

Food Allergy and Quality of Life: What Have We Learned?

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Abstract Health-related quality of life (HRQL) has become an emerging focus of interest in food allergy. Food allergy is a disease characterized by low mortality and symptoms which only occur during an allergic reaction. However, food-allergic patients continuously need to be alert when eating in order to prevent potentially severe allergic reactions, which may be fatal. Fear of such reactions and the need to be continuously vigilant may seriously compromise their HRQL. During the last decade, numerous studies have been published on food allergy and HRQL. The development of reliable, valid and responsive instruments for measuring HRQL in food allergic patients has facilitated this research even further. Such instruments have given insight into the specific problems a patient may face and the impact of food allergy-related interventions from the patient's perspective. This paper focuses on the most significant findings regarding this topic since its first appearance in the literature in 2000.

Keywords Food allergy · Health-related quality of life · HRQL · Interventions

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Abbreviations

DBPCFC	Double-blind placebo-controlled food challenge
FAIM	Food Allergy Independent Measure Questionnaire
FAIS	Food Allergy Impact Scale
FAP-Q	Food Allergy Parent-Questionnaire
FAQLQ-CF -TF, -AF, -PF & -PFT	Food Allergy Quality of Life Questionnaire-Child Form, -Teenager Form, -Adult Form, -Parent Form (0–12 years), and -Parent Form Teenagers (13–17 years)
FAQL-PB	Food Allergy Quality of Life–Parental Burden Questionnaire
FAQL-Teen	Food Allergy Quality of Life Questionnaire for Teenagers
FLIP	Food Hypersensitivity Family Impact Questionnaire
HRQL	Health-related quality of life
MID	Minimal important difference
PFA-QL	Pediatric Food Allergy–Quality of Life questionnaire
QoL	Quality of Life

Introduction

The prevalence of food allergy is increasing [1], but the burden of living with food allergy is commonly underestimated [2•]. Although food-allergic patients only experience symptoms during an allergic reaction, such reactions may be severe or even fatal [3]. The continuous need to be alert when eating in order to prevent potentially severe allergic reactions [4, 5] and

the fear of such reactions [6] has been shown to negatively impact daily life. As food plays an important and social role, food allergy may affect several social activities [7, 8]. Instruments measuring HRQL of food-allergic patients [4, 5, 9–11, 12•] are capable of providing insight into the specific problems a patient may face in daily life and also into the impact of interventions from the patient's perspective. Consequently, HRQL instruments may inform traditional management, which focuses mainly on avoidance of culprit foods and self-management of anaphylaxis. The development and validation of HRQL instruments [4, 5, 9–11, 12•] has facilitated research in this area in recent years. This paper gives an overview of the most important studies on HRQL of food allergic patients since the first studies in 2000.

Definition of Health-related Quality of Life

Quality of life (QoL) is a broadly defined concept and has been defined by the WHO as “the individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” [13] (Fig. 1 [14]). The component of quality of life that pertains to an individual's health is called health-related quality of life (HRQL) and consists of a patient's physical, mental and social well-being. HRQL thus denotes the way patients feel about their health.

Importance of Measuring HRQL in Food Allergy

HRQL is gaining more importance as outcome measure in clinical trials for food allergy [15]. As the technical development of new medical interventions is growing rapidly, instruments are needed which are able to evaluate the gain of these new medical interventions for patients. HRQL instruments can be used for studying the impact of such new interventions from the patient's perspective. Additionally, HRQL instruments may

be used by clinicians to obtain insight into the impact of several aspects of food allergy from the patient's perspective in order to help them cope with their food allergy. HRQL may be of special interest in food allergy, because traditional outcome measures reflecting disease severity (symptom scores, mortality) are inappropriate for food allergy, as the disease is characterized by low mortality and an almost continual absence of symptoms.

Methods for Measuring HRQL in Food Allergy

HRQL can be measured using qualitative or quantitative methods [15]. Qualitative methods are used to discover underlying meanings and patterns of HRQL and to formulate hypotheses. Quantitative methods can be used to support such hypotheses and to provide more precise outcomes regarding these hypotheses [15, 16] using specially designed and validated HRQL instruments. Thus, qualitative methods focus on exploring and understanding HRQL, whereas quantitative methods focus on a systematic and empirical investigation of HRQL.

In order to study HRQL in a quantitative way, two types of HRQL instruments can be used: generic and disease-specific HRQL instruments. Generic HRQL instruments are useful in evaluating and making comparisons between the impacts of different diseases on HRQL [17, 18]. Disease specific instruments are used to investigate HRQL problems related to a particular disease. As they are more sensitive in detecting small but potentially important differences in HRQL [17, 18], they are better suited as an outcome measure evaluating the impact of interventions for a particular disease [15]. The type of instrument that is selected for a clinical trial depends on the purpose of the study.

HRQL instruments can be completed by patients themselves (self-reports) or by external raters such as parents or health-care professionals (proxy-reports). As HRQL is concerned with an individual's perception, self-reports are the primary method of assessment in patients from the age of 8 years [19]. For children below 8 years, shortcomings of such self-reports have been reported [20]. However, proxy-reports are the only method to provide a substitute perspective on the patient's HRQL in patients who are unable to assess their own HRQL or to provide a complementary perspective to complete the view on the patient's HRQL [21, 22].

HRQL can thus be studied using a qualitative or quantitative approach, using generic or disease-specific HRQL instruments and using self-reports or proxy-reports.

Development of Valid and Reliable HRQL-instruments

Differences in development and validation of new HRQL instruments may result in differences between the content,

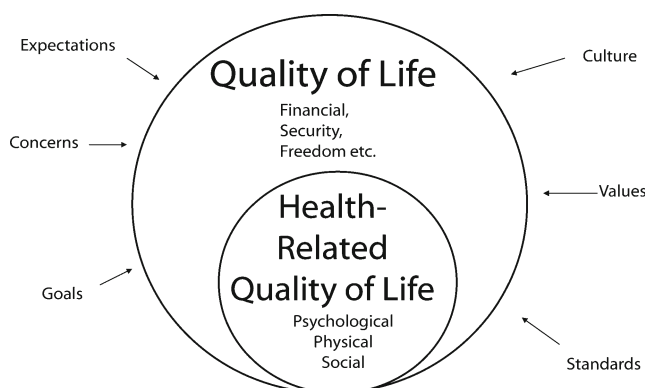


Fig. 1 The concept of quality of life. (From van der Velde [14])

psychometric properties, and outcome of HRQL instruments. In order to develop a suitable instrument for measuring HRQL in food-allergic patients, several steps need to be taken to ensure that the instrument is measuring what it is supposed to measure [23].

First, all potential items for the new questionnaires need to be assembled using different sources such as patient interviews, literature searches, and expert opinions (*phase 1 item generation*). As HRQL instruments evaluate patient's perceptions, it is important to include patients in this first phase.

Secondly, this long list with all potentially relevant items needs to be reduced to select the items that are considered most important by patients (*phase 2 item reduction*). The clinical impact method and factor analysis are common approaches to item reduction [24]. The clinical impact method measures the impact of each item as perceived by the patient by evaluating the proportion of patients experiencing an item as troublesome and the degree to which they find it troublesome. Only items with the highest impact scores are included in the final version of the instrument. Factor analysis is a mathematical approach to item reduction based on calculating inter-item correlations to determine which items best measure HRQL and to divide items into subscales. However, exclusive use of factor analysis lacks the patient's perception of the impact of specific items, which is a crucial element in developing HRQL instruments evaluating patient's perceptions. Different approaches to item reduction may thus result in different HRQL instruments.

Thirdly, it is important to determine to what degree it is likely that an instrument is measuring what it is intended to measure; i.e. to assess the validity of the instrument [25] and to assess whether the instrument is reproducible over time reflecting the reliability of the instrument [26] (*phase 3: cross-sectional validation*).

Fourthly, HRQL instruments that will be used as outcome measures must correlate over time with other relevant measures (longitudinal validity), and must be able to measure small but relevant HRQL changes over time (responsiveness) [27•]. The smallest change in HRQL that is considered to be clinically important by patients is called the minimal important difference (MID) [28]. The MID commonly reaches 0.5 in HRQL questionnaires using a seven-point scale [28, 29], but is currently unknown for HRQL instruments for venom allergy [30] and food allergy [4–6, 10, 11, 12•, 31•, 32]. It may be more difficult to calculate the MID for anaphylactic diseases compared to other diseases, because anaphylactic diseases are characterized by an almost continuous absence of symptoms, whereas food allergy has an on-going impact on HRQL. Consequently, HRQL scores may be poorly correlated with instruments needed to determine the MID (i.e. instruments measuring overall change in HRQL). Despite these challenges, the MID of the Food Allergy Quality of Life Questionnaires (FAQLQs) is currently under investigation (*phase 4: longitudinal validation*).

Finally, in order to use the instrument in different cultures and languages, accurate translation and cross-cultural validation should take place to check the performance of individual items in that language and culture using established WHO guidelines [33] (*phase 5: cross cultural validation*).

Disease-specific HRQL-instruments for Food Allergy

A number of HRQL instruments have been developed for food allergy in recent years [4–6, 8–11, 34, 35•]. Some HRQL instruments were developed to measure the patient's HRQL [4–6, 8–10, 32], others were developed to measure HRQL of the parents [11, 34] or family [35•]. There are large differences between the content, psychometric properties and outcome of these instruments. Therefore, it is important for researchers to carefully choose an HRQL instrument that best fits to the aim of their study. Table 1 gives an overview of all HRQL instruments for food allergy.

Cohen et al. developed the first disease-specific HRQL instrument for food allergy, the Food Allergy Quality of Life Parental Burden questionnaire (FAQL-PB) [11]. This instrument focuses on the parental burden of living with a child with food allergy (5–18 years) and has shown to be internally valid, reliable and responsive in the USA [2•, 11] and the UK [36, 37•].

Thereafter, five food allergy-related HRQL instruments were developed [4, 5, 9, 10, 38] to measure the patient's HRQL for several age-groups: the Food Allergy Quality of Life Questionnaires (FAQLQs). Three FAQLQs were developed to be completed by patients themselves (self-reports): a child-form (FAQLQ-CF, 8–12 years) [10], a teenager-form (FAQLQ-TF 13–17 years) [4], and an adult-form (FAQLQ-AF ≥18 years) [5]. Another two FAQLQs were developed to be completed by parents of food-allergic children to provide a proxy-report on the child's HRQL: a parent-form for children aged 0–12 years (FAQLQ-PF) [9] and a parent-form for teenagers aged 13–17 years (FAQLQ-PFT) [38, 39•]. The FAQLQ-CF, -TF, -AF, and -PF have shown good validity, reliability [4, 5, 9, 10, 26] and responsiveness [27•, 31•]. The FAQLQ-PFT is currently being validated.

Recently, two more instruments were developed to assess HRQL of food-allergic teenagers in the UK [12•] and USA [32]: the You and Your Food Allergy Scale [12•] and the FAQL-Teen [32]. Additionally, the Food Hypersensitivity Family Impact Questionnaire (FLIP) was recently developed for parents of food allergic (especially cow's milk) children (0.5–7 years) to measure HRQL of the family [35•]. This instrument has shown good reliability and validity. However, data on the longitudinal validity and responsiveness of these new instruments are not available yet.

HRQL instruments that have been developed earlier have some limitations [6, 8, 34]. Either they did not include patients

Table 1 Health-related quality of life instruments for food allergy

Instrument	Whose HRQL	Administered by	No. of items	Method of development	Reliability - Internal (α) - External (ICC)	Validity - Internal - External
FAQL-PB [2•, 11, 36, 37••] Cohen et al. 2004, USA	Parents (0–17 years)	Parent	17	Item generation: - patient/parent interview - literature review Item reduction: - expert opinion - clinical impact method - factor analysis Item generation: - patient/parent interview - literature review - expert opinion Item generation: - patient/parent interview - literature review - expert opinion Item generation: - patient/parent interview - literature review - expert opinion	$\alpha=0.95$ ICC=0.93	Internal: inter-item correlations; factor analysis External: face, content, convergent/ discriminant, construct, responsiveness cross-cultural validity: UK
PFA-QL [6, 40•] Avery et al. 2003, UK	Patients (6–16 years)	Parent/Child	25	Item generation: - patient/parent interview - literature review - expert opinion Item generation: - patient/parent interview - literature review - expert opinion	$\alpha=0.77$ –0.82 ICC=0.77	Internal: n.p. External: face, content, convergent/ discriminant, discriminative abilities
FAIS [8] Bollinger et al. 2006, USA	Patients (0–18 years)	Parent	32	Item generation: - patient/parent interview - literature review - expert opinion Item generation: - patient/parent interview - literature review - expert opinion	$\alpha=0.68$ –0.94 ICC=n.p.	Internal: n.p. External: face, content
FAP-Q [34] LeBovidge et al. 2006, USA	Parents (0–18 years)	Parent	18	Item generation: - expert opinion Item generation: - patient/parent interview - literature review - expert opinion Item reduction: - clinical impact method - factor analysis	α 0.32–0.80 ICC=n.p.	Internal: factor analysis External: face, content
FAQLQ-PF [9, 31••, 48•] Dunngalvin et al. 2008 , Ireland	Patients (0–12 years)	Parent	30	Item generation: - patient/parent interview - literature review - expert opinion Item reduction: - clinical impact method - factor analysis	$\alpha=0.89$ –0.94 ICC=0.73–0.89	Internal: inter-item correlations, factor analysis, floor and ceiling effects External: face, content, convergent/ discriminant, construct (0.52–0.73), longitudinal (0.65–0.74), responsiveness, cross cultural validation: USA, Netherlands
FAQLQ-PFT [38, 39•] Knibb, Hamp et al. UK	Patients (13–18 years)	Parent	27	Item generation: - patient/parent interview - literature review - expert opinion Item reduction: - clinical impact method - factor analysis	$\alpha=0.94$ (Dutch version) ICC=n.p.	Internal: inter-item correlations, factor analysis External: Face, content, convergent/ discriminant validity , discriminative abilities, construct (rho=0.64, Dutch version), cross-cultural validity: Netherlands
FAQLQ-CF [10, 27••] Flokstra-de Blok et al. 2009, Netherlands	Patients (8–12 years)	Child	24	Item generation: - patient interview - literature review - expert opinion Item reduction: - clinical impact method - factor analysis	$\alpha=0.94$ ICC=0.91	Internal: inter-item correlations; factor analysis, floor and ceiling effects External: face, content, convergent/ discriminant, construct (0.60), longitudinal (0.51), responsiveness, cross cultural validation: in progress
FAQLQ-TF [4, 27••] Flokstra-de Blok, 2008, Netherlands	Patients (13–18 years)	Teenager	28	Item generation: - patient interview - literature review - expert opinion Item reduction: - clinical impact method - factor analysis	$\alpha=0.92$ ICC=0.98	Internal: inter-item correlations; factor analysis, floor and ceiling effects External: face, content, convergent/ discriminant, discriminative abilities construct (rho=0.57) longitudinal (rho=0.35), responsiveness, cross-cultural validity: in progress

Table 1 (continued)

Instrument	Whose HRQL	Administered by	No. of items	Method of development	Reliability - Internal (α) - External (ICC)	Validity - Internal - External
FAQLQ-AF [5, 27•, 57•] Flokstra-de Blok, 2009, Netherlands	Patients (≥ 18 years)	Adult	29	Item generation: - patient interview - literature review - expert opinion Item reduction: - clinical impact method - factor analysis	$\alpha=0.97$ ICC=0.95	Internal: inter-item correlations; factor analysis, floor and ceiling effects; External: face, content, convergent/ discriminant, construct ($\rho=0.76$) longitudinal ($\rho=0.71$), responsiveness, discriminative abilities, cross-cultural validity: USA
FAQL-teen [32] Resnick et al. 2010, USA	Patients (13–19 years)	Teenager	17	Item generation: - patient interview - literature review - expert opinion Item reduction: - clinical impact method	$\alpha=0.9$ ICC=n.p.	Internal: inter-item correlation; no factor analysis External: Face, content, convergent/ discriminant validity, discriminative abilities, construct
You and your food allergy scale [12•] Mackenzie et al. 2012, UK	Patients (13–18 years)	Teenager	34	Item generation: - patient interview - literature review - expert opinion Item reduction: - factor analysis	$\alpha=0.82$ ICC=0.87	Internal: inter-item correlation; factor analysis External: face, content, convergent/ discriminant, discriminative abilities, construct
FLIP [35•] Mikkelsen et al. 2013, Sweden	Family (0.5–7 years)	Parent	19	Item generation: - patient/parent interview Item reduction: - clinical impact method - factor analysis	$\alpha=0.90$ ICC=0.71	Internal: inter-item correlation; factor analysis External: face, content, convergent/ discriminant, discriminative abilities, construct

n.p. Not performed; *FAIS* Food Allergy Impact Scale; *FAP-Q* Food Allergy Parent-Questionnaire; *FAQLQ-CF*; *-TF*, *-AF*, *-PF* and *-PFT* Food Allergy Quality of Life Questionnaire-Child Form, -Teenager Form, -Adult Form, -Parent Form (0–12 years), and -Parent Form Teenagers (13–17 years); *FAQL-PB* Food Allergy Quality of Life-Parental Burden Questionnaire; *FAQL-Teen* Food Allergy Quality of Life Questionnaire for Teenagers; *FLIP* Food Hypersensitivity Family Impact Questionnaire; *PF4-QL* Pediatric Food Allergy-Quality of Life questionnaire

during the item generation [34] or item reduction [6] and/or they lacked validity and/or reliability [8, 34]. However, the Pediatric Food Allergy Quality of Life Questionnaire (PFA-QL) has recently been validated [6, 40•].

Aspects of Food Allergy Influencing HRQL

The first well-designed study on the impact of food allergy on HRQL was published in 2000 [41]. This study and other early studies showed that food allergy had a considerable impact on HRQL of patients and families in a variety of ways [6, 8, 11, 34, 41–45]; i.e. food allergy affected meal preparation, school attendance, familial activities, and social activities outside the home (sleepover, birthday parties, eating out, shopping) [6–8]. Consequently, if such activities are restricted, this may interfere with developing social skills in children and may sometimes even result in bullying [46]. Although the first studies on food allergy and HRQL revealed some relevant issues, these studies usually focused on parents instead of food-allergic children themselves [8, 11, 41–43]. No appropriate disease-specific HRQL instruments existed at that time for measuring HRQL in food-allergic patients as perceived by patients themselves.

Subsequent studies have made use of validated and disease-specific HRQL instruments completed by food-allergic patients themselves [4, 5, 10]. These studies showed that, particularly, the need for continuous vigilance when eating and dietary restrictions caused by food allergy severely impacted HRQL. Additionally, the change of ingredients of food products, incomplete food labels, fear of allergic reactions, and the need to carry an epinephrine auto-injector compromise HRQL.

Impact of Food Allergy on HRQL Compared to Other Diseases and the General Population

Comparing food allergy to other diseases, the early studies showed that parents of peanut-allergic children reported significantly more disruption in daily activities, familial problems, and social problems than parents of children with rheumatologic disease [41]. Additionally, peanut-allergic children reported poorer HRQL and more fear than children with insulin-dependent diabetes mellitus [6]. On the other hand, food-allergic patients showed less impairment in HRQL than patients with chronic liver disease or irritable bowel syndrome [44]. It was also shown that general health, parental distress and worry of parents of food-allergic children were worse than the general population [42]. However, these studies used HRQL scales that were not validated or measured only a single domain of HRQL. A more recent study used validated HRQL instruments and showed that food-allergic patients had poorer generic HRQL than patients with diabetes mellitus and

the general population, but better generic HRQL than patients with asthma, irritable bowel syndrome, and rheumatoid arthritis [47].

Differing Views on HRQL

Differences Between Parents and Their Food-allergic Children

A recent study showed that child–parent agreement between child–parent perceptions on the child’s HRQL was moderate (ICC=0.57), and that children (8–12 years) systematically reported a significantly greater impact of food allergy on their HRQL than their parents [48•]. In line with these results, a subsequent study on HRQL of food-allergic adolescents (13–17 years) also showed moderate adolescent–parent agreement (ICC=0.61). However, in the latter study, no systematic or significant difference between adolescent- and parent-reports on the adolescent’s HRQL was shown on a group level, but relevant differences appeared at the individual adolescent–parent pair level [39•]: i.e. a clinically important difference between the adolescent-report and parent-report on the adolescent’s HRQL was shown for 63 % of all adolescent–parent pairs. Thus, different forms of child–parent disagreement concerning the child’s HRQL were shown for children as well as adolescents.

Child–parent disagreement is often shown to be moderate [49]. Therefore, it is important for clinicians to include both the child’s and their parent’s perceptions in order to make a complete assessment of the impact of food allergy on the child’s HRQL. Studying both perspectives allows identification of areas that need special attention.

Differences Between Subgroups of Food-allergic Patients

A few studies were performed analyzing the psychosocial impact of food allergy in subgroups of food-allergic patients. Some subgroups that were associated with poorer HRQL of the child and/or the parent were those with associated atopic disease [42, 50], multiple food allergies [8, 34, 51], multiple food products that need to be avoided [42], female gender [43, 51, 52], siblings [50, 51] or a mother [51] with food allergy, and those with a prescription for an epinephrine auto-injector [53]. Additionally, younger age of the child was associated with greater parental anxiety and stress [34], but a better HRQL of the food-allergic children themselves [51]. The presence of parent-reported anaphylaxis was associated with greater anxiety levels, family impact [34], and poorer HRQL [51]. However, the opposite has also been shown [8]. Considering the patient’s perception of disease severity (measured by the Food Allergy Independent Measure, FAIM [54]), it was shown that a higher perceived disease severity was

associated with poorer HRQL [4, 5, 9, 10]. Although larger studies are needed, the psychosocial impact of food allergy is thus likely to differ among different food-allergic subgroups.

Differences Between Cultures

As some items generated and selected for a HRQL instrument in one culture may not always be considered important in other cultures, it is of crucial importance that HRQL instruments are accurately translated and cross-culturally validated in the new language and culture to prevent loss of sensitivity of the translated instruments [55, 56]. Some HRQL instruments have already been translated and validated in other countries [9, 48•, 57•]. For example, the Dutch FAQLQ-AF has successfully been translated and validated in several European countries (unpublished data) as well as the USA [57•]. Interestingly, American food-allergic adults reported a greater impact of food allergy on their HRQL than Dutch food-allergic adults. This may be partly explained by the fact that American adults were prescribed an epinephrine auto-injector more often than Dutch adults, which may negatively impact HRQL [57•]. Additionally, the Irish FAQLQ-PF has successfully been (translated and) validated in the USA [9] and the Netherlands [48•]. The American FAQLQ-PB has also been validated for the UK [36]. The translation and validation of the FAQLQ-CF and -TF are currently being undertaken. When this validation process has been finished, it would be interesting to compare HRQL of food-allergic children and teenagers across several countries.

Impact of Interventions on HRQL in Food-allergic Patients

Impact of Diagnostic Interventions on HRQL: Food Challenges

Although food allergy is usually over-diagnosed by patients [58], it may be under-diagnosed by physicians. Nevertheless, it has been shown that food allergy impairs HRQL regardless of whether or not the condition has been doctor-diagnosed [43]. This might be explained by the fact that a diagnostic test verifying food allergy does not accurately reflect the individual's perception of disease severity [43]. On the other hand, a diagnostic test ruling out food allergy may prevent unnecessary elimination diets and, consequently, may improve HRQL. Therefore, an accurate diagnosis of food allergy is very important.

A double-blind placebo-controlled food challenge (DBPCFC) is considered to be the gold standard for diagnosing food allergy. Although there has been discussion in the literature on the safety and time-consuming aspects of DBPCFCs, several studies have recently shown that

DBPCFCs can be safely performed [59] and that patients and their family benefit from a DBPCFC and its subsequent changes in management. These studies used parent- [31••, 37••, 60–63] and patient-reported outcomes [27••], and qualitative [60–62] as well as quantitative research methods [27••, 31••, 37••, 63].

Studies [31••, 37••, 60–63] on the *parent's perspective* of the impact of food challenges showed that the child's HRQL [31••] and the mother's HRQL [37••] significantly improved, that parental concerns [60] and anxiety [63] were reduced, and that most of the parents were satisfied [61] following a food challenge irrespective of the outcome. This may be explained by the fact that a definitive diagnosis provides a sense of certainty [31••, 60]. Uncertainty and lack of information have been shown to be more worrisome than fear of the challenge procedure [31••, 60]. In agreement with these studies, a more recent study on the *patient's perspective* of the impact of a DBPCFC showed that adults, adolescents, and children benefit from a DBPCFC and its subsequent changes in management, especially when the outcome is negative [27••]. The number needed to treat was shown to be 4 following a negative outcome of a DBPCFC. Thus, for every 4 participants who have a negative DBPCFC, 1 participant has a clinically important improvement in HRQL. Other studies describing the impact of interventions on HRQL of patients suffering from other allergic disorders showed NNTs ranging from 1.4 to 14 [64–67]: An NNT of 4 may thus be considered to reflect a clinically relevant intervention. Although a DBPCFC is already considered to be the gold standard for diagnosing food allergy, these results may provide clinicians with an additional reason to perform a DBPCFC in food-allergic patients from a HRQL point of view.

In addition to providing a sense of certainty following a food challenge, some other elements may influence the psychosocial impact of a food challenge [31••, 37••, 60–63]. Some of these elements may be targets for improving traditional management. Elements shown to negatively influence the parental perception of the child's food challenge were seeing their child fall ill following a positive outcome [61], continuing uncertainty following inconclusive outcome [61], fear of causing harm following reintroduction after a negative outcome [62], inadequate follow-up regardless the outcome [61], recent experience of an allergic reaction [63] or anaphylaxis [31••], having multiple food allergies [31••], and a high patient-perceived disease severity (measured by the FAIM) [31••]. Other elements positively influenced parental perceptions of their child's food challenge: clarification of the severity of the child's peanut allergy, support provided by staff and determining the child was tolerant for peanut, or assessed to be at low risk of anaphylaxis [61]. Although three studies used qualitative methods [60–62] and all studies used parent perceptions rather than patient perceptions, some of these elements may be targets for improving traditional management

from a HRQL point of view (i.e. support provided by staff or coping with fear following reintroduction after a negative food challenge).

Impact of Future Therapeutic Interventions on HRQL: Immunotherapy

Currently, the only available treatment for food allergy is strict avoidance of culprit foods [68]. Promising novel treatment strategies, such as oral immunotherapy, are currently under study. Immunotherapy involves administration of small amounts of native or modified allergens to induce immune tolerance [68]. Although immunotherapy has been proven to be successful in venom and respiratory allergies [67, 69, 70], additional studies are needed to determine side effects and (long-term) efficacy for immunotherapy in food allergy. A recent trial (and pilot study) showed that HRQL of peanut-allergic children and teenagers (5–18 years) [71••] (and cow milk-allergic children (3–12 years) [72]) had significantly improved following immunotherapy. These improvements in HRQL were measured by the FAQLQ-CF [71••], -TF [71••], and -PF [71••, 72]. Thus, immunotherapy seems to be a promising new therapy, also from a HRQL point of view.

Impact of Future Therapeutic Interventions on HRQL: Educational Programs

It has been shown that illness comprehension of food-allergic adolescents may be an important predictor of (dis)agreement on the adolescent's HRQL [39•]. Food allergy knowledge differs among parents of food-allergic children from different countries [73]. Education may therefore be an important target for intervention aimed at improving HRQL. Recently, a study has been published on the results of an educational intervention program for parents of food-allergic children based on the principals of self-regulation [2••]. Self-regulation aims at changing a patient's or parent's behavior and coping strategies through observational and active learning and focuses on engagement of patients and their families [74]. It was shown that HRQL of parents of food-allergic children (measured by the FAQL-PB) improved significantly following this educational program compared to parents of food-allergic children in the control group [2••]. Although further research is needed on educational programs in food allergy, these results are promising and illustrate the benefit of education in food allergy.

Conclusions

During the last decade, HRQL has gradually become an emerging focus of interest in food allergy and many interesting studies have been published on this topic. The recent development and validation of disease-specific HRQL instruments for studying

the impact of food allergy on HRQL has further facilitated such research. Several new insights on HRQL in food allergy have been discussed in this paper, and it is evident that food allergy has a profound impact on HRQL of food-allergic patients and their families.

From the earlier cross-sectional studies on HRQL in food allergy, we have learned that several aspects of food allergy influence HRQL of food-allergic patients. Particularly, the need to be continuously alert when eating and the dietary restrictions caused by food allergy severely impact HRQL. Additionally, the change of ingredients of food products, incomplete food labels on food products, fear of allergic reactions, and the need to carry an epinephrine auto-injector cause compromise of HRQL. Food allergy affects several social activities inside and outside the home. Subgroups that were associated with poorer HRQL of the child and/or the parent were those with associated atopic disease, severe systemic reactions, a higher perceived disease severity, siblings or a mother affected by allergies, multiple food allergies, poorer illness comprehension, and female gender. Finally, we learned that patients have differing views on their HRQL compared to patients in other cultures or compared to their parents.

Recently, a few longitudinal studies have been performed evaluating the impact of (future) interventions on HRQL in food-allergic patients. These interventions have shown to be beneficial from a HRQL point of view (DBPCFC/food challenge, oral immunotherapy in peanut-allergic children and teenagers, and an educational intervention based on self-regulation theory). These results may provide clinicians with an additional reason to perform a DBPCFC in food-allergic patients from a HRQL point of view. However, further studies are needed to evaluate the determinants of changes in HRQL following a DBPCFC, to determine long-term side effects and efficacy for immunotherapy, and to further evaluate the impact of other educational interventions for food allergy.

Although in the last decade several studies have been published that substantially contributed to the current knowledge regarding food allergy-related HRQL, there are still many unanswered research questions that need further investigation. As mentioned, it would be interesting to compare HRQL of food-allergic children and teenagers across several countries and to compare these results to previously published results in adults and parents of food-allergic children. Secondly, future research might focus on the suitability of HRQL instruments for monitoring individual patients. Although several HRQL instruments have shown to be suitable tools for group comparison studies, limited data are available on the suitability of these instruments for monitoring individual patients. Finally, it would be interesting to identify whether HRQL instruments and economic instruments can be used to assess Quality Adjusted Life years in order to evaluate the amount of health years gained by (future) interventions for food allergy.

Compliance with Ethics Guidelines

Conflict of Interest Jantina L. van der Velde, Anthony E.J. Dubois, and Bertine M.J. Flokstra-de Blok declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with animal subjects performed by any of the authors. With regard to the authors' research cited in this paper, all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Sicherer SH, Munoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol*. 2010;125:1322–6.
2. •• 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. *J Allergy Clin Immunol*. 2012;130:263–5.e6. *This study illustrates that an educational program for food allergy based on the principles of self regulation improves quality of life for parents of children with food allergy.*
3. Boden SR, Wesley Burks A. Anaphylaxis: a history with emphasis on food allergy. *Immunol Rev*. 2011;242:247–57.
4. 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;122:139–44. 144.e1–2.
5. 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;64:1209–17.
6. Avery NJ, King RM, Knight S, Hourihane JO. Assessment of quality of life in children with peanut allergy. *Pediatr Allergy Immunol*. 2003;14:378–82.
7. Cummings AJ, Knibb RC, King RM, Lucas JS. The psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families: a review. *Allergy*. 2010;65:933–45.
8. 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. *Ann Allergy Asthma Immunol*. 2006;96:415–21.
9. 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;38:977–86.
10. 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;39:127–37.
11. Cohen BL, Noone S, Munoz-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;114:1159–63.
12. • Mackenzie H, Roberts G, Van Laar D, Dean T. A new quality of life scale for teenagers with food hypersensitivity. *Pediatr Allergy Immunol*. 2012;23:404–11. *This study describes the development and evaluation of a new HRQL instrument for food-allergic adolescents in the UK (the "You and Your Food Allergy Scale").*
13. World Health Organisation. Constitution of the World Health Organisation. Handbook of Basic Documents. Geneva; 1948. pp. 3–20.
14. van der Velde JL. Chapter 1: general introduction. Figure 1. Thesis: Quality of life of food allergic patients. Ridderkerk; 2012. pp. 14.
15. Flokstra-de Blok BM, Dubois AE. Quality of life measures for food allergy. *Clin Exp Allergy*. 2012;42:1014–20.
16. Casebeer AL, Verhoef MJ. Combining qualitative and quantitative research methods: considering the possibilities for enhancing the study of chronic diseases. *Chronic Dis Can*. 1997;18:130–5.
17. Fayers PM, Machin D. Quality of life : the assessment, analysis and interpretation of patient-reported outcomes. 2nd ed. Wiley: Chichester etc.; 2007.
18. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. *Ann Intern Med*. 1993;118:622–9.
19. Riley AW. Evidence that school-age children can self-report on their health. *Ambul Pediatr*. 2004;4:371–6.
20. Cremeens J, Eiser C, Blades M. Characteristics of health-related self-report measures for children aged three to eight years: a review of the literature. *Qual Life Res*. 2006;15:739–54.
21. Connolly MA, Johnson JA. Measuring quality of life in paediatric patients. *Pharmacoeconomics*. 1999;16:605–25.
22. Smith H. Differing views of children and parents: some cautionary tales! *Clin Exp Allergy*. 2011;41:1344–5.
23. Juniper EF, Guyatt GH, Jaeschke R. How to develop and validate a new health-related quality of life instrument. In: Anonymous Spilker B, editor. Quality of life and pharmacoeconomics in clinical trials. Philadelphia: Lippincott-Raven Publishers; 1996. p. 49–56.
24. Juniper EF, Guyatt GH, Streiner DL, King DR. Clinical impact versus factor analysis for quality of life questionnaire construction. *J Clin Epidemiol*. 1997;50:233–8.
25. Testa MA, Simonson DC. Assessment of quality-of-life outcomes. *N Engl J Med*. 1996;334:835–40.
26. 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;18:245–51.
27. •• 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.e2. *This study supports the responsiveness and longitudinal validity of the FAQLQ-CF, -TF and -AF. Additionally, this study illustrates the impact of a DBPCFC from the patient's perspective.*
28. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. *J Clin Epidemiol*. 1994;47:81–7.
29. Deyo RA, Diehr P, Patrick DL. Reproducibility and responsiveness of health status measures. Statistics and strategies for evaluation. *Control Clin Trials*. 1991;12:142S–58S.
30. Oude Elberink JN, de Monchy JG, Golden DB, Brouwer JL, Guyatt GH, Dubois AE. Development and validation of a health-related quality-of-life questionnaire in patients with yellow jacket allergy. *J Allergy Clin Immunol*. 2002;109:162–70.
31. •• 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;40:476–85. *This study supports the responsiveness and validity of the FAQLQ-PF and illustrates that parent-*

- reported HRQL of food-allergic children (0–12 years) improves following a food challenge.
32. Resnick ES, Pieretti MM, Maloney J, Noone S, Munoz-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;105:364–8.
 33. World Health Organization. Process of translation and adaptation of instruments. http://www.who.int/substance_abuse/research_tools/translation/en/. In: 2008.
 34. 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. *Ann Allergy Asthma Immunol.* 2006;96:472–7.
 35. • Mikkelsen A, Borres MP, Bjorkelund C, Lissner L, Oxelmark L. The Food hypersensitivity famiLy ImPact (FLIP) questionnaire - development and first results. *Pediatr Allergy Immunol.* 2013;24: 574–81. *This study describes the development and first results on the validity of the newest HRQL instrument for food allergy, the food hypersensitivity family impact questionnaire (FLIP).*
 36. Knibb RC, Stalker C. Validation of the Food Allergy Quality of Life-Parental Burden Questionnaire in the UK. *Qual Life Res.* 2013;22: 1841–9.
 37. •• 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. *Clin Exp Allergy.* 2012;42:451–9. *This study supports the responsiveness of the FAQL-PB. Additionally, this study illustrates the positive impact of a food challenge on HRQL of mothers of food-allergic children.*
 38. Hamp N, Hourihane J, Knibb RC, Dubois AEJ, Flokstra-de Blok BMJ, DunnGalvin A. Developmental specificity and sensitivity between two age appropriate Health-Related Quality of Life measures in food allergic children and teenagers. *J Allergy Clin Immunol.* 2008;121:S107.
 39. • 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;66:1580–9. *This study illustrates that there is disagreement between parent and adolescent reports on the HRQL of food-allergic adolescents.*
 40. • 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;24:288–92. *This study describes the cross-sectional validity and internal reliability of the previously developed PFA-QL, an instrument to measure parent- and child-reported HRQL of food-allergic children.*
 41. 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. *Clin Exp Allergy.* 2000;30:1135–43.
 42. Sicherer SH, Noone SA, Munoz-Furlong A. The impact of childhood food allergy on quality of life. *Ann Allergy Asthma Immunol.* 2001;87:461–4.
 43. Marklund B, Ahlstedt S, Nordstrom G. Health-related quality of life among adolescents with allergy-like conditions - with emphasis on food hypersensitivity. *Health Qual Life Outcomes.* 2004;2:65.
 44. Calsbeek H, Rijken M, Bekkers MJ, Kerssens JJ, Dekker J, van Berge Henegouwen GP. Social position of adolescents with chronic digestive disorders. *Eur J Gastroenterol Hepatol.* 2002;14:543–9.
 45. Teufel M, Biedermann T, Rapps N, Hausteiner C, Henningsen P, Enck P, et al. Psychological burden of food allergy. *World J Gastroenterol.* 2007;13:3456–65.
 46. Lieberman JA, Weiss C, Furlong TJ, Sicherer M, Sicherer SH. Bullying among pediatric patients with food allergy. *Ann Allergy Asthma Immunol.* 2010;105:282–6.
 47. Flokstra-de Blok BM, van der Velde JL, Vlieg-Boerstra BJ, Oude Elberink JN, DunnGalvin A, Hourihane JO, Duiverman EJ, Dubois AE. Health-related quality of life of food allergic patients measured with generic and disease-specific questionnaires. *Allergy.* 2010;65:1031–8.
 48. • 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;41:1431–39. *This study illustrates that parents of food-allergic children aged 8–12 years report better HRQL for their food-allergic children than children themselves.*
 49. Buyan N, Turkmen MA, Bilge I, Baskin E, Haberal M, Bilginer Y, et al. Quality of life in children with chronic kidney disease (with child and parent assessments). *Pediatr Nephrol.* 2010;25:1487–96.
 50. Marklund B, Ahlstedt S, Nordstrom G. Health-related quality of life in food hypersensitive schoolchildren and their families: parents' perceptions. *Health Qual Life Outcomes.* 2006;4:48.
 51. Wassenberg J, Cochard MM, DunnGalvin A, Ballabeni P, Flokstra-de Blok BM, Newman CJ, Hofer M, Eigenmann PA. Parent perceived quality of life is age-dependent in children with food allergy. *Pediatr Allergy Immunol.* 2012;23:412–9.
 52. DunnGalvin A, Hourihane JO, Frewer L, Knibb RC, Oude Elberink JN, Klinge I. Incorporating a gender dimension in food allergy research: a review. *Allergy.* 2006;61:1336–43.
 53. Pinczower GD, Bertalli NA, Bussmann N, Hamidon M, Allen KJ, DunnGalvin A, et al. The effect of provision of an adrenaline autoinjector on quality of life in children with food allergy. *J Allergy Clin Immunol.* 2013;131:238–40.e1.
 54. van der Velde JL, Flokstra-de Blok BM, Vlieg-Boerstra BJ, Oude Elberink JN, DunnGalvin A, Hourihane JO, et al. Development, validity and reliability of the food allergy independent measure (FAIM). *Allergy.* 2010;65:630–5.
 55. Acquadro C, Conway K, Hareendran A, Aaronson N. European Regulatory Issues and Quality of Life Assessment (ERIQA) Group. Literature review of methods to translate health-related quality of life questionnaires for use in multinational clinical trials. *Value Health.* 2008;11:509–21.
 56. Gjersing L, Caplehorn JR, Clausen T. Cross-cultural adaptation of research instruments: language, setting, time and statistical considerations. *BMC Med Res Methodol.* 2010;10:13.
 57. • 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;41:574–81. *This study describes the cross-cultural validity of the FAQLQ-AF in the USA and illustrates that American food-allergic adults report worse HRQL than Dutch food-allergic adults.*
 58. Marklund B, Ahlstedt S, Nordstrom G. Food hypersensitivity and quality of life. *Curr Opin Allergy Clin Immunol.* 2007;7:279–87.
 59. Vlieg-Boerstra BJ, Duiverman EJ, van der Heide S, Bijleveld CM, Kukler J, Dubois AE. Should children with a history of anaphylaxis to foods undergo challenge testing? *Clin Exp Allergy.* 2008;38:1935–42.
 60. Kemp AS, Allen CW, Campbell DE. Parental perceptions in egg allergy: does egg challenge make a difference? *Pediatr Allergy Immunol.* 2009;20:648–53.
 61. Nguyen M, Wainstein BK, Hu W, Ziegler JB. Parental satisfaction with oral peanut food challenges; perception of outcomes and impact on management of peanut allergy. *Pediatr Allergy Immunol.* 2010;21:1119–26.
 62. Strinnholm A, Brulin C, Lindh V. Experiences of double-blind, placebo-controlled food challenges (DBPCFC): a qualitative analysis of mothers' experiences. *J Child Health Care.* 2010;14:179–88.
 63. Zijlstra WT, Flinterman AE, Soeters L, Knulst AC, Sinnema G, L'Hoir MP, et al. Parental anxiety before and after food challenges in children with suspected peanut and hazelnut allergy. *Pediatr Allergy Immunol.* 2010;21:e439–45.
 64. Barnes ML, Ward JH, Fardon TC, Lipworth BJ. Effects of levocetirizine as add-on therapy to fluticasone in seasonal allergic rhinitis. *Clin Exp Allergy.* 2006;36:676–84.

65. Bisgaard H, Zielen S, Garcia-Garcia ML, Johnston SL, Gilles L, Menten J, et al. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *Am J Respir Crit Care Med*. 2005;171:315–22.
66. Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy*. 2005;60:309–16.
67. Oude Elberink JN, De Monchy JG, Van Der Heide S, Guyatt GH, Dubois AE. Venom immunotherapy improves health-related quality of life in patients allergic to yellow jacket venom. *J Allergy Clin Immunol*. 2002;110:174–82.
68. Beyer K. A European perspective on immunotherapy for food allergies. *J Allergy Clin Immunol*. 2012;129:1179–84.
69. Oude Elberink J. Venom immunotherapy (VIT): clinical efficacy and improvement in quality of life. *Drugs Today (Barc)*. 2008;44(Suppl B): 43–5.
70. Finegold I, Dockhorn RJ, Ein D, Dolen WK, Oppenheimer J, Potter LH. Immunotherapy throughout the decades: from Noon to now. *Ann Allergy Asthma Immunol*. 2010;105:328–36.
71. •• Factor JM, Mendelson L, Lee J, Nouman G, Lester MR. Effect of oral immunotherapy to peanut on food-specific quality of life. *Ann Allergy Asthma Immunol*. 2012;109:348–352.e2. *This study illustrates that oral immunotherapy improves HRQL of peanut-allergic children and teenagers (5–18 years)*.
72. Carraro S, Frigo AC, Perin M, Stefani S, Cardarelli C, Bozzetto S, et al. Impact of oral immunotherapy on quality of life in children with cow milk allergy: a pilot study. *Int J Immunopathol Pharmacol*. 2012;25:793–8.
73. Goossens NJ, Flokstra-de Blok BM, van der Meulen GN, Botjes E, Burgerhof HG, Gupta RS, Springston EE, Smith B, Duiverman EJ, Dubois AE. Food allergy knowledge of parents - is ignorance bliss?. *Pediatr Allergy Immunol*. 2013;24:567–73.
74. Clark NM, Gong M, Kaciroti N. A model of self-regulation for control of chronic disease. *Health Educ Behav*. 2001;28:769–82.