

REVIEW ARTICLE

Disease-specific health-related quality of life instruments for IgE-mediated food allergy

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Abstract

This is one of seven interlinked systematic reviews undertaken on behalf of the European Academy of Allergy and Clinical Immunology as part of their Guidelines for Food Allergy and Anaphylaxis, which focuses on instruments developed for IgE-mediated food allergy. Disease-specific questionnaires are significantly more sensitive than generic ones in measuring the response to interventions or future treatments, as well as estimating the general burden of food allergy. The aim of this systematic review was therefore to identify which disease-specific, validated instruments can be employed to enable assessment of the impact of, and investigations and interventions for, IgE-mediated food allergy on health-related quality of life (HRQL). Using a sensitive search strategy, we searched seven electronic bibliographic databases to identify disease-specific quality of life (QOL) tools relating to IgE-mediated food allergy. From the 17 eligible studies, we identified seven disease-specific HRQL instruments, which were then subjected to detailed quality appraisal. This revealed that these instruments have undergone formal development and validation processes, and have robust psychometric properties, and therefore provide a robust means of establishing the impact of food allergy on QOL. Suitable instruments are now available for use in children, adolescents, parents/caregivers, and adults. Further work must continue to develop a clinical minimal important difference for food allergy and for making these instruments available in a wider range of European languages.

The term 'food allergy' refers to the subgroup of food-triggered reactions in which immunologic mechanisms have been implicated, whether immunoglobulin E (IgE)-mediated,

non-IgE-mediated, or involving a combination of IgE- and non-IgE-mediated etiologies (1). This review focuses on food allergy that is likely to have an IgE-mediated etiology.

Living with a food allergy is more difficult than is generally appreciated (2). Long-term management is focused on the avoidance of the foods that trigger the allergic reactions, which in turn places a psychological burden on patients and carers that can result in stress and anxiety. There is, in addition, often further anxiety relating to the burden of managing acute reactions – particularly if the decision to administer adrenaline (epinephrine) also falls on the patient and/or carer (3–6). In some cases, this can have a considerable impact on the day-to-day lives of patients and carers (7).

The importance of measuring health-related quality of life (HRQL) in patients is that such measurement allows for the estimation of the impact of the disease from a patient perspective; this is important because it is possible for two individuals with clinically similar disease severity to experience very different degrees of impairment in their everyday lives (8).

Health-related quality of life can be measured using generic or disease-specific questionnaires. Useful attributes of generic quality of life (QOL) questionnaires are that they allow comparison between different diseases as well as being sensitive to comorbidities. However, associated limitations of generic instruments include the fact that they are less sensitive and responsive to change than disease-specific instruments, and hence, potentially important differences or changes may be missed. This is particularly relevant in the context of food allergy, where unless individuals are exposed to the specific food, they may have no symptoms or problems other than the anxiety resulting from the need for continued avoidance (9). The disease-specific questionnaires that have been developed are significantly more sensitive in measuring the response to interventions or future treatments as well as estimating the general burden of food allergy (10).

The European Academy of Allergy and Clinical Immunology (EAACI) is in the process of developing the *EAACI Guidelines for Food Allergy and Anaphylaxis*, and this systematic review is one of seven interlinked evidence syntheses that has been undertaken in order to provide a state-of-the-art synopsis of the current evidence base in relation to epidemiology, prevention, diagnosis, and clinical management and impact on QOL, which will be used to inform clinical recommendations. This review will consider only instruments developed for IgE-mediated food allergy.

Aims

We sought to identify which disease-specific, validated instruments can be employed to enable assessment of the impact

of, and the effect of investigations and interventions for, food allergy on HRQL.

Methods

Registration and protocol

This review is registered with the International Prospective Register of Systematic Reviews (PROSPERO; <http://www.crd.york.ac.uk/prospero/>) and has the reference number CRD42013003710. Detailed information on our methods, including the search strategy, study selection, quality assessment strategy, analysis, data synthesis, and reporting, has been reported in advance in our published protocol (11). We provide a brief synopsis of our methods below.

Search strategy

A sensitive search strategy was designed to retrieve all articles combining the concepts of food allergy, QOL, and patient-reported outcomes from electronic bibliographic databases. The search strategy was devised on OVID MEDLINE and then adapted for the other databases (see Appendix S1 in the Supporting Information for full-search strategies). In all cases, the databases were searched from January 1, 1990, to September 30, 2012. Our rationale for searching from 1990 onwards was that this marked the first publication of key allergy HRQL instruments such as the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) and Asthma Quality of Life Questionnaire (AQLQ) (12, 13).

Inclusion and exclusion criteria

We specified that the disease-specific HRQL questionnaire must have been specifically designed for use with patients and carers with food allergy. Any articles relating to the description, development, and/or the validation of the above-identified HRQLs were also eligible for inclusion. Excluded studies included reviews, discussion papers, nonresearch letters, editorials, case studies, and case series.

Study selection

The titles were checked independently by two reviewers (SAS and SSP) according to the selection criteria and categorized as: included, not included, and unsure. For those papers in the unsure category, we retrieved the abstract and recategorized. Any discrepancies were resolved by consensus and, if

Abbreviations

AQLQ, Asthma Quality of Life Questionnaire; CCC, concordance correlation coefficient; DBPCFC, double-blind, placebo-controlled food challenge; EAACI, European Academy of Allergy and Clinical Immunology; FAQL-PB, Food Allergy Quality of Life – Parental Burden; FAQLQ-PF, Food Allergy Quality of Life Questionnaire – Parent Form; 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 – Teenager Form; FAQL-teen, Food Allergy Quality of Life Assessment Tool for Adolescents; HRQL, health-related quality of life; ICC, intraclass coefficient; IgE, immunoglobulin E; MID, minimal important difference; NNT, numbers needed to treat; PFA-QL, Paediatric Food Allergy Quality of Life Questionnaire; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QOL, quality of life; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.

necessary, a third reviewer (AS) was consulted to arbitrate. Full-text copies of potentially relevant studies were obtained and their eligibility for inclusion independently assessed.

Quality assessment strategy

We assessed the development of the instruments identified and their performance properties including validity; generalizability; responsiveness; managing missing data; how variation in patient demography was managed; and cross-cultural and linguistic adaptation, using a previously reported quality assessment tool (14). Assessment of validity focused on the identification of appropriate independent measures and their correlation with partial or total instrument scores. A team of researchers (SAS and SSP) independently assessed the articles against the defined criteria, and any discrepancies were resolved by consensus and, if necessary, a third reviewer (AS) was consulted.

Analysis, data synthesis, and reporting

Data were independently extracted onto a customized data extraction sheet by two reviewers (SAS and SSP), and any discrepancies were resolved by discussion or, if agreement could not be reached, by arbitration by a third reviewer (AS). A descriptive summary with data tables was produced to summarize the literature. Quantitative pooling of data was not meaningful in the context of this review so a narrative synthesis of the data was undertaken.

Results

Study selection

The electronic database searches identified 1255 papers of potential interest. Seventeen studies met the inclusion criteria. The most frequent reason for exclusion was that the questionnaire was not a disease-specific HRQL instrument, was not validated, or was inadequately validated (Fig. 1).

From the 17 studies, seven disease-specific HRQL instruments were identified for food allergy as requiring full-quality appraisal. Further details are found in Table 1. Four subtypes were identified: those to be completed by adults, adolescents, older children, and parent or caregiver. The characteristics of each of the HRQLs are presented in Table 2, a summary of their development is detailed in Table 3, and the psychometric properties of these instruments are summarized in Table 4.

Food allergy disease-specific HRQL for children

Food Allergy Quality of Life Questionnaire – Child Form

The Food Allergy QOL Questionnaire – Child Form (FAQLQ-CF) was developed as the first disease-specific HRQL questionnaire for food-allergic children that can be self-administered, originally in the Dutch language. Four papers were reviewed for the development and validation of the FAQLQ-CF in this review (9, 10, 15, 16).

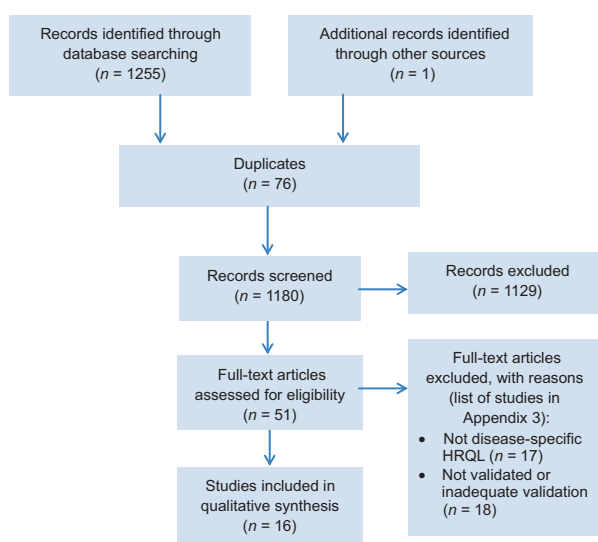


Figure 1 Flow diagram of searches.

Table 1 Disease-specific HRQL instruments

Abbreviation (where stated)	Full name
Children	
FAQLQ-CF (9, 10, 15, 16)	Food Allergy Quality of Life Questionnaire – Child Form
Adolescent	
FAQLQ-TF (10, 20, 21)	Food Allergy Quality of Life Questionnaire – Teenager Form
FAQL-teen (22)	Food Allergy Quality of Life Assessment Tool For Adolescents
You and Your Food Allergy (23)	You and Your Food Allergy
Adults	
FAQLQ-AF (10, 24, 25)	Food Allergy Quality of Life Questionnaire – Adult Form
Parent or caregiver	
FAQL-PB (18, 26–29)	Food Allergy Quality of Life – Parental Burden
FAQLQ-PF (7, 15, 29, 30)	Food Allergy Quality of Life Questionnaire – Parent Form

HRQL, health-related quality of life.

The intended population was for children aged 8–12 years and is a self-report; it contains 24 items and four domains. This instrument was developed as part of the EuroPrevall project, a European multicenter research project on food allergy, to cover all age groups of patients with food allergy.

The FAQLQ-CF was developed following item generation and item reduction (12–14, 17). Cross-sectional validity was assessed through the evaluation of its construct validity, convergent and discriminant validity, discriminative ability and reliability. Food Allergy Independent Measure (FAIM), a disease-specific objective instrument, was developed for the

Table 2 Characteristics of included instruments

Instrument	Aim of the study and target population	No. of validation studies assessed	No. of items/domain	Mode of administration	Time to complete	Original language	Language available in
Food allergy disease-specific HRQL for children FAQLQ-CF (9, 10, 15, 16)	To develop and validate the Food Allergy Quality of Life Questionnaire – Child Form (FAQLQ-CF) Intended population: children aged 8–12 years old	4	24 items and four domains: a – allergen avoidance b – risk of accidental exposure c – emotional impact d – dietary restrictions	Self-administered by children	Not published	Dutch	French Dutch English
Food allergy disease-specific HRQL for adolescent FAQLQ-TF (10, 20, 21)	To develop and validate the Food Allergy Quality of Life Questionnaire – Teenager Form (FAQLQ-TF) Intended population: adolescents aged 13–17 years old	3	28 items and three domains: a – allergen avoidance and dietary restrictions b – emotional impact c – risk of accidental exposure	Self-administered by adolescents	Not published	Dutch	Dutch English
FAQL-teen (9)	To develop a validated Food Allergy Quality of Life assessment tool for US adolescents (FAQL-teen) Intended population: adolescents aged 13–19 years old	1	17 items. Domains not mentioned	Self-administered by adolescents	Not published	English	English
You and Your Food Allergy (23)	To develop and validate a disease-specific HRQL scale for teenagers living in the UK with food hypersensitivity (FHS) Intended population: teenagers aged 13–18 years old	1	34 items and five domains: a – social well-being and independence b – support c – day-to-day activities d – family relations e – emotional well-being	Self-administered by adolescents	Not published	English	English
Food allergy disease-specific HRQL for adults FAQLQ-AF (10, 24, 25)	To report the development and cross-sectional validation of the first disease-specific HRQL questionnaire for adults with food allergy Intended populations: adults over 18 years old with food allergy excluding those with oral allergy syndrome	3	29 items and four domains: a – allergen avoidance and dietary restrictions b – emotional impact c – risk of accidental exposure d – food allergy-related health	Self-administered by adults	Not published	Dutch	Dutch English

Table 2 (Continued)

Instrument	Aim of the study and target population	No. of validation studies assessed	No. of items/domain	Mode of administration	Time to complete	Original language	Language available in
Food allergy disease-specific HRQL for parent or caregiver FAQLQ-PB (18, 26–29)	To create a validated, food allergy-specific HRQL instrument to measure parental burden associated with having a child with food allergy Intended population: parents of children 17 years old and younger	4	17 items and three domains: a – going on vacation b – social activities c – worries and anxieties over the previous week	Self-administered by parents	Not published	English	Chinese English
FAQLQ-PF (7, 15, 29, 30)	To develop a sensitive, multidimensional measure to assess parental perception of the child's HRQL Intended population: parents of children aged 0–12 years old	4	30 items and three domains: a – emotional impact b – food-related anxiety c – social and dietary limitations	Self-administered by parents	Not published	Dutch	French Dutch English

HRQL, health-related quality of life.

validation of the FAQLQ and included four expectation of outcome (EO) questions and two independent measure (IM) questions (18, 19). One study demonstrated a moderate correlation between FAQLQ-CF and FAIM ($p = 0.60$, $P \leq 0.001$) (9), and two studies showed similar internal consistency (Cronbach's $\alpha = 0.94$ – 0.95) (7, 20). The instrument also demonstrated that it could discriminate between children who differed in number of food allergies (>2 food allergies vs ≤ 2 food allergies, total FAQLQ-CF score 4.3 vs 3.6, $P = 0.036$). However, FAQLQ-CF could not discriminate between reported anaphylaxis or not (4.2 vs 3.9, $P = 0.315$) (9).

One of the four studies also evaluated test–retest reliability of the FAQLQ-CF. The intraclass coefficient (ICC) was found to be excellent (ICC = 0.91) (10) and the same study identified the concordance correlation coefficient (CCC) as 0.907, as well as a Bland–Altman plot demonstrating that the mean differences of the test and retest were close to zero for the FAQLQ-CF (10).

One study validated the French version of instrument. The results demonstrated that the converted FAQLQ-CF had a good internal consistency (Cronbach's $\alpha = 0.67$) and a good correlation between FAQLQ-CF and FAIM-CF ($r = 0.84$) (15). One study identified in this review compared child self-reported and parent-proxy-reported HRQL in food-allergic children (8–12 years old). The study assessed the FAQLQ-CF and FAQLQ – Parental Form (PF) in Dutch food-allergic child–parent pairs. Child and parent proxy reports were correlated and tested for significant differences, including the comparison of the internal consistency and construct validity. The results demonstrated the correlation coefficient between the total FAQLQ-CF and FAQLQ-PF to be 0.56 ($P \leq 0.001$). The ICC was 0.57 ($P \leq 0.001$). The Bland–Altman plot showed that the mean between the FAQLQ-CF and FAQLQ-PF score was 1.06 (SD = 1.10) (15).

Food allergy disease-specific HRQL for adolescents

Food Allergy Quality of Life Questionnaire – Teenager Form

This tool was developed as the first disease-specific HRQL questionnaire for food-allergic adolescents, originally in the Dutch language. Three papers were reviewed for the development and validation of the Food Allergy Quality of Life Questionnaire – Teenager Form (FAQLQ-TF) (10, 20, 21).

The intended population included patients aged 13–17 and is a self-report; it contains 28 items and three domains.

This instrument was developed as part of the EuroPrevall project and followed the development and validation method of the FAQLQ-CF. Assessment demonstrated a correlation between FAQLQ-TF and FAIM ($p = 0.57$, $P \leq 0.001$) with an internal consistency (Cronbach's $\alpha = 0.92$). Additionally, the instrument demonstrated that it could discriminate between adolescents who reported two or more food allergies compared to adolescents who only reported one (1 food allergies vs >2 food allergies, total FAQLQ-TF score 4.3 vs 3.5, $P = 0.037$). However, FAQLQ-TF could not discriminate between those who did or did not have reported anaphylaxis (4.5 vs 4.0, $P = 0.184$) (20).

Table 3 Summary of development properties of included HRQL instruments

Instrument	Prestudy hypothesis	Intended population	Actual content area (face validity)	Item identification	Item selection	Unidimensionality	Response scale	Scoring	Instrument translated and validated in English-speaking population
Food allergy disease-specific HRQL for children									
FAQLQ-CF (9, 10, 15, 16)	✓✓	✓✓	✓✓	✓✓	✓✓	✓	✓✓	✓✓	✓
Food allergy disease-specific HRQL for adolescents									
FAQLQ-TF (10, 20, 21)	✓✓	✓✓	✓✓	✓✓	✓✓	✓	✓✓	✓✓	✓
FAQL-teen (22)	✓✓	✓✓	✓✓	✓✓	✓✓	✓	✓	✓	✓✓
You and Your Food Allergy (23)	✓✓	✓✓	✓✓	✓✓	✓✓	✓	✓✓	✓✓	✓✓
Food allergy disease-specific HRQL for adults									
FAQLQ-AF (10, 24, 25)	✓✓	✓✓	✓✓	✓✓	✓✓	✓	✓✓	✓✓	✓✓
Food allergy disease-specific HRQL for parent or caregiver									
FAQL-PB (18, 26–29)	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓
FAQLQ-PF (7, 15, 29, 30)	✓✓	✓✓	✓✓	✓✓	✓✓	✓	✓✓	✓✓	✓✓

HRQL, health-related quality of life.

For definitions, refer to Appendix S2.

One of the three studies also evaluated the test–retest reliability of the FAQLQ-TF, which was excellent (ICC = 0.976 and CCC = 0.975). The Bland–Altman plot also illustrated that the mean differences of the test and retest were close to zero for the FAQLQ-TF (10). Another study identified in this review went on to further compare adolescent self-reported and parent-proxy-reported HRQL of food-allergic adolescents and to investigate the factors that may influence any disagreements between the two; this was an area which had not been previously studied (21). This third study assessed the Teenager Form (TF) and Parental Form (PF) of the FAQLQ but also FAIM and Brief Illness Perception Questionnaire (Brief-IPQ). The results comparing FAQLQ-TF and FAQLQ-PF showed that there was a moderate correlation (ICC = 0.61, $P \leq 0.001$) and there was no significant difference (3.78 vs 3.56, $P = 0.103$) between adolescent self-reported and parent-proxy-reported HRQL at group level. The Bland–Altman plot showed relevant differences (exceeding the minimal important difference) for 63% of the adolescent–parent pairs (21).

Food Allergy Quality of Life Assessment Tool for Adolescents (FAQL-teen)

One study was identified which reviewed the development and validation of the FAQL-teen (22). The instrument was developed for adolescents in the United States (US) and the intended population was adolescents aged 13–19 years and is a self-report; it contains 17 items, but the domains were not mentioned in the study. The FAQL-teen was developed following guidelines available at the time; validation of the instrument included assessing the internal validity and discriminative ability (22).

This instrument showed a strong internal validity (Cronbach's $\alpha = 0.90$), as well as demonstrating discriminative ability by disease severity; adolescents with a history of anaphylaxis had significantly lower QOL than those without a history of anaphylaxis (mean FAQL-teen score for anaphylaxis was 2.5 vs 2.0 in those without anaphylaxis, $P = 0.003$). However, discriminative ability was not seen in adolescents with two or fewer food allergies ($n = 95$, mean score 2.2) vs those with greater than two food allergies ($n = 108$, mean score 2.5) (22).

You and Your Food Allergy

One study was identified which reviewed the development and validation of a disease-specific HRQL scale of teenagers aged 13–18 years with food hypersensitivity living in the UK (17). It is a self-report and contains 34 items and five domains.

The HRQL scale was developed in four stages: stage one was the development of a preliminary HRQL scale, and stage two involved pretesting the preliminary scale. Stage three was the testing of the pilot scale to identify problematic items, and stage four reduced the number of items in the field test scale to those best measuring HRQL.

The whole scale involved internal consistency (Cronbach's $\alpha = 0.92$) and the test–retest reliability (ICC = 0.87) (23). The scale correlated with a generic HRQL scale (PedsQL) and discriminated by disease severity. For the known-groups analysis, there was a significant difference between the whole scale scores of those allergic to ≤ 2 foods [mean (SD) = 71.7 (13.1)] and the whole scale scores of those allergic to > 2 foods [mean (SD) = 67.5 (14.1)]. This supports the

Table 4 Summary of psychometric properties of included HRQL instruments

Instrument	Other evidence for construct validity, e.g., discriminant validity					Assessment of validity (cross-sectional, longitudinal, or both)	Test-retest agreement	Interobserver agreement or intermode agreement	Person/item separation reliability	Interpretation	Responsiveness
	Convergent validity	Discriminant validity	Predictive validity	criterion, discriminant							
Food allergy disease-specific HRQL for children											
FAQLQ-CF (9, 10, 15, 16)	✓✓	✓✓	0	FAIM CHQ-CF87	Cross-sectional	✓✓	✓✓	✓✓	0	✓	0
Food allergy disease-specific HRQL for adolescents											
FAQLQ-TF (10, 20, 21)	✓✓	✓✓	0	FAIM CHQ-CF87	Cross-sectional	✓✓	✓✓	✓✓	0	✓	0
FAQL-teen (22)	✓✓	✓✓	0	PedsQL	Cross-sectional	0	0	0	0	✓	0
You and Your Food Allergy (23)	✓✓	✓✓	0	PedsQL	Cross-sectional	✓✓	✓✓	✓✓	0	✓✓	0
Food allergy disease-specific HRQL for adults											
FAQLQ-AF (10, 24, 25)	✓✓	✓✓	0	FAIM RAND-36	Cross-sectional	✓✓	✓✓	✓✓	0	✓	0
Food allergy disease-specific HRQL for parent or caregiver											
FAQL-PB (18, 26-29)	✓✓	✓✓	0	CHQ-PF50	Cross-sectional	✓✓	✓✓	✓✓	0	✓	0
FAQLQ-PF (7, 15, 29, 30)	✓✓	✓✓	0	FAIM	Both	✓✓	✓✓	✓✓	0	✓✓	✓✓

HRQL, health-related quality of life.

For definitions, refer to Appendix S2.

scales ability to distinguish between the groups hypothesized to have differing HRQL ($t = 2.459$, $df = 287$, $P < 0.05$) (23).

Food allergy disease-specific HRQL for adults

Food Allergy Quality of Life – Adult Form (FAQLQ-AF)

The Food Allergy QOL – Adult Form was developed, in Dutch, as the first disease-specific HRQL questionnaire for adults. Three papers were reviewed for the development and validation of the FAQLQ-AF in this systematic review (10, 24, 25). The intended population for the questionnaire was patients over the age of 18 years and is a self-report; it contains 29 items and four domains.

This instrument was developed as part of the EuroPrevall project and followed the development and validation method of the FAQLQ-CF and FAQLQ-TF. This instrument was the last of the HRQL questionnaires, in a series of questionnaires developed in the EuroPrevall project. The FAQLQ-AF was developed following item generation and item reduction (12–14, 17). Cross-sectional validity was assessed through the evaluation of its construct validity, convergent and discriminant validity, discriminative ability and reliability. Assessment of this tool demonstrated a good correlation between FAQLQ-AF and FAIM ($\rho = 0.76$, $P \leq 0.001$) with internal consistency (Cronbach's $\alpha = 0.97$) (25).

Additionally, the instrument demonstrated that it could discriminate between patients who differ in severity of symptoms (anaphylaxis vs nonanaphylaxis, total FAQLQ-AF score 4.9 vs 4.1 $P = 0.041$) and number of food allergies (>3 food allergies vs ≤ 3 food allergies, total FAQLQ-AF score 5.2 vs 4.2, $P = 0.008$) (25). In addition, one of the studies evaluated the test–retest reliability of the FAQLQ-AF, which was excellent (ICC = 0.952 and CCC = 0.952).

In 2010, the FAQLQ-AF was translated from Dutch to English for an online version to be used in the US. One study identified in this review validated this translated instrument. The online FAQLQ-AF also demonstrated a good construct validity (correlation with FAIM $\rho = 0.72$; $P \leq 0.001$), internal consistency (Cronbach's $\alpha = 0.95$) and was discriminative for anaphylaxis vs nonanaphylaxis (total FAQLQ-A score 5.4 vs 4.9; $P = 0.03$). Discriminative ability was also shown in American participants allergic to more than three foods vs participants allergic to three or fewer foods (5.7 vs 5.1; $P \leq 0.001$) (24).

Food allergy disease-specific HRQL for parent or caregiver

Food Allergy Quality of Life – Parental Burden

A total of five studies were identified describing the development and validation of the Food Allergy Quality of Life – Parental Burden (FAQL-PB) instrument (18, 26–29). It is a self-report on the parent or caregiver's HRQL and contains 17 items and three domains.

One study focused on the creation and validation of a food allergy-specific HRQL instrument to measure parental burden associated with having a child with food allergy: the FAQL-PB (18).

The FAQL-PB was originally in English and was developed following item generation and item reduction (12–14, 17), resulting in a questionnaire with 17 items. The validation showed a strong internal validity (Cronbach's $\alpha = 0.95$) and a good correlation with expectation of outcome questions ($r = 0.412$, $P \leq 0.01$). FAQL-PB was also able to demonstrate the ability to discriminate by disease burden; parents whose children had multiple (more than 2) food allergies were more affected than parents whose children had fewer allergies (scores, 3.1 vs 2.6, $P \leq 0.001$) (18).

One study reviewed the impact of pediatric food allergy on caregiver QOL (21). One study showed that mother and child reported lower anxiety ($P = 0.043$ and $P < 0.001$) when the child was prescribed an epinephrine auto-injector (27).

One study tested the robustness of the Chinese Food Allergy QOL – Parental Burden Questionnaire (Chinese FAQL-PB). The internal validity of the instrument was excellent (Cronbach's $\alpha = 0.976$ and an ICC = 0.701, $P < 0.001$). The authors did not use the FAIM tool to assess construct validity. However, confirmatory factor analysis (CFA) was undertaken to ensure that any domains found were genuinely present. The CFA revealed good correlations between the FAQL-PB items (28, 29).

Food Allergy Quality of Life Questionnaire – Parental Form

Four studies were reviewed for the development and validation of the Food Allergy Quality of Life Questionnaire – Parental Form (FAQLQ-PF) in this review (7, 15, 28, 30). The intended population is for parents of children aged 0–12 years with food allergy and is a proxy-report where parents report on their children's HRQL. It contains 30 items and three domains. This instrument was developed, initially in English, as part of the EuroPrevall project and followed the development and validation method of the FAQLQ-CF, FAQLQ-TF, and FAQLQ-AF.

The FAQLQ-PF was developed following item generation and item reduction (12–14, 17). Cross-sectional validity was assessed through the evaluation of its construct validity, convergent and discriminant validity, discriminative ability and reliability.

One study revealed the design of a sensitive multidimensional measure to assess parental perception of HRQL in children aged 0–12 years. This was developed in four stages; internal consistency was moderate (Cronbach's $\alpha > 0.7$) for subscales and total score. Construct validity was demonstrated by significant correlations between relevant scales of the Child Health Questionnaire (CHQ)-28 and FAQLQ-PF subscales ($r = 0.69$ – 0.77 , $P < 0.01$) and between FAQLQ-PF subscales and FAIM ($r = 0.52$ – 0.73 , $P \leq 0.01$) (29).

One study compared child and parent proxy reports on HRQL in Dutch food-allergic children (8–12 years old). Seventy-four child–parent pairs were included. The FAQLQ-CF score was significantly higher than the FAQLQ-PF score (3.74 vs 2.68, $P < 0.001$, where 1 indicates no impairment and 7 indicates extreme impairment). The internal consistency for the FAQLQ-PF ($\alpha = 0.95$) and the construct validity were confirmed for the Dutch translation of the FAQLQ-PF ($\rho = 0.58$, $P < 0.001$) (7).

One study reviewed the validation of the FAQLQ-PF instrument in a French translation. The results demonstrated a strong correlation between FAQLQ-PF and FAIM ($r = 0.85$) and a good internal consistency (Cronbach's $\alpha = 0.748$) (15).

The fourth study assessed the longitudinal measurement properties of the FAQLQ-PF instrument. The results showed that domains and total score improved significantly at post-challenge time-points for both groups (all $P < 0.05$). Sensitivity was demonstrated by differences between positive and negative groups at 6 months [$F(2, 59) = 6.221, P < 0.003$] and by differing improvement on relevant subscales ($P < 0.05$). Minimal important difference (MID) was 0.45 on a seven-point response scale. Poorer QOL at baseline increased the odds by over 2.0 of no improvement in HRQL scores 6-month time-point. The internal reliability of the overall score on the FAQLQ-PF (at 6 months) was found to be very good with Cronbach's α of 0.89–0.9, and the reliability of the change score (ICC of change) in the instrument subscales and total score ranged from 0.90 to 0.92 (30). Hence, FAQLQ-PF is sensitive to change and has excellent longitudinal validity and reliability in a food-allergic patient population.

Discussion

Principal findings

This comprehensive systematic review has identified and formally appraised the underpinning evidence for available HRQL instruments for use in patients and parents of children with food allergy. We have found a number of instruments with good developmental and psychometric properties, and it is important that these are now widely used in research and clinical contexts. The inability at present to define a clinical minimal important difference remains a concern that needs urgently to be addressed, as does the need for making these instruments available in a wider range of European languages.

Strengths and limitations

The main strengths of this work include the use of formal systematic review methods, including the development of a formal systematic review protocol, which was published in advance (11), and the involvement of a multidisciplinary group of experts from a range of European countries.

The limitations of this work include the fact that our focus was on IgE-mediated food allergy (19), even though non-IgE-mediated and mixed IgE-/non-IgE-mediated food allergy also occur and can have a profound impact on QOL. This decision, however, reflected the expert opinion that such instruments have yet to be developed; this therefore reflects an important outstanding research need.

In addition to Dutch and French, the FAQLQ-CF has been validated in English, Spanish, and Polish (N.J. Goossens et al., submitted) and translated into nine other European languages. In addition to Dutch and English, the

FAQLQ-AF has been validated in French, Greek, Icelandic, Italian, Polish, Spanish, Swedish (N.J. Goossens et al., submitted) and translated into four other European languages. Also, the FAQLQ-TF and FAQLQ-PF have been translated into a number of European languages and some of them are also validated (www.faqlq.com). A parent-administered instrument for adolescents (where parents report on their teenager's HRQL) is under development in the UK (29). After the time period of the search of this review, the FAQL-PB was validated in the UK (31) and a new Paediatric Food Allergy Quality of Life Questionnaire (PFA-QL) was validated in the UK (32). Additionally, the development of the Pediatric Quality of Life Inventory Eosinophilic Esophagitis Module by Franciosi et al. (33) is currently undergoing multicenter field testing, but this tool does not limit itself to IgE-mediated food allergy.

The time period of the search excluded an important study assessing longitudinal validity and responsiveness of the FAQLQ-AF, FAQLQ-TF, and FAQLQ-CF and the impact of a double-blind, placebo-controlled food challenge (DBPCFC) on HRQL (34). The results of the study demonstrated responsiveness of the FAQLQs through improved HRQL scores after a DBPCFC, with greater improvements in HRQL scores after a negative outcome (food allergy ruled out) than a positive outcome (food allergy confirmed). Additionally, longitudinal validity of these questionnaires was supported by significant correlations between the change (follow-up minus baseline) in FAQLQ and FAIM. FAQLQ-AF (Pearson's correlation coefficient = 0.71, $P < 0.001$), FAQLQ-TF (Pearson's correlation coefficient = 0.35, $P = 0.018$), and FAQLQ-CF (Pearson's correlation coefficient = 0.51, $P < 0.001$) (34).

Interpretation of findings

The seven included HRQL questionnaires for food allergy were appraised as having relatively high quality of development properties (Table 3) and psychometric properties (Table 4). Regarding the development properties, the quality scores of the seven HRQL differed only slightly, ranging from 15 of 18 (FAQL-teen) to 18 of 18 (FAQLQ-PF). For the psychometric properties, more variance was seen in the quality scores with the FAQL-teen having the worst score (5 of 16) and the FAQLQ-PF having the best score (12 of 16). For the adolescent age group, three questionnaires are available. The FAQLQ-TF and the You and Your Food Allergy are comparable and have high-quality development and psychometric properties. However, the FAQL-teen scored considerably lower on quality of psychometric properties and was specially developed for US adolescents, which may limit its generalizability. It is also worth noting that in cases of 'excellent' internal consistency ($\alpha > 0.9$), redundancy possibly exists and some items may be measuring very similar things. This might mean that the scale is capturing quite a narrow range of quality of life issues and/or could be made shorter without losing internal reliability.

When selecting an HRQL questionnaire, it is important to choose a questionnaire that is appropriate for the setting,

diagnosis, and age of the patient. In addition, it should be available in the appropriate language. Choosing the appropriate HRQL questionnaire in food-allergic patients will be extensively discussed in the Guideline of the European Academy of Allergy and Clinical Immunology on Food Allergy HRQL measures.

Implications for research, policy, and practice

To date, none of the instruments developed have provided a clinical minimal important difference (MID). One instrument (FAQLQ-PF) has ascertained the statistical MID, which is useful in deciding whether differences or changes are unlikely to be due to spontaneous variation in HRQL. It does not answer the question of whether patients find the difference or change in HRQL clinically important. This is therefore an unmet need in this area, as a clinical MID allows interventions to be assessed quantitatively by permitting calculation of numbers needed to treat (NNT) resulting from the intervention being studied.

Because non-IgE-mediated food allergies are not the focus of this study and have not been studied, we anticipate the problems patients encounter to be quite different from those with immediate-type symptoms or anaphylaxis. So we cannot make any specific suggestions or predictions about the HRQL tools used for non-IgE-mediated symptoms, suffice to say that the construction of any such instrument should adhere to the methodological principles of making a quality of life instrument.

Disease-specific, rather than generic, QOL tools are necessary to provide an in-depth picture of the day-to-day concerns of patients, particularly in the context of long-term conditions. Disease-specific measures are also able to capture small but potentially important changes in HRQL that may occur as a result of clinical treatment and care. Disease-specific instruments also allow the separation of the effects of an intervention on a target disorder from the effects on comorbid conditions. Because many patients with food allergy also suffer from asthma, allergic rhinitis, and/or atopic eczema/dermatitis, having disease-specific instruments for food allergy is particularly relevant in this regard.

Conclusions

This is the first review, to our knowledge, that has systematically assessed the literature on disease-specific QOL tools

for food allergy. This systematic review demonstrated that there are a limited number of health-related QOL tools specifically for IgE-mediated food allergy. It is unlikely that the instruments described here will be useful for non-IgE-mediated food allergy where the problems patients face are quite different. Healthcare workers should be aware of the impact of food allergy on an individual's life and their families. Use of a HRQL questionnaire to evaluate HRQL in children, adolescent, adults with food allergy, and their caregivers may be useful in clinical practice. For research purposes, use of properly validated instruments is critical to the accurate evaluation of HRQL in food-allergic study participants.

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Author contributions

AS, AM, GR, and AEJD conceived this review. It was undertaken by SAS with the support of AEJD, BMJF-deB, SP, and SSP. SAS and AEJD led the drafting of the manuscript, and all authors critically commented on drafts of the manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search strategies.

Appendix S2. Quality assessment tool for evaluation of patient-reported outcome measures.

Appendix S3. Excluded studies.

References

1. Chafen JJS, Newberry SJ, Riedl MA, Bravata DM, Maglione M, Suttrop MJ et al. Diagnosing and managing common food allergies: a systematic review. *JAMA* 2010;**303**:1848–1856.
2. DunnGalvin A, Gaffney A, Hourihane JO. Developmental pathways in food allergy: a new theoretical framework. *Allergy* 2009;**64**:560–568.
3. Gallagher M, Worth A, Cunningham-Burley S, Sheikh A. Strategies for living with the risk of anaphylaxis in adolescence: qualitative study of young people and their parents. *Prim Care Respir J* 2012;**21**:392–397.
4. Akeson N, Worth A, Sheikh A. The psychosocial impact of anaphylaxis on young people and their parents. *Clin Exp Allergy* 2007;**37**:1213–1220.
5. Gallagher M, Worth A, Cunningham-Burley S, Sheikh A. Epinephrine auto-injector use in adolescents at risk of anaphylaxis: a qualitative study in Scotland, UK. *Clin Exp Allergy* 2011;**41**:869–877.
6. Monks H, Gowland MH, MacKenzie H, Erlewyn-Lajeunesse M, King R, Lucas JS et al. How do teenagers manage their food allergies? *Clin Exp Allergy* 2010;**40**:1533–1540.

7. van der Velde JL, Flokstra-de Blok BM, DunnGalvin A, Hourihane JO, Duiverman EJ, Dubois AE. Parents report better health-related quality of life for their food-allergic children than children themselves. *Clin Exp Allergy* 2011;**41**:1431–1439.
8. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. *Ann Intern Med* 1993;**118**:622–629.
9. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, Hourihane JO et al. Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for children. *Clin Exp Allergy* 2009;**39**:127–137.
10. van der Velde JL, Flokstra-de Blok BM, Vlieg-Boerstra BJ, Oude Elberink JN, Schouten JP, DunnGalvin A et al. Test-retest reliability of the Food Allergy Quality of Life Questionnaires (FAQLQ) for children, adolescents and adults. *Qual Life Res* 2009;**18**:245–251.
11. Salvilla SA, Panesar SS, Patel S, Rader T, Muraro A, Roberts G et al. Disease-specific health-related quality of life (HRQL) instruments for food allergy: protocol for a systematic review. *Clin Transl Allergy* 2013;**3**:15.
12. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy* 1991;**21**:77–83.
13. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax* 1992;**47**:76–83.
14. Pesudovs K, Burr JM, Harley C, Elliott DB. The development, assessment, and selection of questionnaires. *Optom Vis Sci* 2007;**84**:663–674.
15. Wassenberg J, Cochard MM, DunnGalvin A, Ballabeni P, Flokstra-de Blok BM, Newman CJ et al. Parent perceived quality of life is age-dependent in children with food allergy. *Pediatr Allergy Immunol* 2012;**23**:412–419.
16. DunnGalvin A, de BlokFlokstra BM, Burks AW, Dubois AE, Hourihane JO. Food allergy QoL questionnaire for children aged 0–12 years: content, construct, and cross-cultural validity. *Clin Exp Allergy* 2008;**38**:977–986.
17. Jaeschke R, Guyatt G. How to develop and validate a new quality of life instrument. In: Spilker B, editor. *Quality of Life Assessments in Clinical Trials*. New York: Raven Press; 1990: 47–57.
18. 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.
19. van der Velde JL, Flokstra-de Blok BMJ, Vlieg-Boerstra BJ, Oude Elberink JNG, Schouten JP, DunnGalvin A et al. Development, validity and reliability of the food allergy independent measure. *Allergy* 2010;**65**:630–635.
20. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, Hourihane JO et al. Development and validation of the self-administered Food Allergy Quality of Life Questionnaire for adolescents. *J Allergy Clin Immunol* 2008;**122**:139–144.
21. van der Velde JL, Flokstra-de Blok BM, Hamp A, Knibb RC, Duiverman EJ, Dubois AE. Adolescent-parent disagreement on health-related quality of life of food-allergic adolescents: who makes the difference? *Allergy* 2011;**66**:1580–1589.
22. Resnick ES, Pieretti MM, Maloney J, Noone S, Muñoz-Furlong A, Sicherer SH. Development of a questionnaire to measure quality of life in adolescents with food allergy: the FAQL-teen. *Ann Allergy Asthma Immunol* 2010;**105**:364–368.
23. Mackenzie H, Roberts G, Van Laar D, Dean T. A new quality of life scale for teenagers with food hypersensitivity. *Pediatr Allergy Immunol* 2012;**23**:404–411.
24. Goossens NJ, Flokstra-de Blok BM, Vlieg-Boerstra BJ, Duiverman EJ, Weiss CC, Furlong TJ et al. Online version of the food allergy quality of life questionnaire-adult form: validity, feasibility and cross-cultural comparison. *Clin Exp Allergy* 2011;**41**:574–581.
25. Flokstra-de Blok BM, van der Meulen GN, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ et al. Development and validation of the Food Allergy Quality of Life Questionnaire – Adult Form. *Allergy* 2009;**64**:1209–1217.
26. Springston EE, Smith B, Shulruff J, Pongracic J, Holl J, Gupta RS. Variations in quality of life among caregivers of food allergic children. *Ann Allergy Asthma Immunol* 2010;**105**:287–294.
27. Cummings AJ, Knibb RC, Erlewyn-Lajeunesse M, King RM, Roberts G, Lucas JS. Management of nut allergy influences quality of life and anxiety in children and their mothers. *Pediatr Allergy Immunol* 2010;**21**:586–594.
28. Leung TF, Yung E, Wong YS, Li CY, Wong GW. Quality-of-life assessment in Chinese families with food-allergic children. *Clin Exp Allergy* 2009;**39**:890–896.
29. Knibb RC, Stalker C. Validation of the Food Allergy Quality of Life-Parental Burden Questionnaire in the UK. *Qual Life Res* 2013;**22**:1841–1849.
30. DunnGalvin A, Cullinane C, Daly DA, Flokstra-de Blok BM, Dubois AE, Hourihane JO. 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.
31. Hamp A, Hourihane JO, Knibb RC, Dubois A, deBlok-Flokstra B, DunnGalvin A. Developmental specificity and sensitivity between 2 age appropriate health related quality of life measures in food allergic children and teenagers. *J Allergy Clin Immunol* 2008;**121**:S107.
32. Knibb RC, Ibrahim NF, Petley R, Cummings AJ, King RM, Roberts G et al. Validation of the Paediatric Food Allergy Quality of Life Questionnaire (PFA-QL). *Pediatr Allergy Immunol* 2013;**24**:288–292.
33. Franciosi JP, Hommel KA, Greenberg AB, Debrosse CW, Greenler AJ, Abonia JP et al. Development of the Pediatric Quality of Life Inventory™ Eosinophilic Esophagitis module items: qualitative methods. *BMC Gastroenterol* 2012;**12**:135.
34. van der Velde JL, Flokstra-de Blok BM, de Groot H, Oude-Elberink JN, Kerkhof M, Duiverman EJ 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.

ONLINE SUPPLEMENT

Long title: Disease-specific health-related quality of life (HRQL) instruments for IgE-mediated food allergy

Short title: Quality of life instruments for food allergy

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Appendix 1: Search strategies

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
<1946 to Present>

Search Strategy:

1	exp Food Hypersensitivity/
2	food allerg*.mp.
3	food hypersensitivity.mp.
4	food hypersensitivities.mp.
5	allergy, food.mp.
6	or/1-5
7	(rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine or animal?).ti.
8	(animal\$ not human\$).sh,hw.
9	7 or 8
10	6 not 9
11	Quality of Life/
12	QOL.ti,ab.
13	Health Status/
14	Health Status Indicators/
15	Activities of Daily Living/
16	Quality-Adjusted Life Years/
17	(quality adj4 life).ti,ab.
18	(well adj4 being).ti,ab.
19	HRQL.tw.
20	QALY\$.tw.
21	(Health\$ adj2 state).ti,ab.
22	(Life adj3 quality).ti,ab.
23	(Health\$ adj2 year\$ adj2 equivalent\$).ti,ab.
24	(subjective adj2 health adj2 status).ti,ab.
25	(Health Care)"/
26	(patient adj2 reported adj2 outcome adj2 measure\$).ti,ab. (530)
27	(patient adj2 outcome).ti,ab.
28	patient preference\$.ti,ab.
29	*Patient Participation/
30	*"Patient Acceptance of Health Care"/
31	consumer satisfaction.ti,ab.
32	*Patient Satisfaction/
33	*Questionnaires/
34	*Health Surveys/
35	tool\$.ti,ab.
36	*Psychometrics/
37	Utilit\$.ti,ab.
38	Short form 36.mp.
39	Short form 12.mp.
40	(SF 12 or SF 36 or SF-12 or SF-36).ti,ab.

41	Euroqol.mp.
42	EQ-5D.tw.
43	Health Utilities Index.mp.
44	HUI.mp.
45	Medical Outcomes Survey.mp.
46	MOS.tw.
47	QWB.tw.
48	Rosser.mp.
49	*"Reproducibility of Results"/
50	valid\$.ti,ab.
51	reliab\$.tw.
52	(effect adj1 size).ti,ab.
53	(Sensitiv\$ adj2 change).tw.
54	Reproduc\$.ti,ab.
55	Utility measure\$.ti,ab.
56	or/11-55
57	10 and 56

Database: Embase <1980 to 2012 Week 32>

Search Strategy:

1	exp Food Hypersensitivity/
2	food allerg*.mp.
3	food hypersensitivity.mp.
4	food hypersensitivities.mp.
5	allergy, food.mp.
6	or/1-5 (21168)
7	(rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine or animal?).ti. (1586460)
8	(animal\$ not human\$).sh,hw.
9	7 or 8
10	6 not 9
11	Quality of Life/
12	QOL.ti,ab.
13	Health Status/
14	Health Status Indicators/
15	Activities of Daily Living/
16	Quality-Adjusted Life Years/
17	(quality adj4 life).ti,ab.
18	(well adj4 being).ti,ab.
19	HRQL.tw.
20	QALY\$.tw.
21	(Health\$ adj2 state).ti,ab.
22	(Life adj3 quality).ti,ab.
23	(Health\$ adj2 year\$ adj2 equivalent\$).ti,ab.

24	(subjective adj2 health adj2 status).ti,ab.
25	*"Outcome Assessment (Health Care)"/
26	(patient adj2 reported adj2 outcome adj2 measure\$).ti,ab.
27	(patient adj2 outcome).ti,ab.
28	patient preference\$.ti,ab.
29	*Patient Participation/
30	*"Patient Acceptance of Health Care"/
31	consumer satisfaction.ti,ab.
32	*Patient Satisfaction/
33	or/11-32
34	*Questionnaires/
35	*Health Surveys/
36	tool\$.ti,ab.
37	*Psychometrics/
38	Utilit\$.ti,ab.
39	Short form 36.mp.
40	Short form 12.mp.
41	(SF 12 or SF 36 or SF-12 or SF-36).ti,ab.
42	Euroqol.mp.
43	EQ-5D.tw.
44	Health Utilities Index.mp.
45	HUI.mp.
46	Medical Outcomes Survey.mp.
47	MOS.tw.
48	QWB.tw.
49	Rosser.mp.
50	*"Reproducibility of Results"/
51	valid\$.ti,ab.
52	reliab\$.tw.
53	(effect adj1 size).ti,ab.
54	(Sensitiv\$ adj2 change).tw.
55	Reproduc\$.ti,ab.
56	Utility measure\$.ti,ab.
57	or/34-56
58	33 and 57
59	10 and 58
60	limit 59 to yr="1990 - 2012"

Database: CINAHL – Ebscohost

Search strategy:

S24	S10 and S23
S23	S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20
S20	(MH "Short Form-36 Health Survey (SF-36)") OR "(SF 12 or SF 36 or SF-12 or SF-36)"
S19	"EQ-5D"

S18	"Euroqol"
S17	"patient preferences"
S16	(MH "Health Status Indicators") OR (MH "Health Status")
S15	(MH "Quality-Adjusted Life Years")
S14	"patient reported outcomes"
S13	"proms"
S12	(MH "Outcomes (Health Care)") OR (MH "Outcome Assessment")
S11	(MH "Quality of Life")
S10	S1 or S8
S9	S1 or S8
S8	S6 and S7
S7	S4 or S5
S6	S2 or S3
S5	AB allergy or allergic or hypersensitive or hypersensitivity or sensitive or sensitivity or intolerant or intolerance or reaction
S4	TI allergy or allergic or hypersensitive or hypersensitivity or sensitive or sensitivity or intolerant or intolerance or reaction
S3	AB food or nutrient
S2	TI food or nutrient
S1	(MM "Food Hypersensitivity")

Database: ISI Web of Science: Science Citation Index, Conference Proceedings Citation

Search strategy:

Topic=((food or nutrient) AND (allergy or allergic or hypersensitive or hypersensitivity or sensitive or sensitivity or intolerant or intolerance or reaction)) AND Topic=((PROMs or PROM or patient reported outcome measure* or questionnaire* or HRQL or QOL or HRQL of life or patient satisfaction or consumer satisfaction or patient preference or patient participation or "patient acceptance of healthcare" or patient outcome or patient based outcome or functional status or health status or subjective health status or health status indicator or health status assessment) AND (methodol* or psychometric* or validity or reliability or responsiveness or effect size or sensitivity to change or reproducibility or acceptability or utility measure*))

Timespan=All Years. Databases=CPCI-S.

Lemmatization=On

Appendix 2: Quality assessment tool for evaluation of patient reported outcome measures

Property	Definition	Quality Criteria*
Development of the instrument		
Pre-study hypothesis	The pre-study specification of the aim of the instrument and the intended population	✓✓ A clear description is provided of the aim of the instrument and the intended population ✓ Only one of the above ✗ Neither reported
Intended population	The extent to which the instrument has been studied in the intended population	✓✓ Intended population studied ✓ Partly studied only or sample size was small (less than 50 patients) ✗ Not studied in the intended population, only generic
Actual content area (face validity)	The extent to which the study checked for face validity <i>The extent to which the content meets the pre-study hypothesis specifications</i>	✓✓ A clear description is provided of how face validity was checked within the intended population. <i>Content as intended, and is relevant to the intended population</i> ✓ Some of the intended content areas missing ✗ Content area not relevant to intended population
Item identification	Selection of the items relevant to the target population for inclusion in the pilot instrument	✓✓ Comprehensive consulting with patients, (focus groups or in-depth interviews), experts and a literature review. ✓ Minimal consultation with patients and experts opinion and literature review ✗ No consultation with patients
Item selection	Determining the items included in the final instrument	✓✓ A pilot instrument was developed and tested with Rasch or factor analysis or clinical impact and statistical justification provided for removing items, plus items with floor and ceiling effects removed and the amount of missing data considered. ✓ Only some of above techniques were used ✗ No pilot instrument OR no statistical justification of items included in the final instrument
Unidimensionality	Demonstration that all the items fit with a single underlying construct	✓✓ Rasch analysis using fit statistics (0.7-1.3) or item-trait interaction or Factor analysis on Rasch scores (1 st factor loadings >0.4 for all items) or item scores ✓ Rasch fit statistic mostly within 0.7-1.3 range but some less well fitting items retained, or Cronbach's α >0.7, and <0.9 or factor analysis on raw scores (1 st factor loadings >0.4 for all items)

		X Rasch analysis does not support unidimensionality or Factor analysis does not support unidimensionality or Cronbach's α <0.7, or >0.9 OR No checks for unidimensionality reported
Response scale	Categories used to rate the items	✓✓ Response scale identified with a to/from range, any comments about missing data in the scales development ✓ Some, but not all of above X Response scale not identified
Scoring	A description of how the instrument should be scored	✓✓ Rasch scoring or summary scoring of a statistically justified response scale ✓ Summary score of a statistically justified response scale X Scoring system not described or scoring of a statistically unjustified or faulty scale
Instrument translated and validated in English speaking population	The extent to which the instrument has been translated and validated in English speaking population	✓✓ Instrument developed in English or translated into English and validated in English speaking population ✓ Instrument translated to English but not validated in English speaking population X Instrument has not been translated to English nor validated in English speaking population
Performance of the instrument		
Validity		
Convergent validity	Amount of correlation with a related measure	✓✓ Tested against appropriate measure, correlates between 0.3 and 0.9 ✓ Debatable choice of measure, but correlation between 0.3 and 0.9 X Tested and correlates <0.3 or >0.9
Discriminant validity	The degree to which an instrument is not similar to (diverges from) other instruments that it should not be similar to	✓✓ Tested against appropriate measure, correlates <0.3 ✓ Debatable choice of measure, but correlation <0.3 X Tested and correlates >0.3
Predictive validity	The extent to which the instrument can predict a future event	✓✓ Tested against appropriate measure, correlates >0.3 or significant difference between groups ✓ Debatable choice of measure, but correlation >0.3 or significant difference between groups X Tested and correlates <0.3 or non-significant difference between groups

Other evidence for construct validity e.g. criterion, discriminant	Any other hypothesis driven testing	✓✓ Hypothesis stated, tested and proven
		✓ Construct validity claimed but debatable under scrutiny
		✗ Construct validity claimed but does not hold up to scrutiny
Test-retest agreement	The extent to which the results are repeatable when taken by the same observer or same person if self-report	✓✓ Bland Altman plot LOA appear tight and less than MID, or weighted Kappa or ICC ≥ 0.8
		✓ LOA broader but still close to MID, or weighted Kappa or ICC 0.60 to 0.79, or correlation ≥ 0.7
		✗ LOA $\gg$ MID, weighted Kappa or ICC < 0.60 or incorrect statistical test or inadequate sample (< 30 subjects)
Interobserver agreement/intermode agreement	The extent to which the results are repeatable between observers/the extent to which the results are repeatable between modes of administration	✓✓ LOA appear tight and less than MID, or weighted Kappa or ICC ≥ 0.70
		✓ LOA broader but still close to MID, or weighted Kappa or ICC 0.50 to 0.69
		✗ LOA $\gg$ MID, weighted Kappa or ICC < 0.50 or incorrect statistical test or inadequate sample (< 30 subjects)
Person or item separation reliability	A Rasch analysis indication of reliability – the proportion of true variance in the observed variance	✓✓ Reliability of ≥ 0.8 for both person and item separation or a G value or separation ratio > 2
		✓ Only one of person or item separation of ≥ 0.8 , or a G value or separation ratio > 2
		✗ Person or item separation of < 0.8 , or a G value or separation ratio < 2
		0 Not reported (not a Rasch scaled measure)
Interpretation	The extent to which score differences are meaningful	✓✓ Normative data (Mean scores and SD) and MID given for a representative target population, and test population demographic reported
		✓ MID or normative data or demographic details of study populations, or ad hoc population
		✗ No normative data and no MID
Responsiveness	The extent to which the instrument can detect clinically important changes over time	✓✓ Score changes $> \text{MID}$ for measures of progression over time or changes with intervention. Effect size or responsiveness statistic given
		✓ Changes over time but relationship to MID not reported, small sample, and inadequate time frame
		✗ Score changes $\leq \text{MID}$

✓✓ Positive rating; ✓ Minimal acceptable rating; ✗ Negative rating.

MID – minimal important difference; LOA – limits of agreement; ICC – intra-class coefficient; SD – standard deviation.

Adapted from Pesudovs et al, 2007.

Appendix 3: Excluded studies

1. Kulthanan K, Chiawsirikajorn Y, Jiamton S. Acute urticaria: Etiologies, clinical course and quality of life. *Asian Pacific Journal of Allergy & Immunology* 2008;26(1):1-9.
2. Avery NJ, King RM, Knight S, Hourihane JOB. Assessment of quality of life in children with peanut allergy. *Pediatric Allergy & Immunology* 2003;14(5):378-82.
3. Van Der Velde JL, Flokstra-De Blok BMJ, Vlieg-Boerstra BJ, Oude Elberink JNG, Dunngalvin A, Hourihane JO, et al. Development, validity and reliability of the food allergy independent measure (faim). *Allergy: European Journal of Allergy and Clinical Immunology* 2010;65(5):630-5.
4. Valentine AZ, Knibb RC. Exploring quality of life in families of children living with and without a severe food allergy. *Appetite* 2011;57(2):467-74.
5. Marklund B, Ahlstedt S, Nordstrom G. Health-related quality of life among adolescents with allergy-like conditions - with emphasis on food hypersensitivity. *Health and Quality of Life Outcomes* 2004;2(65).
6. Marklund B, Ahlstedt S, Nordstrom G. Health-related quality of life in food hypersensitive schoolchildren and their families: Parents' perceptions. *Health & Quality of Life Outcomes* 2006;4:48.
7. Flokstra-de Blok BMJ, Dubois AEJ, Vlieg-Boerstra BJ, Oude Elberink JNG, Raat H, DunnGalvin A, et al. Health-related quality of life of food allergic patients: Comparison with the general population and other diseases. *Allergy* 2010;65(2):238-44.
8. Sicherer SH, Noone SA, Munoz-Furlong A. The impact of childhood food allergy on quality of life. *Annals of Allergy, Asthma and Immunology* 2001;87(6):461-64.
9. Ostblom E, Egmar AC, 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.
10. King RM, Knibb RC, Hourihane JOB. Impact of peanut allergy on quality of life, stress and anxiety in the family. *Allergy* 2009;64(3):461-8.
11. Roy KM, Roberts MC. Peanut allergy in children: Relationships to health-related quality of life, anxiety, and parental stress. *Clinical Pediatrics* 2011;50(11):1045-51.
12. Primeau MN, Kagan R, Joseph L, Lim H, Dufresne C, Duffy C, et al. The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children. *Clinical & Experimental Allergy* 2000;30(8):1135-43.
13. Knibb RC, Armstrong A, Booth DA, Platts RG, Booth IW, MacDonald A. Psychological characteristics of people with perceived food intolerance in a community sample. *Journal of Psychosomatic Research* 1999;47(6):545-54.
14. Knibb RC, Ibrahim NF, Stiefel G, Petley R, Cummings AJ, King RM, et al. The psychological impact of diagnostic food challenges to confirm the resolution of peanut or tree nut allergy. *Clinical and Experimental Allergy* 2012;42(3):451-9.

15. Kiotseridis H, Cilio CM, Bjermer L, Aurivillius M, Jacobsson H, Tunsater A. Swedish translation and validation of the pediatric allergic disease quality of life questionnaire (padqlq). *Acta Paediatrica, International Journal of Paediatrics* 2011;100(2):242-7.
16. Mo F, Choi BC, Li FC, Merrick J. Using health utility index (hui) for measuring the impact on health-related quality of life (hrql) among individuals with chronic diseases. *The Scientific World Journal* 2004;4:746-57.
17. Chen YM, He LP, Mai JC, Hao YT, Xiong LH, Chen WQ, et al. Validity and reliability of pediatric quality of life inventory version 4.0 generic core scales in Chinese children and adolescents. [chinese]. *Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi* 2008;29(6):560-3.
18. Marklund B, Wilde-Larsson B, Ahlstedt S, Nordstrom G. Adolescents' experiences of being food-hypersensitive: A qualitative study. *BMC Nursing* 2007;6:8.
19. Vally H, de Klerk N, Thompson PJ. Asthma induced by alcoholic drinks: A new food allergy questionnaire. *Australian & New Zealand Journal of Public Health* 1999;23(6):590-4.
20. Sivaraj H, Rajakulendran M, Lee BW, Shek L. Challenges faced by expatriate children with food allergy in an asian country. *Annals of Allergy, Asthma, & Immunology* 2010;105(4):323-4.
21. Lebovidge JS, Stone KD, Twarog FJ, Raiselis SW, Kalish LA, Bailey EP, et al. Development of a preliminary questionnaire to assess parental response to children's food allergies. *Annals of Allergy, Asthma, & Immunology* 2006;96(3):472-7.
22. Factor JM, Lester MR, Mendelson LM, Lee JO, Sproviero J, Nouman G. The effects of peanut oral immunotherapy on food allergy related quality of life. *Journal of Allergy and Clinical Immunology* 2012;1:AB29.
23. Gupta RS, Kim JS, Barnathan JA, Amsden LB, Tummala LS, Holl JL. Food allergy knowledge, attitudes and beliefs: Focus groups of parents, physicians and the general public. *BMC Pediatrics* 2008;8:36.
24. Gupta RS, Springston EE, Smith B, Kim JS, Pongracic JA, Wang X, et al. Food allergy knowledge, attitudes, and beliefs of parents with food-allergic children in the united states. *Pediatric Allergy and Immunology* 2010;21(6):927-34.
25. Hourihane JOB, Flokstra-DeBlok BMJ, Dubois AEJ, Kahlon R, DunnGalvin A. Food challenge has a rapidly established and persistent positive effect on quality of life of children 0-12 years irrespective of the clinical outcome of the challenge. *Journal of Allergy and Clinical Immunology* 2009;1:S143.
26. Bollinger ME, Dahlquist LM, Mudd K, Sonntag C, Dillinger L, McKenna K. The impact of food allergy on the daily activities of children and their families. *Annals of Allergy, Asthma, & Immunology* 2006;96(3):415-21.
27. Mills C. Improved quality of life to food allergic consumers. *Molecular Nutrition & Food Research* 2007;51(1):148-9.

28. Flokstra-de Blok BMJ, Oude Elberink JNG, Vlieg-Boerstra BJ, Duiverman EJ, Dubois AEJ. Measuring health-related quality of life: Fundamental methodological issues. *Clinical & Experimental Allergy* 2009;39(11):1774; author reply 175.
29. Ravid NL, Annunziato RA, Ambrose MA, Chuang K, Mullarkey C, Sicherer SH, et al. Mental health and quality-of-life concerns related to the burden of food allergy. *Immunology & Allergy Clinics of North America* 2012;32(1):83-95.
30. Ganemo A, Svensson A, Lindberg M, Wahlgren CF. Quality of life in swedish children with eczema. *Acta Dermato-Venereologica* 2007;87(4):345-49.
31. Flokstra-de Blok BMJ, Dubois AEJ. Quality of life measures for food allergy. *Clinical & Experimental Allergy* 2012;42(7):1014-20.
32. Baptist AP, Dever SI, Greenhawt MJ, Polmear-Swendris N, McMorris MS, Clark NM. A self-regulation intervention can improve quality of life for families with food allergy. *Journal of Allergy & Clinical Immunology* 2012;130(1):263-5.e6.
33. Van Der Velde J, Flokstra-de Blok B, Vlieg-Boerstra B, Oude Elberink J, Duiverman E, Dubois A. Should previous responses be shown to study objects; a comparison of informed versus blind administration of the food allergy quality of life questionnaire-adult form (faqlq-af). *Journal of Allergy and Clinical Immunology* 2010;125(2):AB169.
34. Elberink JNGO. Significance and rationale of studies of health-related quality of life in anaphylactic disorders. *Current Opinion in Allergy and Clinical Immunology* 2006;6(4):298-302.
35. Dorner T, Muller KH, Schmidl H, Freidl W, Stronegger WJ, Lawrence K, et al. Subjective health and impaired quality of life due to allergies in a representative population survey. *Wiener Medizinische Wochenschrift* 2007;157(11-12):243-7.