35)	31	PedsQL