Development, validation and outcome of health-related quality of life questionnaires for food allergic patients

The studies described in this these were funded by the EU through the EuroPrevall project (FOOD-CT-2005-514000).

The publication of this thesis was financially supported by:
EuroPrevall, University of Groningen (RuG), University Medical Center Groningen (UMCG), Graduate School for Drug Exploration (GUIDE), Stichting Astmabestrijding (SAB), UCB Pharma B.V., ALK-Abelló B.V. and Phadia B.V.

ISBN: 978-90-367-3759-3

Lay out: Helga de Graaf, Studio Eye Candy, Groningen (www.proefschrift.info)
Printed by: Printpartners Ipskamp, Enschede

rijksuniversiteit groningen

Development, validation and outcome of health-related quality of life questionnaires for food allergic patients

Proefschrift

ter verkrijging van het doctoraat in de
Medische Wetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, dr. F. Zwarts,
in het openbaar te verdedigen op
woensdag 27 mei 2009
om 14.45 uur

door

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geboren op 1 juni 1982
te Havelte

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Contents

Chapter

Introduction: the impact of food allergy on quality of lifes

Aims and outline of this thesis

Bertine M.J. de Blok
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In: ENC Mills, H Wichers, K Hoffmann-Sommergruber, editors. Managing allergens in food. Cambridge: Woodhead Publishing Limited, 2006 (ISBN 1 84569 028 1)

Introduction

Food is an essential element in our lives; it is essential for staying alive and it is an important part of our cultural identity. For patients with a food allergy some sources of food may be fatal [1;2]. Consequently, the lives of these patients may be seriously disrupted by the continuous vigilance required to avoid foods to which they are allergic.

Adverse food reactions or hypersensitivities include any abnormal reaction resulting from the ingestion of food and might be the result of food intolerance (nonallergic food hypersensitivity) or food allergy [3;4]. Food intolerance is a non-immunologic response, such as may be seen in certain metabolic disorders (e.g., lactase deficiency). Food allergy is an adverse immunological reaction that may be due to IgE- or non-IgE-mediated immune mechanisms and the symptoms may involve the skin, gastrointestinal tract, respiratory tract, and cardiovascular system [5]. Although any food may provoke a reaction, relatively few foods are responsible for the vast majority of food allergic reactions: milk, egg, peanuts, tree nuts, fish and shellfish [6].

Prevalence of food allergy

The prevalence of food allergy is the greatest in the first few years of life. It has been estimated that up to six per cent of children less than three years of age experience food-induced allergic disorders [7]. Most children outgrow their sensitivity and approximately two per cent of the adult population experience food-induced allergic disorders [8]. Although it was once thought that peanut, tree nut and, seafood allergies were never outgrown, it has become apparent that clinical tolerance develops in about 20% of young children with peanuts allergy [9;10]. However, many studies show that food allergy prevalence is increasing in most Western countries. The prevalence of peanut allergy was found to have doubled in American children less than five years old in a five-year period [11]. Emergency room visits due to food allergy have increased by a factor of six in the United Kingdom. This increase in prevalence of food allergy is also accompanied by an increase of anaphylaxis caused by food allergy, which is potentially fatal [12].

Management of food allergy

Tools for diagnosis and management of food allergy have not changed much in the past two decades. The diagnosis includes clinical history, physical examination, tests for specific IgE antibody to suspected foods, elimination diets and oral food challenges. The management includes restriction diets and provision of medications such as epinephrine for emergency treatment [13]. Once properly diagnosed by double-blind placebo-controlled food challenges (DBPCFC), strict avoidance of the implicated food or foods is the only proven form of treatment. In addition, proper patient education about their allergy, avoidance strategies and dealing with reactions in cases of accidental exposure, allows patients to control their disease as much as possible. In many patients clinical tolerance will develop over time, and

therefore follow-up food challenges are often indicated [14]. Promising new methods for diagnosing food allergy such as individualised analysis of allergenic epitope recognition patterns [15] and novel strategies for treatment, including immunotherapy, are under development but are not yet commonly available [16].

Health-related quality of life

Quality of life has various meanings, which encompasses factors such as financial security, freedom, spiritual contentment, quality of environment, health, and the way these factors interrelate. It has been defined by the World Health Organisation (WHO) as 'the individual's perception of their position of life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns' [17]. A simpler definition of quality of life is 'the subjective value a person places upon satisfaction with his or her own life' [18]. The component of overall quality of life that pertains to an individual's health is called health-related quality of life (HRQL) and may be defined as 'the effects of an illness and its consequent therapy upon a patient, as perceived by the patient' [19]. HRQL incorporates the definition of health of the WHO; 'a state of complete physical, mental, and social well-being and not merely the absence of disease and infirmity' [20]. HRQL can be seen as a multidimensional concept that includes physical status and functional abilities, psychological status and well-being, social and professional interaction, and the patient's health perception [21]. It is important to understand that a similar level of objective clinical impairment may have a different impact on HRQL in different patients because individuals vary in their tolerance level. In addition, unlike objective clinical measures, HRQL focuses on the patient's perspective of their disease and measures the impairments that patients consider to be important [19].

Impact of food allergy on quality of life

There is no cure currently available for patients with food allergy. Food allergic patients must carefully avoid the causal foods every day, and this is a great burden to themselves and their families. Despite taking precautions, accidental exposure may occur and for some patients this may be fatal. Once a patient has experienced anaphylaxis, there is a great risk that he or she will experience recurrence [22]. This may create an additional burden of fear. In daily life, food allergic patients are burdened with a variety of tasks, including careful label reading of manufactured products, obtaining information about cross-contamination of foods with allergens, avoiding accidental exposures that may occur and limiting common social activities associated with eating.

Joshi et al. [23] found that most parents of children on restricted diets are unable to identify common allergenic food ingredients. Only seven per cent of the parents correctly identified milk, 22% correctly identified soy protein and 54% correctly identified peanut. Most parents correctly identified wheat and egg. These findings strongly support the need for improved labelling and education for patients and parents about reading labels. These recommendations are in accordance with the

findings of Gowland [24]. She discusses food allergen avoidance from the patient's viewpoint and states that the vigilance required to avoid food allergens depends on information that is often hidden or misleading. This uncertainty may lead to stress and social exclusion. In order to reduce the allergen risk and in addition to improve the quality of life of food allergic patients, Gowland [24] states that there should be clear food allergen labelling on manufactured products. Moreover, there should be integration of food allergy into all primary professional training for cooks, caterers and all those who prepare food for the public. And finally, there should be clear allergen management in food hygiene controls for all food businesses.

Accidental exposure to allergenic food often occurs outside the home and it accounts for the majority of deaths reported from food allergy [1;2]. In Britain 14% of food allergic patients reported reactions in restaurants [25] and in the United States almost 14% of self-selected registered peanut and / or tree nut allergic patients reported reactions in restaurants or other food establishments [26]. Establishments commonly reported in the latest study were Asian food restaurants (19%), ice cream shops (14%), and bakeries / doughnut shops (13%). Among meal courses, desserts were a common cause (43%). In most of the cases (78%) someone in the establishment knew that the food contained peanut or tree nut as an ingredient; in 50% of these incidents the food item was 'hidden' in sauces, dressing etc. In 22% of the cases, exposure resulted from contamination caused primarily by shared cooking or serving supplies [27]. These data show that patients with a food allergy are faced with a number of challenges when eating in restaurants and other food establishments. Given the effort required to avoid accidental exposures and the inherent uncertainty of success, living with a food allergy may be expected to have a negative influence on the quality of life.

Why measure HRQL?

HRQL measurements offer the opportunity to study the impact of disease from the patient's perspective. Measurement of an objective disease parameter provides information to clinicians, but are of limited interest to patients. These measures are often poorly correlated with areas in which patients are most interested and familiar, such as functional capacity and well being. Moreover, two patients with the same objective clinical impairment may have very different degrees of impairment in their HRQL [28]. For example, two patients with the same severe reaction to peanut following accidental exposure may have different social function and well-being. Although some patients may continue going to social events without anxiety, others may stay at home and feel isolated. Therefore, HRQL instruments allow quantification of differences between patients with similar objective disease burdens.

HRQL measurements also offer the opportunity to study the effect of a treatment from the patient's perspective. HRQL instruments allow quantification of changes within patients over time due to diagnostic or therapeutic interventions [28]. Especially in allergic diseases where mortality is low, HRQL issues are of importance in the management of patients. This is also true in food allergy, especially in cases

where patients only intermittently have symptoms and need to undertake extensive measures in order to prevent exposure to foods to which they are allergic.

These considerations explain why measuring HRQL is important in general and especially in patients with food allergy. It gives clinicians additional information about the impact of disease from the patient's perspective and it can be used for measuring clinical effectiveness of management strategies.

Approaches to study quality of life

Types of HRQL instruments

There are two major types of HRQL instruments used in clinical trials and practice: generic and disease-specific questionnaires. Generic instruments can be used to evaluate and compare different disease states, treatment interventions and, populations. The disadvantages of generic instruments are that they are by design comprehensive, so they may not focus adequately on problems specific to a particular disease. Furthermore, they may not be responsive enough to detect small but clinically meaningful changes in HRQL in a given disease state [28].

Disease-specific instruments are more responsive than generic instruments and they can by targeted to a specific population, disease, or function. This allows evaluation of HRQL restricted solely to the disease studied. These disease-specific instruments are much more likely than generic instruments to detect clinically important changes in patients' impairments. However, disease-specific instruments do not allow comparison between different diseases [28].

In some situations both generic and disease-specific instruments are of value and can be used in combination to compare populations (generic) and identify specific areas of problems within patient groups (disease-specific) [29].

Structure and administration of HRQL instruments

HRQL questionnaires are made up of items, grouped into a number of domains. A domain refers to a set of HRQL behaviours or experiences that one is trying to measure. HRQL questionnaires can be self-completed, or may be administered by a face-to-face or telephone interview. In some cases a surrogate responder such as a parent, completes the questionnaire. A face-to-face interview maximises the rate of response, minimises missing items and errors of misunderstanding, but requires more resources and training of the interviewer and may reduce willingness to acknowledge problems. Telephone interviews, are less resource intensive than face-to-face interviews. On the other hand, there is a greater likelihood of low response rates, missing items and misunderstanding, if questionnaires are self-completed. Surrogate completion reduces stress for the target group (e.g. in very elderly or sick persons), but the surrogate's perception of HRQL may differ from the patient group's perception [28]. Parents may complete HRQL questionnaires by proxy in young children. Older children can make judgements about their own health

state and may complete HRQL questionnaires by themselves. Obvious discrepancy between the judgements of children and parents about quality of life is often cited as a problem, but children differ from adults in their understanding of health and have their own views about quality of life. In addition, children's view about quality of life changes with age [30].

Development of disease-specific HRQL instruments

The fundamental characteristics of a good instrument are reliability, validity and responsiveness [31]. A measure is regarded as reliable if the same result is obtained when the same unchanged subject is measured again. Validity is a measure of the instrument's ability to actually measure what it is intended to measure. Responsiveness relates to the ability of the questionnaire to detect small but potentially important changes in HRQL over time, which is important for use in clinical settings.

The development of a disease-specific measure may involve a number of steps: item generation, item reduction, cross-sectional validation and longitudinal validation. Translation and cross-cultural validation are necessary for application of the instrument in different languages and in different cultural settings. Each of these steps will now be described in more detail.

Item generation

Item generation is a process by which all potential items for a new measure are assembled. Sources for possible items are patients or parents, experts and the literature. Items can be generated through interviews and focus groups. Patients or parents are asked to think of quality of life items related to their own or their child's disease. Experts may be asked which HRQL items their patients cite in the clinical setting. Individual interviews and focus group sessions can be used. Focus groups involve a small number (usually less than ten) of people who discuss a certain subject (in this case HRQL) freely, under the guidance of a experienced facilitator [32]. Items are generated and organised into domains or groups of related items, such as emotions, social functioning, or activities of daily living. The number of items that may be generated is in principal unlimited, but item generation is complete when no important new items are named or identified. It is important to ensure that the spectrum of patients contributing items (i.e. with regard to the limits of the age group and difference of severity of disease) is complete, or as complete as possible. The end product of this first step, called the extended instrument, is a relatively long list of HRQL items worded as problems.

Item reduction

This aims to eliminate redundant or personal items and to reduce the questionnaire to a manageable and feasible number of items. The extended instrument is presented to other patients or parents to indicate which items are troublesome for themselves or their children. The answer to this question is a simple 'yes' or 'no', followed by a grading of importance for the 'yes' answers on a five-point response scale with

responses varying from 'almost unimportant' to 'extremely important'. Alternate wordings may be tested.

Each candidate item is than scored for overall importance, which is the product of the frequency with which an item is identified as being important by patients and the mean impact of that importance using the five-point scale [33;34]. This allows for a selection of items for a prototype instrument. The number of items selected depends on the need to cover all areas of HRQL and the need to produce a manageable instrument. In general, HRQL instruments become unmanageable if they take more than 20 minutes to complete [35]. The prototype HRQL instrument is now suitable for validation.

It is important that the questionnaire is appropriately formatted. Each question should be easy to understand, free of medical jargon and inconsistencies, clear with respect to the time frame to which they refer, and encompass only one item. Also, the response options should be clear, brief and consistent. In paediatric questionnaires these formatting details are even more important. Moreover, it is extremely important that the reading level of the questionnaire is age-appropriate. Pilot testing the questionnaire will assess whether the format, wording, and feasibility are appropriate [32].

Cross-sectional validation

Validation may occur by comparing the HRQL questionnaire with an independent measure. This measure is independent of HRQL and is often a disease-specific parameter that reflects the severity of disease (e.g. FEV_1 in asthma). However, in patients with food allergy such a disease-specific parameter is not available, because symptoms caused by foods only occur following exposure, and such accidental exposures are relatively infrequent. Therefore, the perceived risk of the chance of and consequences of accidental exposure is the driving force of quality of life and this perceived expectation of outcome may be used as the independent measure. A specific instrument that is capable of capturing this expectation may be developed: the Expectation of Outcome measure [36].

The Expectation of Outcome measure asks patients or parents what they expect the outcome to be of their disease in the future. For example, in patients with food allergy a possible question that could be considered for the Outcome Expectation measure is: What chance do you think you have/your child has of accidentally ingesting the food to which you are allergic? Answers to these questions are expressed on a seven-point scale with responses varying from 'a negligible chance' to 'a very great chance'. The correlation between the Expectation of Outcome measure and the answers to the individual questions of the HRQL questionnaire are calculated. This method allows for selection of a small number of items having the best correlation for use in the final instrument. Consistency of the questionnaire can be further confirmed by calculating the correlation between an individual item and the other items of the questionnaire (i.e. Cronbach's alpha). The end product of this third step is a cross-sectionally validated HRQL instrument.

Longitudinal validation

In order to investigate if a cross-sectionally validated instrument will be capable of measuring within patient differences over time, the instrument must be longitudinally validated. This can be done in patients in whom HRQL is expected to change because of diagnostic and / or therapeutic interventions [37]. With regard to food allergy, one can think of studies involving improved diagnosis, counseling, and expert dietary intervention. Food allergic patients in these studies would be expected to have an improvement in their HRQL if they would be included in the active intervention group. Patients would receive the HRQL instrument and the Expectation of Outcome measure at the beginning of the study. After the intervention, patients would need to be followed for a period of time during which they could become accustomed to their new health state. This usually requires several months. After this period, the HRQL instrument and the Expectation of Outcome measure could be re-administered. Changes in the average score for the total instrument are then correlated to changes in the Expectation of Outcome measure, comparing values before and after the intervention described. Good correlation between the Expectation of Outcome measure and the HRQL scores validate the instrument longitudinally and simultaneously demonstrate the impact on HRQL of the intervention used. The final product is the definitive HRQL instrument and the impact of the intervention on HRQL can be reported.

Translation and cross-cultural validation

In order to use the HRQL instrument in different languages and cultural settings, translation of the questionnaire to the language of the patient population studied is required to reliably compare data across populations. Forward and backward translation may be used in order to check content comparability. However, translation alone, without consideration of cultural differences, may not be sufficient. Cross-sectional validation in the new language and cultural setting allows for the assessment of the performance of individual items in that language and culture [38;39]. Good cross-sectional correlation coefficients indicate validity for that particular language setting. Low correlation coefficients may be encountered if the translation is inaccurate or if the item does not appear to be a problem in the new cultural context. If cultural comparisons are made before the item reduction phase, it may be possible to identify items that are applying to only certain cultural settings or countries. Following successful cross-sectional validation in the new language and cultural setting, a final instrument can be generated by incorporating it into a longitudinal study in the new language as indicated above.

Current knowledge regarding food allergy and quality of life

Studies on quality of life and food allergy

There are only a few studies that have measured the HRQL in patients with a food allergy. Of the published five studies, three used general questionnaires to measure quality of life and two used disease-specific questionnaires. In three of these five studies the parents or caregivers completed the questionnaires.

Primeau et al. [40] compared the quality of life and family relations of children and adults with a peanut allergy to that of children and adults with a rheumatological disease. To quantify the impairment in quality of life, they used a vertical visual analogue scale (VAS) adapted from the European Quality of Life questionnaire (EQ-5D) [41]. The impact of the peanut allergy or rheumatological disease on the family was measured by the Impact on Family Questionnaire (IFQ) [42]. This questionnaire contains four dimensions of family life: familial-social, personal strain, financial burden, and mastery. They found that the parents of peanut-allergic children reported that their children had significantly more disruption in their daily activities as compared to the parents of children with a rheumatological disease. Furthermore, the parents of peanut-allergic children reported more impairment in the familial-social dimension of the IFQ. According to the authors this parental perception of considerable disruption of daily and social activities of the peanut-allergic child may be due to the perceived risk of death of their child. The lose of parental mastery when someone else cares for the child makes some parents even refuse to allow their child to go, for example, to birthday parties or school excursions.

Sicherer et al. [43] studied the impact of childhood food allergy on quality of life. The parental perceptions of physical and psychological functioning of the food-allergic child were measured with the Child Health Questionnaire (CHQ-PF50) [44]. This questionnaire contains twelve scales of general health: 1) physical functioning, 2) role social / emotional, behavioural, 3) role social / physical, 4) bodily pain, 5) general behaviour, 6) mental health, 7) self-esteem, 8) general health, 9) parental impact-emotional, 10) parental impact-time, 11) family activities, and 12) family cohesion. They showed that the parents of children with food allergy scored significantly lower on the scales of general health perception, emotional impact on the parent and limitation on family activities as compared to established norms.

Marklund et al. [45] studied the HRQL among adolescents with allergy-like conditions, with emphasis on food hypersensitivity. They investigated the magnitude of self-reported allergy-like conditions and used the Medical Outcome Trust Short Form 36 Health Survey (SF-36) to measure HRQL [46]. The SF-36 consists of 36 items divided into eight scales: 1) physical functioning, 2) role functioning-physical, 3) bodily pain, 4) general health, 5) vitality, 6) social functioning, 7) role functioning-emotional, and 8) mental health. The adolescents with allergy-

like conditions reported significantly lower HRQL on seven of the eight SF-36 scales (not on physical functioning), compared with adolescents without allergy-like conditions. This finding was regardless of whether the condition had been doctor-diagnosed or not. Nineteen percent of the respondents reported food hypersensitivity. Females with food hypersensitivity scored significantly lower on bodily pain, general health, and social functioning than females with other allergy-like conditions. Males with food hypersensitivity did not show this HRQL impairment.

In contrast to the above-mentioned studies, Avery et al. [47] used a disease-specific questionnaire that was self-completed by the children. Avery et al. compared the quality of life in children with a peanut allergy to that of children with insulin-dependent diabetes mellitus. To measure quality of life, they used two disease-specific quality of life questionnaires. One was designed by themselves and the other was adapted from the Vespid Allergy Quality of Life Questionnaire [36]. However, they do not describe how they designed or adapted these questionnaires. Moreover, these two questionnaires were not tested for reliability and validity. Therefore, caution is needed by the interpretation of these results. The results of this study were that children with a peanut allergy reported a poorer quality of life than children with insulin-dependent diabetes mellitus. Children with peanut allergy reported more fear of an adverse reaction and more anxiety about eating and only peanut allergic children reported fear of death.

Recently Cohen et al. [48] developed a disease-specific questionnaire to measure quality of life in families with a child with food allergy: the Food Allergy Quality of Life – Parental Burden (FAQL-PB) questionnaire. This questionnaire is completed by the parents and measures the parental burden associated with having a child with food allergy. They used the principles of item generation, item reduction and cross-sectional validation previously established in the development of other disease-specific HRQL questionnaires [49-51]. They reported strong internal and cross-sectional validation. However, the instrument was not longitudinally validated.

Is quality of life affected by food allergy, how much and by what?

The few studies that have measured the HRQL in patients with a food allergy all showed that the HRQL is negatively affected in these patients. There may be some variables that influence the magnitude of the impact of food allergy on HRQL.

First, the food to which one is allergic. Primeau et al. and Avery et al. investigated solely peanut-allergic patients while the other studies included patients with different food allergies although peanut and tree nut were most frequently reported. From these latest studies, only Sicherer et al. compared the HRQL of patients with peanut allergy to those with other food allergies, but found no differences. The other studies have not investigated the differences between different food allergies. Hence, it is not known if for example milk allergy has a greater negative impact on quality of life than, for example, peanut allergy. However, it is a fact that some foods are easier to avoid than others and may make living with a food allergy easier.

Second, the severity of the allergy, because it is reasonable that the lives of patients who have experienced an anaphylactic reaction are more disrupted than patients who have only experienced dermal reactions. Only Cohen et al. studied this and found that parents who reported an anaphylactic reaction in the past scored significantly lower on the FAQL-PB questionnaire than parents not reporting anaphylaxis.

Third, the number of foods to which one is allergic. This topic was investigated in two of the above mentioned studies. Sicherer et al. found that seven of the twelve CHQ-PF50 scales were significantly lower in families with multiple food allergies as compared to families with one or two food allergies. Also Cohen et al. found a significantly lower total score on the FAQL-PB questionnaire in families whose children had three or more food allergies compared to those with two or fewer food allergies. Moreover, the mean score of thirteen of the seventeen individual questions of the FAQL-PB questionnaire differed significantly in these two populations.

Fourth, many allergic patients have co-morbid conditions (e.g. atopic dermatitis, allergic rhinitis, or asthma) and this may have an additional negative impact on quality of life. Sicherer et al. showed that only the CHQ-PF50 scale general health was significantly impacted by co-morbid conditions. In agreement with this, Marklund et al. showed that adolescents with food hypersensitivity who also reported allergic diseases, scored significantly lower on the SF-36 scales bodily pain and general health compared to adolescents who only reported food hypersensitivity. However, co-morbid conditions will affect outcome using generic HRQL instruments, but it should not affect outcome of disease-specific HRQL instruments.

Fifth, gender may play a role in the impact of food allergy on quality of life. Most of the above-mentioned studies did not take this topic into account. Only Marklund et al. gave special attention to gender differences and, as previously stated, they found that females with food hypersensitivity scored significantly lower on the SF-36 scales bodily pain, general health, and social functioning than females with other allergy-like conditions. Males with food hypersensitivity did not show this HRQL-deterioration. Unfortunately, Marklund et al. did not make a comparison between females and males within the food hypersensitivity condition. However, in patients allergic to yellow jacket venom HRQL was significantly more impaired in women than in men [51].

Finally, it is interesting that Marklund et al. found that adolescents with allergy-like conditions had similar scores on the SF-36 whether they had verified allergy or not. Apparently, the perception of having a food allergy with the consequences of food avoidance is associated with deterioration in HRQL comparable to a verified food allergy. This underlines the importance of a correct diagnosis in order to abandon self-perceived but unproven food allergies and to prevent needless deterioration of HRQL.

Future priorities for research

As described above, there are only a few studies that have investigated the quality of life in patients with food allergy. This is remarkable because food allergy appears to have a significant negative impact on the quality of life. It is important to develop good food allergy specific HRQL questionnaires in order to identify the specific disabilities and problems of food allergic patients. Such questionnaires can provide additional information to the measurements of usual outcomes namely, insight into the burden and consequences of food allergy. It can also be used to study the relationship between management strategies and the improvement in HRQL [52].

Currently, there is only one HRQL questionnaire specific for food allergy available. This has only recently been published and represents a significant milestone in this field. However, this FAQL-PB questionnaire developed by Cohen et al. [48] has some significant limitations. First, it was developed to measure HRQL in children. Therefore, it can not be used in adults with food allergy. Second, the questionnaire is completed by parents and measures the parental burden associated with having a child with food allergy. Therefore, it provides no information about the impact of having a food allergy on quality of life perceived by the child. Third, the instrument is used for children across all age groups (range two months to seventeen years). No distinction is made between the problems associated with having a newborn, schoolchild, or teenager with food allergy, in which the problems are presumably different. Fourth, the questionnaire is not longitudinally validated. This means that the capability of this questionnaire to measure within patients differences over time is not documented. And finally, the questionnaire was developed and validated in the United States of America and may therefore not suitable for Europe. Moreover, it should be noted that the term food allergy covers a spectrum of disorders and perceived disorders. Over time it might be necessary to examine the impact on quality of life of specific food allergies, such as milk or peanut, whose impacts on quality of life may differ significantly.

In the scope of a large European multicenter research project funded by the European Union known as EuroPrevall, several new food allergic-specific HRQL instruments will be developed. In order to overcome the limitations of the FAQL-PB, questionnaires will be developed that will be completed by the parents and questionnaires that will be completed by the child. It may be interesting to compare the outcomes of the questionnaires completed by the patents to the outcomes of the questionnaires completed by children themselves. Moreover, different questionnaires for different age groups of childhood and also a specific questionnaire for adults with food allergy will be developed. A questionnaire specific for adults with oral allergy may be developed when it turns out that these patients experience other quality of life items than patients with a systemically reaction.

The new HRQL questionnaires will be cross-sectionally and longitudinally validated by the method described above. The longitudinal study will investigate if these questionnaires are capable of measuring within-patient differences over time.

It will also aim to show the impact of quality of life following the intervention (diagnosis by double-blind placebo-controlled food challenges). HRQL may be negatively influenced in patients with self-perceived food allergy. A good diagnosis may give certainty to the patient and HRQL may improve, even when the diagnosis is verified and even more if the diagnosis is rejected. This hypothesis has never been investigated and will be one of the topics of this study.

The new questionnaires will be subsequently translated into different languages followed by cross-sectional and longitudinal validation in the new language in different European countries. By doing so, reliable and valid disease-specific HRQL questionnaires will be provided for patients with food allergy that can be used in different age groups and in different European countries. These instruments will be usable to measure changes in quality of life in food allergic patients from any cause, including spontaneous fluctuation or following interventions. Next to this, other possibilities for future research are comparison of HRQL measured by disease-specific instruments and generic instruments or to combine the measurement of HRQL with economic calculations.

Aims and outline of this thesis

The main aim of this thesis was to develop and validate disease-specific health-related quality of life (HRQL) questionnaires for children (8-12 years), adolescents (13-17 years) and adults (18 years and older) with food allergy (**chapters 3, 4 and 5**). Additional aims were to investigate the reliability of these three questionnaires (**chapter 6**) and to investigate HRQL outcomes measured with these disease-specific questionnaires as compared to other generic questionnaires (**chapter 7**). Finally, this thesis aims to give an overview of current knowledge in the field of food allergy and HRQL at the beginning of the EuroPrevall project (**chapter 2**) and towards the end of the project (**chapter 8**).

Chapter 2

Chapter 2 contains a EuroPrevall state of the art paper describing a framework for measuring the social impact of food allergy across Europe. It describes the current knowledge on food allergy and HRQL at the beginning of the EuroPrevall project and how HRQL could be measured in food allergy. Finally, relevance and practical implementation of HRQL questionnaires are discussed.

Chapter 3

In **chapter 3**, we describe the development and validation of the Food Allergy Quality of Life Questionnaire - Child Form (FAQLQ-CF) in the Dutch language. This questionnaire was specially developed for food allergic children aged 8 to 12 years and the questionnaire is completed by the children themselves.

Chapter 4

Chapter 4 describes the development and validation of the Food Allergy Quality of Life Questionnaire - Teenager Form (FAQLQ-TF) in the Dutch language. This questionnaire was specially developed for food allergic adolescents aged 13 to 17 years and the questionnaire is completed by the adolescents themselves.

Chapter 5

In **chapter 5** we describe the development and validation of the Food Allergy Quality of Life Questionnaire - Adult Form (FAQLQ-AF) in the Dutch language. This questionnaire was specially developed for food allergic adults 18 years and older.

Chapter 6

Chapter 6 contains the results of test-retest reliability of the FAQLQ-CF, -TF, -AF. The questionnaires were completed by the same patients twice with a 10-14 day interval and we investigated the reproducibility of the questionnaires over time when no change in the condition has taken place.

Chapter 7

In **chapter 7**, a study is presented on HRQL of food allergic patients measured with generic and disease-specific questionnaires. The aim of this study was to compare generic HRQL of food allergic patients with the general population and other diseases. In addition, it compares the HRQL of food allergic patients measured with generic and disease-specific questionnaires.

Chapter 8

In **chapter 8**, we present a review on how HRQL can be measured in food allergy and we discuss recent findings on how food allergy might impact HRQL.

Chapter 9

In **chapter 9**, a general summary and discussion are provided and future perspectives are discussed.

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Chapter 2

A framework for measuring the social impact of food allergy across Europe: a EuroPrevall state of the art paper

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Allergy 2007; 62:733-737

Abstract

This state of the art paper has been developed through EuroPrevall, a European multi-centre research project funded by the European Union (EU) which aims to improve quality of life for food allergic individuals. Food allergy (whether clinically diagnosed or self-perceived) represents a major health issue in Western societies and may have a considerably greater impact on society than was previously believed. However, the social impact of food allergy has never been systematically investigated using validated instruments. Combining the information from studies on health-related quality of life (HRQL) with epidemiological data on prevalence will ultimately give some indication of the magnitude of the social impact of food allergy in Europe. HRQL can be assessed with disease-specific questionnaires, which are being developed in EuroPrevall. These instruments will be used to identify HRQL problems associated with food allergy, and to assess the effectiveness of interventions and to guide the development of regulatory policies.

Introduction

Adverse reactions to foods, including IgE-mediated food allergies, represent a major health-issue in Western societies. It has been estimated that in the general population approximately 4-6% of children and 1-3% of adults experience food allergy [1]. There is some evidence to suggest that the prevalence has increased over the last 10 years [2]. This is demonstrated by the increase in emergency room visits due to food allergy in the United Kingdom, which have increased by a factor of six over a decade, accompanied by an increase in the incidence of anaphylaxis caused by food allergy [3]. Another remarkable observation is that the prevalence of perceived food allergy seems to be much higher than verified food allergy, up to 22% of the adult population [4]. This may be related to inadequate diagnosis of food allergy, in part reflecting the lack of adequate provision of relevant health services.

Adverse reactions to foods (including IgE-mediated allergies), clinically or self-diagnosed, may have a considerably greater impact on society than has previously been believed. The social functioning of individuals with a food allergy, or activities in families with an allergic child or family member, may be seriously disrupted by the need for continuous vigilance to avoid foods to which they are (or believe to be) allergic [5]. In cases of individuals with self-diagnosed food allergy, the majority may be restricting their diet unnecessarily and consequently running the risk of nutritionally compromising themselves or becoming deficient in specific nutrients [6;7]. Furthermore, such dietary management disrupts social or family life, and could be costly to implement both in time and money [8]. However, the effects of food allergy are not only limited to individuals or households. The food industry may also experience an extra burden of costs due to food allergy [9]. This may, for example, result from legislative changes aimed at improving consumer protection such as the new EU-legislation on food labelling that came into force in November 2005 (EU Directive 2003/89/EC amending Directive 2000/13/EC). The onus of responsibility falls to the food manufacturer, who is required to manage production processes to ensure allergenic ingredients are labelled. At the present time, the potential social impact and economic costs of food allergy on the individual, families, related health services and food industry are not well understood.

EuroPrevall is a European multidisciplinary and multi-centre research project funded by the European Union (EU). Its mandate is to investigate the prevalence, cost, and basis of food allergy, and to improve quality of life for food allergic people [10]. In order to assess the socio-economic impact of food allergy, and provide benchmarks to assess the effectiveness of interventions developed to manage the disease, validated instruments are needed. One of the major objectives of EuroPrevall is to develop and validate instruments to determine the impact of food allergy on the health-related quality of life (HRQL) of allergy sufferers and their families, and to assess the economic costs. A framework for measuring costs of food allergy to society has already been published [11]. However, there is an urgent need to initiate a similar enquiry into the social impact of food allergy. We will provide an overview of current knowledge and limitations in this area, and describe the

research strategies being developed in the EuroPrevall project to obtain this missing information. Finally, the importance of assessing the social impact of food allergy and the practical implications will be discussed.

Social impact of food allergy

The social impact of food allergy can be assessed using measurements of HRQL in food allergic individuals. Quality of life is a broad concept that pertains to an individual's overall satisfaction with his or her life. It has been defined by the World Health Organisation (WHO) as "the individual's perception of their position of life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [12]. The component of overall quality of life that pertains to an individual's health is called health-related quality of life and is defined as the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient [13]. It contains three domains: the social, the psychological and the physical state. It is important to understand that a similar level of objective clinical impairment may have a different impact on HRQL in different patients because individuals vary in their tolerance levels and subjective perceptions of ill-health [14]. In addition, HRQL measures the impairments that patients themselves consider to be important, rather than focusing on what is considered important by external observers such as doctors or nurses [15].

HRQL is measured using specially designed and tested instruments, which measure people's ability to function in their everyday lives. There are two major types used in clinical trials and practice: generic and disease-specific instruments. Generic instruments can be used to evaluate and compare different disease states. Disease-specific instruments do not allow comparison between different diseases, but are more responsive than generic instruments and therefore more likely to detect small but clinically important changes in patients' impairments resulting from a specific disease or disorder [16].

There are only a few studies that have investigated the impact of food allergy on HRQL. By using generic questionnaires (Impact on Family Scale (IFS)) it has been shown that daily life is significantly more disrupted in peanut allergic individuals than in individuals with a rheumatic disease [17]. Moreover, general health perception, emotional impact on the parent and limitation of family activities of parents with food-allergic children were found to be impaired compared to established norms, using the Child Health Questionnaire (CHQ) [18]. In addition, it has also been reported, using the Medical Outcome Trust Short Form 36 Health Survey (SF-36), that females with food allergy showed significantly more bodily pain and impairment of general health and social functioning in comparison with females with other allergy-like conditions [19]. Recently, two studies were published on the development of preliminary questionnaires to asses the parental adjustment to and coping with children's food allergy [20] and to determine the impact of food

allergy on the daily activities of food allergic children and their families [21]. Both questionnaires are administered to the parents. The last study reported that food allergy had a significant impact on almost all aspects of daily life.

Currently, there is only one validated HRQL questionnaire specific for food allergy available: the Food Allergy Quality of Life – Parental Burden (FAQL-PB) questionnaire [22]. It is administered to the parents and measures the parental burden associated with having a child with food allergy. Internal validity, reliability and cross-sectional validity were established, but the instrument was not longitudinally validated. This questionnaire represents a milestone in the field of food allergy and quality of life. However it has some significant limitations. First, the questionnaire was developed for allergic children and is therefore not suitable for allergic adults. In addition, the questionnaire measures the parental quality of life, not the quality of life of the child, and third no distinction was made between different age groups of children in the development of the questionnaire. Moreover, the questionnaire is time bound, inquiring only about allergic incidents during the week preceding administration.

Assessing HRQL in EuroPrevall

In order to complement the existing instruments, and to develop instruments that can assess broader questions related to the quality of life of food allergic patients, new HRQL questionnaires will be developed and validated within the EuroPrevall project in the Netherlands and Ireland. These questionnaires will cover all ages in childhood and adulthood. Questionnaires for the youngest children will be parent-administered and questionnaires for the older children, adolescents and adults will be self-administered. In addition, the reporting period will be less restricted. The development of these questionnaires will start with item generation in which all possible problems associated with food allergy are generated, followed by item reduction in which the most important items are selected. These prototype questionnaires will be cross-sectionally validated followed by longitudinal validation. The final questionnaires will be translated into the languages used in different European countries enabling cross-cultural comparison of the questionnaires. A more detailed description of the development of these questionnaires can be found elsewhere [23].

In EuroPrevall it will be of interest to compare the outcomes of the questionnaires completed by the parents to the outcomes of the questionnaires completed by the children themselves in order to investigate the agreement or disagreement between them. In addition, special emphasis will be put on the gender dimension, because there may be considerable differences between men and women in how they experience and cope with their food allergy [24]. To date, one study has assessed gender differences in the quality of life of the family members of children with peanut allergy. The results showed that mothers experienced significantly poorer psychological quality of life, greater anxiety and

stress than fathers or sibling(s). In addition, mothers rated their child's quality of life significantly worse compared to the peanut allergic child's own ratings or the proxy ratings of the sibling and father [25].

In addition to the development of questionnaires to measure HRQL, research will be conducted to assess how the quality of life of food allergic consumers can be improved. One of the research topics will focus on how to optimise information provision through effective allergen labelling. The existing literature indicates that food allergic consumers experience stress and potentially impaired quality of life as a result of poor labelling practices and lack of information about their food allergy [26]. Despite the new EU labelling legislation, allergic consumers are still not completely sure about the safety of products. This uncertainty could be caused by fear of cross-contamination, unlabelled products (for example those which are not packaged), changes in ingredients, and the difficulty of understanding product labels [27-31]. It has been suggested that improved product ingredient labelling will reduce allergic reactions and simplify allergy management. However, it may also increase choice restriction when allergen-derived ingredients are indicated on the label that are tolerated by allergic individuals [32]. In addition to the EU labelling legislation, companies use precautionary labelling to alert consumers on the chance of contamination during the production process, which may increase the choice restriction of food allergic consumers even more [33].

In order to improve labelling practices, consumer preferences for different food labelling strategies will be investigated, as well as the benefits of new Information and Communication Technology (ICT) approaches to delivering targeted information. Consumer preferences for the implementation of such new approaches, together with feasibility of adoption, will be assessed. This will provide the basis for a tested and implementable set of guidelines underpinning the development of new approaches to deliver necessary information to the allergic consumer, which is essential if food allergic consumers are to lead a life which is as normal as possible [34]. Such information interventions may have a positive effect on the quality of life of food allergic consumers, which can be assessed using 'before and after' evaluations of the HRQL instruments.

Relevance and practical implementation

Magnitude of social impact of food allergy across Europe

One of the major aims of the EuroPrevall project is to assess the social impact of food allergies, and their potential mitigation, to the European Community. In order to realise this, it is important to combine the information from studies on HRQL with epidemiological data on prevalence. This will ultimately give some indication of the magnitude of the social impact of food allergy in Europe. The impact of food allergy on HRQL may differ according to the type of food to which a particular individual is allergic, the severity of allergy symptoms, and the number of foods

to which one is allergic (single or multiple). Furthermore, the impact may also be dependent on threshold (the amount of an allergic food that is needed to trigger an allergic reaction), or the age and gender of the allergic individual in question. This information is essential if health-care planning and food safety assessments are to be deployed with best effect to support the allergic consumer in managing their condition.

In a European context, it is important to determine whether cross-cultural differences in the social impact of food allergy can be identified. A case in point, it has been shown that the prevalence of perceived food allergy differs significantly across multiple countries, ranging from 4.6% in Spain to 19.1% in Australia [35]. This is probably due to differences in the prevalence of real food allergy, but may also be due to cultural differences. In addition, the impact of food allergy on quality of life may differ due to cultural differences. It is important to take this into account when measuring HRQL in different countries.

Determinate problems, effectiveness of interventions and prioritising

The effect of legislation regarding food allergy on the social impact of food allergies, on both allergy sufferers and the wider community, has never been assessed. For example, it is not understood to what extent the new labelling legislation improves the quality of life of allergy sufferers. Nor has an assessment been made of how resulting benefits to consumers can be balanced against the costs to the food industry when implementing much more stringent hazard control procedures in food manufacturing. Such costs are ultimately passed on to the consumer. In order to assess the impact of (regulatory) interventions, it is important to first quantify the impact of food allergy on HRQL.

By using HRQL questionnaires, it may for example be ascertained that the quality of life of food allergic patients is negatively affected by the need for continuous vigilance when eating outside the home. In this case, regulations need to be developed that enforce the need for effective training in the catering sector. If some food allergies have a greater impact on quality of life, these should be prioritised in terms of regulatory interventions and legislative measures. Other applications of HRQL measures include the identification of the effectiveness of interventions in clinical trials. For example, if proper diagnosis, expert dietary interventions, counselling regarding accidental exposure management, or a future treatment is found to have a positive effect on HRQL, then resources can be directed towards these interventions.

Conclusions

A necessary first step to assess the social impact of food allergy is the development of new HRQL instruments. When these instruments are available, HRQL problems associated with food allergy can be identified and this may be followed by the

development of improved approaches to manage these problems. The instruments may also be used to assess the usefulness of new legislation and guidelines regarding allergen management in food manufacturing and catering industries. Finally, HRQL measurement may also facilitate the more efficient allocation of resources within health services, for example to support more effective clinical diagnostic methods, if these can be demonstrated to have a significant positive impact. Continuous application of such instruments and analysis of changes with time may identify emerging social problems associated with food allergy, and identify differences across European populations.

Acknowledgements

This work was funded by the EU through the EuroPrevall project (FOOD-CT-2005-514000). CM was also supported by the BBSRC Competitive strategic grant.

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Chapter 3

Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for children

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Clin Exp Allergy 2009; 39:127-137

Abstract

Background:
Having a food allergy may affect Health-Related Quality of Life (HRQL). Currently no validated, self-administered, disease-specific HRQL questionnaire exists for children with food allergy.

Objective:
To develop and validate the Food Allergy Quality of Life Questionnaire - Child Form (FAQLQ-CF) in the Dutch language.

Methods:
Interviews with food allergic children (n=13, 8-12 years) generated 139 HRQL items. The most important items were identified by 51 food allergic children using the clinical impact method. This resulted in the FAQLQ-CF containing 24 items (total score range 1 'not troubled' to 7 'extremely troubled'). The FAQLQ-CF, the Food Allergy Independent Measure (FAIM) and a generic HRQL questionnaire (CHQ-CF87) were sent to 115 food allergic children for cross-sectional validation of the FAQLQ-CF.

Results:
Construct validity was demonstrated by the correlation between the FAQLQ-CF and the FAIM (rho=0.60, $p<0.001$). The FAQLQ-CF had an excellent internal consistency (Cronbach $\alpha=0.94$) and discriminated between children who differed in number of food allergies (>2 food allergies vs. $\leq$2 food allergies, total FAQLQ-CF score, 4.3 vs. 3.6; $p=0.036$), but did not discriminate between reported anaphylaxis or not. The total FAQLQ-CF score correlated with 8 of the 11 CHQ-CF87 sub-scales which demonstrated convergent/discriminant validity.

Conclusion:
The FAQLQ-CF is the first self-administered disease-specific HRQL questionnaire for food allergic children. This questionnaire has strong internal consistency and cross-sectional validity. It discriminates between children who differ in number of food allergies and it was short and easy to use in the population studied. Therefore, the FAQLQ-CF may be a useful tool in clinical research.

Introduction

Avoidance of foods causing allergic reactions and emergency treatment are the only proven forms of treatment of food allergy [1]. Children with food allergy and their families thus need to be continuously alert with regard to food in numerous situations and settings and this may have an impact on daily life [2]. The avoidance of implicated foods along with the fear of an allergic reaction following possible exposure may have a negative impact on the quality of life of food allergic children.

Quality of life can be measured with generic or disease-specific questionnaires. While generic questionnaires are useful and allow for comparison of quality of life between different diseases, their limitation is that they are generally less sensitive than disease-specific questionnaires, so that potentially important differences or changes may be missed. This is particularly true in the case of food allergy, where, unless they are exposed to the relevant food, patients will have no symptoms other than those related to the need to avoid foods or fear of accidental ingestion. In addition, generic questionnaires are sensitive to co-morbidities, whereas disease-specific questionnaires allow assessment of a single disease. This is also relevant to allergic diseases such as food allergy where many patients also have atopic dermatitis, asthma and/or allergic rhino conjunctivitis.

There are a few studies that have investigated the impact of food allergy on Health-Related Quality of Life (HRQL) in children and all found that HRQL was impaired. However, these studies used generic HRQL questionnaires [3-6] or disease-specific HRQL questionnaires which were not validated [7-9]. By using generic questionnaires (Child Health Questionnaire-Parent Form (CHQ-PF28)) it was found that quality of life was more impaired in children with food allergy than in children with allergic diseases other than food allergy or non allergic children [3], and that food allergy by itself was associated with a deterioration of children's quality of life regardless of additional allergic diseases [4]. Moreover, general health perception, emotional impact on the parent and limitation of family activities of parents with food-allergic children were found to be impaired compared to established norms, using the CHQ-PF50 [5]. By using the Impact on Family Scale (IFS) it has been shown that daily life is significantly more disrupted in peanut allergic children than in children with a rheumatic disease [6].

A few studies describe the development of preliminary disease-specific questionnaires to assess the parental adjustment to and coping with children's food allergy [7], to determine the impact of food allergy on the daily activities of food allergic children and their families [8] and to compare quality of life of food allergic children with children with diabetes mellitus [9]. The first two questionnaires were completed by the parents, the last one by the child. However, these questionnaires have not been validated which is critical in order to determine whether the questionnaire is measuring that part of quality of life which is determined by the target disorder [10]. The only validated disease-specific HRQL questionnaire for food allergy which is currently available, is administered to parents and measures the parental burden associated with having a child with food allergy [11].

Since no validated food allergy specific HRQL questionnaire exists which can be administered to children, we developed such a questionnaire. We targeted children old enough to complete the questionnaire themselves ($\geq$ 8 years) but not yet teenage ($\leq$ 13 years) where social and developmental differences were likely to result in differences in content of the questionnaire. This questionnaire was developed as part of the EuroPrevall project, a European multi-centre research project on food allergy [12]. This article will describe the development and cross-sectional validation of the Food Allergy Quality of Life Questionnaire – Child Form (FAQLQ-CF) in the Dutch language. Validation was accomplished by ascertaining construct validity between the items of the FAQLQ-CF and the Food Allergy Independent Measure (FAIM) as well as a generic quality of life instrument, the Children's Health Questionnaire-Child Form (CHQ-CF87). In both cases only moderate correlations were expected, as disease-specific questionnaires cover a wider range of issues than most independent measures can capture [13] and generic instruments cover a wider range of issues than disease-specific instruments can capture [14]. In addition, the FAQLQ-CF was tested to see if it could discriminate between children who had previous anaphylactic reactions and those who had not as well as children allergic to many foods and those allergic to only a few foods.

Methods

Participants

During all stages of questionnaire development and validation children aged 8 to 12 years were included. All common food allergies and different types and severities of symptoms were represented. During the item generation, children were recruited from our outpatient paediatric allergy clinic. During the item reduction and cross-sectional validation, children were recruited from our outpatient paediatric allergy clinic or were recruited through food allergy support organisations (the Dutch Foundation for Food Allergy and the Dutch Anaphylaxis Network) and by advertisement in local newspapers.

Procedure

During the item reduction and cross-sectional validation phase, children and their parents were instructed that the children should fill out the questionnaire by themselves. Parents were allowed to explain a question when needed, but they were not allowed to tell the child which answer to give. In addition, during all stages of questionnaire development, descriptive characteristics were asked on age, sex, type and number of food allergies, type of symptoms, time since most severe allergic reaction, and diagnosis. For completing these descriptive questions, parents were allowed to help their child when needed.

Item generation

Potential items for the new questionnaire were assembled during the item generation phase. A semi-structured interview was administered to thirteen food allergic children (aged 8-12 years). Such interviews are flexible while a framework of themes, concerning unpleasant or troublesome things about having a food allergy in daily life, is explored. Additional sources for items were literature review and expert opinion. This resulted in an extended item list of 139 items. The items were divided into the following themes: shopping/labelling (5 items), food preparing (5 items), eating in general (10 items), eating out (20 items), social activities (29 items), emotions (35 items), holidays (21 items), school/leisure activities (10 items) and medication (4 items).

Item reduction

Subsequently, item reduction was carried out by using the clinical impact method [15;16]. The clinical impact method asks patients to identify the impairments that are most important to them in their everyday lives. Items identified most frequently and rated the most important are selected for the final questionnaire. The extended item list was sent to a different group of 54 food allergic children (aged 8-12 years). Items were formulated as questions to which the answer was 'yes' or 'no.' For example, 'Do you read labels because of your food allergy?' The children could indicate whether an item was applicable to them or not and, if applicable, they were asked to indicate on a five-point scale ranging from 'not' to 'extremely' the impact of that item on their life. The five-point scale was illustrated by drawings of faces (smileys) ranging from a smiling face to a sad face. For each item we counted the number of times that an item was applicable (i.e. *frequency*). Frequency divided by the total number of children gives the *percentage* by which an item was identified as being important. Then, we calculated the mean importance (MI) for each item. The MI of an item is the sum of impact scores (based on the five-point scale) divided by the *frequency*. The overall importance (OI) of each item was calculated by multiplying the *percentage* with the MI. The maximum possible OI score was 5.0 [17;18].

The items with the greatest OI were selected for the Food Allergy Quality of Life Questionnaire – Child Form (FAQLQ-CF). To prevent redundancies, one of any pair of items with an inter-item correlation >0.85 and/or overlapping content (face validity) was eliminated. Our goal was to create a brief questionnaire that could be administered within half an hour, taking into account that it takes one minute to complete one item [19]. The selected items were worded as questions with a seven-point response scale ranging from 'not troubled' to 'extremely troubled' [16;18] and were illustrated by drawings of faces (smileys) ranging from a smiling face to a sad face. A consultant/teacher for sick children and a linguist reviewed the FAQLQ-CF for clarity and ease of use.

Cross-sectional validation

The complete questionnaire packages, containing the FAQLQ-CF, the Food Allergy Independent Measure (FAIM) and a generic HRQL questionnaire (CHQ-CF87),

were pretested in three children (aged 8, 10 and 12 years). No major problems emerged during this pretest. The 8 year old child reported that her parents read the questions aloud and that she marked the right answers herself. The questionnaire packages were then sent by mail to 115 food allergic children. A part of these children had participated in the item generation (10%) or item reduction phase (45%). For the children recruited from our clinic, we checked the patient records to determine whether or not the food allergy was diagnosed by a double-blind placebo-controlled food challenge (DBPCFC).

Reliability

The internal consistency of the FAQLQ-CF and the domains were measured by calculating Cronbach's alpha. An alpha greater than 0.70 indicates good internal consistency [20].

The test-retest reliability of the FAQLQ-CF was assessed by administering the questionnaire to 28 children on two occasions 10 to 14 days apart and the intraclass correlation coefficient (ICC) of the repeated FAQLQ-CF measurement was calculated. An ICC greater than 0.70 indicates good test-retest reliability [21].

Cross-sectional validation

Construct validity

In order to demonstrate the construct validity of the FAQLQ-CF, correlations were calculated between the FAQLQ-CF and a Food Allergy Independent Measure (FAIM). The FAIM was developed for this study and includes four Expectation of Outcome (EO) questions and two Independent Measure (IM) questions. The use of EO and IM questions to validate disease-specific HRQL questionnaires has already been successfully implemented to validate HRQL questionnaires [11;18] and it is of special use in anaphylactic disorders where no objective measurement of the extent or severity of disease exists [13]. The four EO questions concern the chance of accidental exposure, chance of having a severe reaction when accidentally exposed, chance of dying when accidentally exposed and chance of not acting effectively when accidentally exposed. Children could indicate their answer on a seven-point scale ranging from 'never' (0% chance) to 'always' (100% chance). The two IM questions concern the number of foods one needs to avoid (question 5) and the impact of food allergy on social life (question 6). Children could indicate their answer on a seven-point scale ranging from 'almost none' to 'almost all' (question 5) and ranging from 'so little I don't actually notice it' to 'a very great deal' (question 6). We expected a moderate correlation coefficient (0.40-0.70) [22] between the FAQLQ-CF and the FAIM.

Discriminative ability

In order to establish the discriminative ability of the FAQLQ-CF, we compared the total FAQLQ-CF score for children who reported anaphylaxis versus children who did not. Anaphylaxis was defined as children who reported two or more of the following cardiovascular symptoms; dizziness, feeling your heart beat fast,

loss of vision, inability to stand, light headedness, collapse, loss of consciousness/ passing out. In addition, we compared the total FAQLQ-CF score for children who reported many food allergies versus children who reported fewer food allergies. We investigated which cut off in number of reported food allergies revealed a significant difference in the total FAQLQ-CF score. Additionally, the total FAQLQ-CF score was compared for girls versus boys, since gender may influence quality of life [23]. Finally, we compared the total FAQLQ-CF score for children who were recruited from our clinic versus children who were recruited by advertisement.

Convergent and discriminant validity

In order to demonstrate convergent and discriminant validity, a generic HRQL questionnaire was administrated: the Child Health Questionnaire-Child Form (CHQ-CF87). The CHQ-CF87 was developed in the USA and has since been validated in several other countries and languages [24;25]. This questionnaire is self-administrated by the child and contains 87 items divided into twelve sub-scales: physical functioning, role functioning-emotional, role functioning-behaviour, role functioning-physical, bodily pain, general behaviour, mental health, self-esteem, general health perceptions, change in health (single item), family activities, and family cohesion. The Dutch version was found to be reliable and valid with good internal consistency (only one sub-scale had a Cronbach's alpha below 0.70) and with good test-retest reliability (only two sub-scales had non significant intraclass correlation coefficients). Finally, all sub-scales were able to differentiate between subgroups with and without two or more reported chronic conditions [25]. We expected a low correlation coefficient (0.10-0.30) between the FAQLQ-CF and the CHQ-CF87, because the FAQLQ-CF is a disease-specific quality of life questionnaire whereas the CHQ-CF87 measures generic quality of life.

Translation

The Dutch FAQLQ-CF was translated into English using the guidelines of the World Health Organization [26]. The Dutch FAQLQ-CF and the FAIM were translated into English by a native English speaker and back translated by a native Dutch speaker. The original Dutch version was compared with the back translated Dutch version. No important differences in content or meaning of questions emerged. The English version of the FAQLQ-CF and the FAIM may be found as Appendix 1 and 2.

Statistical analyses

The raw FAQLQ-CF and FAIM scores 0 to 6 were recoded as 1 to 7. The total FAQLQ-CF score is the mean score of all items with a range of 1 'no impairment' to 7 'maximal impairment'. The dataset was not normally distributed, therefore non-parametric tests were used. In order to demonstrate construct validity, Spearman's correlation coefficients were calculated for the individual items and total FAQLQ-CF scores with the individual FAIM questions and the mean of the FAIM. The items of the FAQLQ-CF were allocated to domains based on factor analysis (principal component analysis with Varimax rotation) [27] and face validity determined by a

clinical expert panel (BMJFdB, JNGOE and AEJD) [28;29]. The discriminative ability of the FAQLQ-CF was analysed by using the Mann-Whitney test. Finally, convergent and discriminant validity was demonstrated by calculating Spearman's correlation coefficients for the domain and total FAQLQ-CF scores with the CHQ-CF87 subscales. Statistical analyses were performed with SPSS for Windows (version 14).

Ethical approval

The study was approved by the local medical ethics review commission (METc 2005/051) who deemed that permission from the commission was not required. Parents and children received written information indicating that participation in the study was voluntary.

Results

Item generation and item reduction

Descriptive characteristics of the children involved in the item generation and item reduction are shown in Table 1. The extended item questionnaire was returned by 51 children (response rate 94%). The OI scores of all 139 items of the extended item questionnaire ranged from 0.00 to 3.22. The 25 non-overlapping most important items (OI≥1.57) were selected for the FAQLQ-CF (Table 2). These selected items came from the following original themes: shopping/labelling (4 items), food preparing (1 item), eating in general (5 items), eating out (4 items), social activities (4 items), emotions (6 items), holidays (0 item), school/leisure activities (1 item) and medication (0 item). Although children did bring up items concerning sadness, embarrassment and teasing, most of these items did not reach a high enough OI for inclusion in the questionnaire.

Cross-sectional validation

Participants

The FAQLQ-CF with the FAIM and the CHQ-CF87 were returned by 84 children (response rate 73%). The questionnaires of three children were excluded from the analysis because no current food allergies were reported and one questionnaire was excluded because the descriptive characteristics were missing. For one child the CHQ-CF87 was missing. Forty-eight children (60%) were recruited from our clinic, of which 25 (31%) had a food allergy confirmed by a DBPCFC. The other children from our clinic had a physician-diagnosed food allergy (skin prick and/or blood test) and the majority was awaiting DBPCFC. All children recruited by advertisement (40%) reported physician-diagnosed food allergies. Descriptive characteristics of the children involved in the cross-sectional validation are shown in Table 1. There were no significant differences in descriptive characteristics between boys and girls or between children who were recruited from our clinic and children who were recruited by advertisement.

Table 1. Descriptive characteristics of the children involved in the item generation, item reduction and cross-sectional validation.

	Item generation	Item reduction	Cross-sectional validation
Patients (n)	13	51	80
Sex (m/f)	9/4	29/22	46/34
Age, mean in years (SD)	10.1 (1.3)	9.8 (1.3)	10.2 (1.3)
Food allergy, n (%)			
Peanut	10 (76)	33 (65)	60 (75)
Tree nuts	11 (85)	38 (75)	58 (73)
Egg	8 (62)	19 (37)	30 (38)
Milk	5 (38)	17 (33)	22 (28)
Fish	1 (8)	3 (6)	2 (3)
Shell fish	0	6 (12)	7 (9)
Wheat	4 (31)	6 (12)	10 (13)
Sesame	2 (15)	7 (14)	15 (19)
Soy	2 (15)	6 (12)	12 (15)
Celery	0	1 (2)	1 (1)
Number of food allergies, n (%)			
1 food	1 (8)	12 (24)	20 (25)
2 foods	3 (23)	16 (31)	22 (28)
3 foods	3 (23)	8 (16)	18 (24)
>3 foods	6 (46)	15 (29)	20 (25)
Type of symptoms, n (%)			
Cardiovascular[1]	2 (15)	10 (20)	15 (19)
Respiratory tract[2]	8 (62)	28 (55)	40 (50)
Gastrointestinal tract[3]	2 (15)	8 (16)	14 (18)
Skin[4]	1 (8)	5 (9)	8 (10)
Other[5]	0	0	3 (4)

[1] dizziness, feeling your heart beat fast, loss of vision, inability to stand, light headedness, collapse, loss of consciousness / passing out. [2] tightening throat, difficulty swallowing, hoarseness / hoarse voice, difficulty breathing in, shortness of breath, wheezing, cough. [3] sick to your stomach, stomach cramps, vomiting, diarrhoea. [4] itchy skin, red rash, hives, worsening eczema, swelling of the skin. [5] oral allergy, swollen tongue or lips, symptoms of the nose or eyes.

Construct validity

Most items of the FAQLQ-CF correlated significantly with at least one of the FAIM questions and most items correlated significantly with the mean of the FAIM questions. One item ('Jealous of other people who don't have a food allergy') did not correlate with any of the FAIM questions and was therefore excluded. The validated FAQLQ-CF therefore consists of 24 questions. The total FAQLQ-CF score correlated significantly with the mean FAIM (rho 0.60, $p<0.001$) and with the individual FAIM questions (Table 3). The correlation coefficients for the FAQLQ-CF with the FAIM were the same for children with a food allergy diagnosed by DBPCFC and children with a physician-diagnosed food allergy (total FAQLQ-CF score with the mean FAIM, rho 0.56, $p=0.003$ and rho 0.59, $p<0.001$, respectively). These results demonstrated the construct validity of the FAQLQ-CF, i.e. the FAQLQ-CF is measuring quality of life that is affected by food allergy.

Table 2. Selected items for Food Allergy Quality of Life Questionnaire - Child Form (FAQLQ-CF).

Item	%	MI	OI
Can eat fewer things	94	3.42	3.22
Must always watch what you eat	98	3.04	2.98
The ingredients of a food change	76	3.77	2.88
Limited in buying things you like	80	3.22	2.59
Frightened of an allergic reaction	65	3.88	2.51
Tasting or trying fewer things when eating out	84	2.95	2.49
Frightened of eating the wrong food by accident	69	3.43	2.35
Hesitate eating certain foods when you doubt that it is safe	90	2.59	2.33
Concerned that you will never get rid of your food allergy	57	3.79	2.16
The label states: "May contain traces of...."	67	3.15	2.10
Disappointed when people don't take your food allergy into account	59	3.53	2.08
Not knowing how things taste which you can't eat	67	3.06	2.04
Frightened of eating something you have never eaten before	69	2.94	2.02
Less easily stay for a meal with someone	53	3.74	1.98
Checking yourself whether you can eat something when eating out	80	2.46	1.98
Having to read labels	86	2.16	1.86
Jealous of other people who don't have a food allergy	51	3.62	1.84
Others can eat the food you are allergic to when you do things with other people	82	2.24	1.84
Don't get anything when someone is giving treats at school	47	3.88	1.82
Feeling disappointed because you have a food allergy	59	3.03	1.78
Having to tell beforehand about what you are not allowed to eat when eating out	73	2.43	1.76
Having to explain to people around you that you have a food allergy	88	2.00	1.76
Watching out when touching certain foods	59	2.87	1.69
People around you forget that you have a food allergy	55	3.04	1.67
Refusing food when you do things with others	49	3.20	1.57

MI, mean importance. OI, overall importance.

Domain structure

The 24 items of the FAQLQ-CF were subjected to factor analysis (principal component analysis) and revealed 5 components with eigenvalues >1. To aid in the interpretation of these components, Varimax rotation was performed for 5, 4 and 3 factors. An expert panel reviewed these groupings and based on face validity the grouping of 4 factors made the most sense, explaining 66% of the variance. This revealed the domains: Allergen Avoidance (AA), Risk of Accidental Exposure (RAE), Emotional Impact (EI), and Dietary Restrictions (DR). All factors showed a number of strong loadings (AA, 0.807-0.578; EI, 0.818-0.516; RAE, 0.768-0.611 and DR, 0.877-0.497)). Based on face validity, the expert panel allocated 3 items to a more appropriate domain (Table 3). The domains correlated significantly ($p<0.001$) with the mean FAIM (AA, rho 0.42; RAE, rho 0.60; EI, rho 0.68; and DR, rho 0.38).

Table 3. Spearman correlation coefficients for the FAQLQ-CF with the FAIM and internal consistency (Cronbach's α) of the FAQLQ-CF.

	FAIM							α
	EO1	**EO2**	**EO3**	**EO4**	**IM1**	**IM2**	**Mean**	
Total FAQLQ-CF	**0.34**	**0.35**	**0.46**	**0.38**	**0.43**	**0.56**	**0.60**	0.94
Allergen Avoidance (AA)								0.88
Checking yourself whether you can eat something when eating out	0.12	0.07	0.11	0.34	**0.29**	**0.25**	0.21	
Having to tell beforehand about what you are not allowed to eat when eating out	0.13	0.14	0.17	0.29	**0.28**	**0.28**	**0.25**	
Hesitate eating certain foods when you doubt that it is safe	0.22	0.07	0.14	0.15	0.23	0.21	**0.23**	
Less easily stay for a meal with someone	**0.29**	**0.26**	**0.28**	0.35	**0.52**	**0.48**	**0.47**	
Having to read labels	**0.27**	-0.02	0.08	**0.38**	0.17	0.18	0.15	
Tasting or trying fewer things when eating out	**0.26**	**0.26**	**0.24**	0.35	**0.35**	**0.47**	**0.42**	
Having to explain to people around you that you have a food allergy*	0.18	**0.42**	**0.41**	0.36	**0.31**	**0.49**	**0.50**	
Risk of Accidental Exposure (RAE)								0.82
People around you forget that you have a food allergy	0.18	**0.42**	**0.45**	0.15	**0.32**	**0.54**	**0.57**	
Others can eat the food you are allergic to when you do things with other people	0.22	**0.34**	**0.40**	0.32	**0.42**	**0.47**	**0.52**	
The label states: "May contain traces of…."	0.19	0.18	**0.41**	0.06	0.21	**0.33**	**0.37**	
The ingredients of a food change	**0.37**	**0.36**	**0.45**	0.09	0.23	**0.32**	**0.49**	
Watching out when touching certain foods**	0.13	**0.31**	**0.51**	0.34	**0.30**	**0.58**	**0.51**	
Emotional Impact (EI)								0.87
Frightened of an allergic reaction	**0.37**	**0.42**	**0.53**	0.29	**0.29**	**0.34**	**0.55**	
Frightened of eating the wrong food by accident	**0.31**	**0.49**	**0.60**	0.28	**0.28**	**0.43**	**0.60**	
Concerned that you will never get rid of your food allergy	**0.36**	**0.40**	**0.40**	**0.40**	**0.27**	**0.44**	**0.53**	
Feel disappointed because you have a food allergy	**0.32**	**0.27**	**0.29**	**0.46**	**0.25**	**0.40**	**0.43**	
Frightened of eating something you have never eaten before	**0.24**	**0.43**	**0.52**	0.27	0.23	**0.51**	**0.56**	
Disappointed when people don't take your food allergy into account***	**0.25**	**0.31**	**0.43**	0.28	**0.31**	**0.45**	**0.49**	
Dietary Restriction (DR)								0.83
Can eat fewer things	0.12	-0.01	0.01	0.16	**0.30**	**0.33**	0.19	
Refusing food when you do things with others	0.05	0.10	0.10	0.28	**0.34**	**0.32**	**0.28**	
Not knowing how things taste which you can't eat	**0.23**	0.05	0.06	0.37	0.13	0.21	0.18	
Must always watch what you eat	**0.25**	0.17	**0.29**	0.28	**0.27**	**0.45**	**0.40**	
Limited in buying things you like	0.22	**0.30**	**0.36**	0.29	**0.41**	**0.41**	**0.45**	
Don't get anything when someone is giving treats at school	0.19	0.17	0.15	0.29	**0.28**	0.25	**0.33**	

Bold indicates $p<0.05$. FAQLQ-CF, Food Allergy Quality of life Questionnaire-Child Form. FAIM, Food Allergy Independent Measure. EO1, Chance of accidental exposure. EO2, Chance of severe reaction when accidentally exposed. EO3, Chance of dying when accidentally exposed. EO4, Chance of not acting effectively when accidentally exposed. IM1, Number of foods one needs to avoid. IM2, Impact of food allergy on social life. Based on face validity, the expert panel allocated *item from EI to AA, **item from AA to RAE, and ***item from RAE to EI.

Table 4. Spearman's correlation coefficient for the total FAQLQ-CF score and domains of the FAQLQ-CF with the CHQ-CF87 sub-scales.

	Total FAQLQ-CF	Domains of the FAQLQ-CF			
CHQ-CF87 sub-scales		**AA**	**RAE**	**EI**	**DR**
Physical functioning	-0.13	-0.03	-0.10	-0.14	-0.14
Role functioning- Emotional	**-0.29**	-0.21	**-0.24**	-0.17	**-0.32**
Role functioning-Behaviour	-0.15	-0.12	-0.13	-0.05	-0.17
Role functioning-Physical	**-0.26**	-0.18	-0.21	**-0.26**	**-0.24**
Bodily pain	**-0.23**	-0.13	-0.21	**-0.27**	-0.19
General behaviour	**-0.31**	**-0.34**	-0.12	-0.22	**-0.29**
Mental health	**-0.29**	-0.22	-0.09	**-0.25**	**-0.32**
Self esteem	**-0.29**	**-0.24**	-0.14	**-0.24**	**-0.31**
General health perceptions	**-0.36**	**-0.27**	**-0.35**	**-0.44**	-0.15
Family activities	**-0.45**	**-0.39**	**-0.35**	**-0.41**	**-0.32**
Family cohesion	-0.19	-0.12	-0.04	-0.18	**-0.25**

Bold indicates p<0.05. FAQLQ-CF, Food Allergy Quality of Life Questionnaire-Child Form. AA, Allergen Avoidance. RAE, Risk of Accidental Exposure. EI, Emotional Impact. DR, Dietary Restrictions. Correlation coefficients are negative because a high score on the FAQLQ-CF indicates maximal impairment of quality of life, whereas a high score on the CHQ-CF87 indicates better health status.

Reliability

The FAQLQ-CF and the domains had excellent internal consistency with Cronbach's α exceeding 0.70 (Table 3). The total FAQLQ-CF score intraclass correlation coefficient was 0.91 (95% confidence interval, 0.81-0.96), indicating excellent test-retest reliability.

Discriminative ability

The HRQL of children who reported more than two food allergies was clinically (i.e. >0.5 which is the minimal importance difference [30]) and statistically significantly more impacted than the HRQL of children who reported two or less food allergies (total FAQLQ-CF score 4.3 vs. 3.6; p=0.036). There was no difference in total FAQLQ-CF score between children who reported anaphylaxis (i.e. cardiovascular symptoms) and children who did not report anaphylaxis (4.2 vs. 3.9; p=0.315). If children with respiratory symptoms were added to the group of children with cardiovascular symptoms, the difference in total FAQLQ-CF score was still not significant (p=0.267). In addition, no difference in total FAQLQ-CF score was found between boys and girls (3.8 vs. 4.1; p=0.397) and between children who were recruited from our clinic and children who were recruited by advertisement (3.7 vs. 4.3; p=0.057).

Convergent and discriminant validity

The FAQLQ-CF correlated weakly with 8 of the 11 CHQ-CF87 sub-scales. The highest correlation was found with the CHQ-CF87 sub-scale "Family activities".

In addition, the FAQLQ-CF domains AA, RAE, EI and DR correlated with four, three, six and seven CHQ-CF87 sub-scales, respectively (Table 4). The presence of some correlation, albeit low, indicates that both questionnaires are measuring constructs partly related (i.e. convergent validity). On the other hand, these low correlations indicate that the generic CHQ-CF87 is not as sensitive as the disease-specific FAQLQ-CF and therefore justifies the need of a disease-specific quality of life instrument in food allergic children (i.e. discriminant validity).

Discussion

This report describes the development and cross-sectional validation of the first self-administered disease-specific HRQL questionnaire for food allergic children: the FAQLQ-CF. The content of this questionnaire measures the most important issues that food allergic children have to deal with in their daily life and consequently impairs their quality of life. By using the clinical impact method for selection of the items for the FAQLQ-CF, this questionnaire consists exclusively of items that are regarded as important by children.

In addition, the items of the FAQLQ-CF point to important issues for health care providers, catering industries, food manufacturers and governments to develop and implement regulations that may improve the quality of life of food allergic children [12]. The impact on quality of life of items such as 'Must always watch what you eat' and 'Having to explain to people around you that you have a food allergy' may be reduced if awareness of food allergy is enhanced in the general public. Although recently the labelling legislation has been improved for food allergic patients in Europe and USA [31], the use of precautionary labelling has also increased. The impact of this phenomenon on quality of life is shown by the item 'The label states; "May contain traces of …" Items such as 'Able to eat fewer things' and 'Limited in buying things you like' indicates the desirability of developing new therapeutic interventions which may allow food allergic children to eat the food to which they are allergic and consequently improve quality of life.

In order to validate the FAQLQ-CF, we developed the FAIM, which includes four EO questions and two IM questions. The FAIM measures the child's perception of the severity of his/her condition. The FAIM is based on the approach of expectation of outcome questions that has already been successfully implemented to validate disease-specific HRQL questionnaires [11;18] and these HRQL questionnaires were able to measure relevant and plausible changes over time (i.e. longitudinal validity) [32]. The method of expectation of outcome questions as independent measure is of special use in anaphylactic disorders where no objective measurement of the extent or severity of disease exists [13]. Moreover, purely symptom-based clinical measures would be less applicable to food allergic patients who only experience symptoms when they are exposed to a food to which they are allergic while their HRQL is continuously affected by their condition [4]. The EO questions are based on the

perceived expectation of patients of what will happen following exposure which is likely to be a driving force of quality of life [13]. The IM questions are based on the same principle and ask about the perceived number of foods one needs to avoid and perceived impact on social life. The correlation coefficient we found between the FAQLQ-CF and FAIM (0.60), is in accordance with other studies using solely EO questions to validate the disease-specific HRQL questionnaires, which found correlation coefficients of 0.69 [18] and 0.41 [11], respectively. Finally, validation of the FAQLQ-CF was carried out in the Dutch language and carefully translated into English using the guidelines of the World Health Organization. The validity of the questionnaire in English and eight other European languages is currently being investigated.

The items for the FAQLQ-CF were selected by using the clinical impact method which reveals items that are clinically most important as perceived by food allergic children. This is in contrast to the method of selecting items based on mathematical linkage between items by performing factor analyses. The latter method has the potential drawback that it may result in excluding items with a high clinical impact [29]. However, because we included items based on clinical importance rather than mathematical linkage between the items, the allocation of items into domains revealed by the factor analysis did not always make intuitive sense. Therefore, the allocation of items into domains was based on factor analysis supplemented by allocation based on face validity determined by an expert panel. Calculation of Cronbach's alpha showed that these domains were internally consistent because they all had a Cronbach alpha exceeding 0.70.

In the current study, the clinical impact method may also have some limitations. The number of children included in the item reduction was relatively small compared to the number of items of the extended item questionnaires. If the sample size was larger, it may be that other items gained more impact and would possibly be included in the questionnaire. However, although the sample size was relatively small, it was a representative sample, and therefore we think that the extended item questionnaire was reduced to the correct items. Another limitation of the clinical impact method may be that the selected items cover a relatively narrow range of items, resulting in a very high overall Cronbach's alpha.

Typically, HRQL questionnaires inquire about events during a specific period, e.g. one week or one month. However, such a restricted reporting period may result in missing important issues outside the reporting period. Moreover, many patients verbalized discontent with the short and framed reporting period of one week of the Food Allergy Quality of Life – Parental Burden (FAQL-PB) questionnaire [11]. Therefore, we used a less restricted reporting period. Patients were asked to complete the questionnaire according to their current state. This method will allow for before-after comparison in intervention studies and analysing changes over time without loss of important information by a restricted reporting period.

The FAQLQ-CF discriminates well between children who reported more than two food allergies and children who reported two or fewer food allergies, but there was no difference in total FAQLQ-CF score in children who reported anaphylaxis

(i.e. cardiovascular symptoms) and children who did not report anaphylaxis. There may be two possible explanations for this finding. The first possibility is that many children may not remember an anaphylactic reaction well [33]. Indeed, in our patient group with a mean age of 10.2 (SD 1.3) years, we found that the most severe reaction occurred a mean of 4.2 (SD 3.4) years ago. However, we could not find any relation between the time since the most severe reaction and the total FAQLQ-CF score (rho -0.08, p=0.490) making this explanation unlikely. We thus speculate that children may be too young to realize the potentially life-threatening consequences of severe anaphylactic reactions to food. This suggests that in children, the day-to-day consequences of the food allergy itself, including the avoidance requirements and the possibility of an allergic reaction, impairs quality of life irrespective of the severity of symptoms in the past.

It is known from the literature that the minimal importance difference (MID) of HRQL questionnaires with a seven-point scale is approximately 0.5. The MID is the smallest difference in score which patients perceive as beneficial and which would mandate, in absence of troublesome side effects and excessive cost, a change in the patient's management [30]. Therefore, the difference in total FAQLQ-CF score between children who reported more than two food allergies and children who reported two or less food allergies was not only a statistically significant difference but also a clinically significant difference. Although the MID of 0.5 is a robust estimate for HRQL questionnaires with a seven-point scale, the specific MID of the FAQLQ-CF remains to be estimated in a longitudinal survey.

The FAQLQ-CF is the first disease-specific HRQL questionnaire for food allergic children that asks children to assess their own quality of life. It is important to ask children themselves about their quality of life, because children and parents differ in their views and judgments about quality of life [34]. In general, parents are less able to make judgments regarding the experience of symptoms, relationships with peers or worries about the future [35]. On the other hand, it is obvious that in very young children one can only make use of the proxy ratings of the parents. A parent administered instrument has been developed in the context of the EuroPrevall project (FAQLQ-PF) [36] and studies are in progress to determine in which age groups one or both of these questionnaires may be used to obtain optimal measurements of HRQL in food allergic children. Possible drawbacks of a self-administered questionnaire for children are that the result may be affected by reading limitations of children or that parents may interfere with the completion of the questionnaire. However, it has been reported that children aged 8 to 12 years can self-report reliably on their health-status [37]. In addition, children are likely to express a level of concern regarding their food allergy that is in keeping with their usual level of concern in the home environment, and we therefore asked them to complete questionnaires at home. This also made the study less burdensome for these children and thus more feasible. To reduce unwanted parental influence as much as possible, we emphatically instructed parents and children that the children should fill out the questionnaire by themselves.

In summary, we have described for the first time a disease-specific HRQL questionnaire for food allergic children. The FAQLQ-CF is valid, reliable and short and it measures the most important issues that food allergic children have to face. In addition, it discriminates between children who differ in number of food allergies and it was easy to use in the population studied. Therefore, the FAQLQ-CF is a suitable questionnaire for studies of food allergic children in which HRQL is the outcome of interest. Examples include investigation of the effect of emerging treatments such as oral immunotherapy and anti-IgE therapy on quality of life. The instrument may be accessed directly from this publication and it is available in numerous European language translations from the author.

Acknowledgements

This work was funded by the EU through the EuroPrevall project (FOOD-CT-2005-514000). We would like to thank Arnaud Boom, consultant/teacher for sick children, and Karel Verbeek, linguist, for reviewing the extended item questionnaire and the FAQLQ-CF and Tina van der Velde for performing the test-retest of the FAQLQ-CF.

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Appendix 1: Food Allergy Quality of Life Questionnaire – Child Form (8-12 years)

Instructions
The questions are about the influence of your food allergy on your quality of life. It is important that you fill out the answers yourself. You may ask your parents for help, but they are not allowed to tell you which answer to give. Answer every question by putting an 'x' in the proper box. You may choose from the following answers.

not barely a little bit fairly quite very extremely

How *troublesome* do you find it, because of your food allergy, that you ...	
1 must always watch what you eat?	☐ ☐ ☐ ☐ ☐ ☐ ☐
2 can eat fewer things?	☐ ☐ ☐ ☐ ☐ ☐ ☐
3 are limited in buying things you like?	☐ ☐ ☐ ☐ ☐ ☐ ☐
4 have to read labels?	☐ ☐ ☐ ☐ ☐ ☐ ☐
5 have to refuse food when you do things with others?	☐ ☐ ☐ ☐ ☐ ☐ ☐
6 can less easily stay for a meal with someone?	☐ ☐ ☐ ☐ ☐ ☐ ☐
7 can taste or try fewer things when eating out?	☐ ☐ ☐ ☐ ☐ ☐ ☐
8 have to tell beforehand about what you are not allowed to eat when eating out?	☐ ☐ ☐ ☐ ☐ ☐ ☐
9 have to check yourself whether you can eat something when eating out?	☐ ☐ ☐ ☐ ☐ ☐ ☐
10 hesitate eating certain foods when you don't know if it is safe?	☐ ☐ ☐ ☐ ☐ ☐ ☐
11 must watch out when touching certain foods?	☐ ☐ ☐ ☐ ☐ ☐ ☐
12 don't get anything when someone is giving treats at school?	☐ ☐ ☐ ☐ ☐ ☐ ☐

not barely a little bit fairly quite very extremely

How *troublesome* is it, because of your food allergy, ...	
13 that the ingredients of a food change?	☐ ☐ ☐ ☐ ☐ ☐ ☐
14 that the label states: "May contain traces of...."?	☐ ☐ ☐ ☐ ☐ ☐ ☐
15 that you have to explain to people around you that you have a food allergy?	☐ ☐ ☐ ☐ ☐ ☐ ☐
16 that people around you forget that you have a food allergy?	☐ ☐ ☐ ☐ ☐ ☐ ☐
17 that others can eat the food you are allergic to when you do things with other people?	☐ ☐ ☐ ☐ ☐ ☐ ☐
18 that you don't know how things taste which you can't eat?	☐ ☐ ☐ ☐ ☐ ☐ ☐

How *frightened* are you because of your food allergy ...	
19 of an allergic reaction?	☐ ☐ ☐ ☐ ☐ ☐ ☐
20 of eating the wrong food by accident?	☐ ☐ ☐ ☐ ☐ ☐ ☐
21 to eat something you have never eaten before?	☐ ☐ ☐ ☐ ☐ ☐ ☐

Answer the following questions:	
22 How *concerned* are you that you will never get rid of your food allergy?	☐ ☐ ☐ ☐ ☐ ☐ ☐
23 How *disappointed* are you when people don't take your food allergy into account?	☐ ☐ ☐ ☐ ☐ ☐ ☐
24 How *disappointed* do you feel because you have a food allergy?	☐ ☐ ☐ ☐ ☐ ☐ ☐

Appendix 2: Food Allergy Independent Measure – Child Form (8-12 years)

The following four questions are about the chance that you think you have of something happening to you because of your food allergy. Choose one of the answers. This is followed by two more questions about your food allergy. Answer every question by putting an 'x' in the box next to the proper answer.

0 never (0% chance)	**1** very small chance	**2** small chance	**3** fair chance	**4** big chance	**5** very big chance	**6** always (100% chance)

How big do you think the chance is that you ...	0	1	2	3	4	5	6
a. will accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
b. will have a severe reaction if you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
c. will die if you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
d. can *not* do the right things for your allergic reaction should you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐

e. **How many foods are you unable to eat because of your food allergy?**	f. Everyone does things with other people, such as; playing with friends, going to a birthday party, visiting, staying over with someone for a meal or eating out. **How much does your food allergy affect things you do with others?**
☐ almost none	☐ so little I don't actually notice it
☐ very few	☐ very little
☐ a few	☐ a little
☐ some	☐ moderately
☐ many	☐ a good deal
☐ very many	☐ a great deal
☐ almost all	☐ a very great deal

Chapter 4

Development and validation of the self-administered Food Allergy Quality of Life Questionnaire for adolescents

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J Allergy Clin Immunol 2008;122:139-144

Abstract

Background:
Food allergy may affect health-related quality of life (HRQL). Currently no validated, self-administered, disease-specific HRQL questionnaire for adolescents with food allergy exists.

Objective:
To develop and validate the Food Allergy Quality of Life Questionnaire-Teenager Form (FAQLQ-TF) in the Dutch language.

Methods:
Ten food allergic adolescents (13-17 years) were interviewed and generated 166 HRQL items. The most important items were identified by 51 food allergic adolescents using the clinical impact method, resulting in the FAQLQ-TF containing 28 items (score range 1 'no impairment' to 7 'maximal impairment'). The FAQLQ-TF, the Food Allergy Independent Measure (FAIM) and a generic HRQL questionnaire (CHQ-CF87) were sent to 98 food allergic adolescents for cross-sectional validation of the FAQLQ-TF.

Results:
Construct validity was assessed by the correlation between the FAQLQ-TF and the FAIM (rho 0.57, $p<0.001$). The FAQLQ-TF had excellent internal consistency (Cronbach α 0.92) and discriminated between adolescents who differed in number of food allergies (1 food allergy vs. $\geq$2 food allergies, total FAQLQ-TF score, 4.3 vs. 3.5; $p=0.037$), but did not discriminate between reported anaphylaxis or not. The FAQLQ-TF correlated weakly with 6 of the 11 CHQ-CF87 scales, demonstrating convergent/discriminant validity.

Conclusion:
The FAQLQ-TF is the first self-administered, disease-specific HRQL questionnaire for food allergic adolescents. It has good construct validity and excellent internal consistency and discriminates between adolescents who differ in number of food allergies. The FAQLQ-TF is short and easy to use and may therefore be a useful tool in clinical research.

Introduction

Having a food allergy can be fatal and adolescents are at the highest risk of death from food allergy [1-3]. It is estimated that 2.3% of adolescents are food allergic [4]. The only effective form of treatment of food allergy is strict avoidance of the implicated food(s) and provision of medications for emergency treatment [5]. In spite of the high risk of death, food allergic adolescents actually reported social isolation as the most disturbing aspect of their disease [6]. In addition, some adolescents reported depression as a result of food allergy and this may lead to difficulties in school performance and leisure activities [7]. Thus, food allergic adolescents need to be continuously alert as to what they are eating in numerous situations and settings and, along with the fear of allergic reactions, this may have a negative impact on quality of life.

At present, no validated self-administered, food-allergy-specific health-related quality of life (HRQL) questionnaire exists for use in adolescents. A few studies have reported that food allergy has a negative impact on HRQL in adolescents. However, three limitations arise when interpreting these studies. First, no distinction was made between adolescents and younger children [8-13], whereas HRQL in adolescents needs to be addressed separately, because HRQL may be influenced by the stage of neurocognitive and emotional development of an individual [14;15]. Second, HRQL questionnaires were administered to parents thus measuring parents' perceptions [8-13]. However, children and parents differ in their views and judgments about quality of life [16]. Finally, studies used generic HRQL questionnaires [11-13;17] or disease-specific questionnaires which have not been validated [8;10], whereas generic HRQL questionnaires are not as sensitive as disease-specific HRQL questionnaires [18] and validation is extremely important in order to determine whether the questionnaire is measuring that part of quality of life which is determined by the target disorder [19].

Therefore, we have developed and cross-sectionally validated the first self-administered, food-allergy-specific HRQL questionnaire for adolescents, the Food Allergy Quality of Life Questionnaire-Teenager Form (FAQLQ-TF). This questionnaire has been developed as part of the EuroPrevall project, a European multi-center research project on food allergy. The FAQLQ-TF complements the recently developed self-administered Food Allergy Quality of Life Questionnaire-Child Form (FAQLQ-CF) for children aged 8 to 12 years (B.M.J. Flokstra-de Blok et al., unpublished data, June 2008) and the parent-administered Food Allergy Quality of Life Questionnaire-Parent Form (FAQLQ-PF) for parents of food allergic children aged 0 to 12 years [20].

Methods

Participants and procedure

During item generation, participants were recruited only from our outpatient pediatric allergy clinic. Two adolescents were approached during a double-blind placebo-controlled food challenge (DBPCFC) and, based on patient records, eight adolescents were approached by phone. All approached adolescents (n=10) agreed to participate in an interview on the impact of food allergy on their daily life.

During item reduction and cross-sectional validation, participants were recruited from our outpatient pediatric allergy clinic (based on patient records or appointments for DBPCFC) or were recruited by advertisement in local news papers and through food allergy support organizations (the Dutch Foundation for Food Allergy and the Dutch Anaphylaxis Network). A letter of invitation, the questionnaire and a pre-paid return envelop was sent to suitable adolescents from our clinic and to adolescents who responded to the advertisement. The letter of invitation stressed that participation was completely voluntary. When the questionnaire was not returned within a month, the adolescent was contacted by phone as a reminder. Adolescents were not paid for their participation in any stage of questionnaire development or validation.

Before cross-sectional validation, the questionnaire was pretested in three adolescents (aged 13, 15 and 17 years). No major problems emerged during this pretest. Thereafter, the FAQLQ-TF, the Food Allergy Independent Measure (FAIM) and the CHQ-CF87, a generic quality of life questionnaire, were sent by mail to 98 food allergic adolescents. Some of them had participated in the item generation (10%) or item reduction (49%). Descriptive characteristics were asked regarding age, sex, type and number of food allergies, type of symptoms and diagnosis. For the adolescents recruited from our clinic, we checked patient records to determine whether food allergy had been diagnosed by a DBPCFC.

During all stages of questionnaire development and validation, all common food allergies and different types and severities of symptoms were represented. The study was approved by the local medical ethics review commission (METc 2005/051) who deemed that permission from the commission was not required.

Development

Item generation

For the development and validation of the FAQLQ-TF, the same methodology was used as for the development and validation of the FAQLQ-CF, which is described in more detail elsewhere (B.M.J. Flokstra-de Blok et al., unpublished data, June 2008). Briefly, potential items for the new questionnaire were generated by interviewing 10 food allergic adolescents (aged 13-17 years). In addition, literature review and expert opinion were consulted. This resulted in an extended item questionnaire of 166 items.

Item reduction

The extended item questionnaire was sent to a different group of 51 food allergic adolescents to identify the most important items by using the clinical impact method [21;22]. The adolescents were asked to indicate the importance of applicable items using a five-point scale. Frequency (percentage) was multiplied by mean importance (MI), resulting in the overall importance (OI) of each item. The maximal possible OI was 5.0 [23;24]. Items with the greatest OI were selected for the FAQLQ-TF, except one of any pair of items with an inter-item correlation >0.85 and/or overlapping content (face validity). The selected items were worded as questions having a seven-point response scale ranging from 'not troubled' to 'extremely troubled'[22;24]. A psychologist and a linguist reviewed the FAQLQ-TF for clarity and ease of use.

Cross-sectional validation

Construct validity

Construct validity was investigated by calculation of correlation coefficients for the FAQLQ-TF with the Food Allergy Independent Measure (FAIM). This approach has already been successfully implemented to validate disease-specific HRQL questionnaires [9;20;24] and it is especially useful in anaphylactic disorders where no objective measurement of the extent or severity of disease exists [25]. The FAIM includes four Expectation of Outcome (EO) questions and two Independent Measure (IM) questions. The EO questions are based on the perceived expectation of patients of what will happen following exposure which is likely to be a driving force of quality of life [25]. The IM questions are based on the same principle and ask about the perceived number of foods one needs to avoid and perceived impact on social life. We expected moderate correlation coefficients (0.40-0.60) for the FAQLQ-TF with the FAIM. The validation of the FAQLQ-TF was carried out in the Dutch language. The English version of the FAQLQ-TF and the FAIM may be found as Appendix 1 and 2. The Dutch FAQLQ-TF and the FAIM were translated into English by a native English speaker and back translated by a native Dutch speaker, according to the guidelines of the World Health Organization [26]. The original Dutch version was compared with the back translated Dutch version. No important differences in content or meaning of questions emerged.

Discriminative ability

To establish the discriminative ability of the FAQLQ-TF, we compared the total FAQLQ-TF score for adolescents who reported anaphylaxis (i.e. adolescents who reported two or more of the following cardiovascular symptoms; dizziness, feeling your heart beat fast, loss of vision, inability to stand, light headedness, collapse, loss of consciousness/passing out) versus adolescents who did not, for adolescents who reported many food allergies versus adolescents who reported few food allergies, for boys versus girls [27] and for adolescents who were recruited from our clinic versus adolescents who were recruited by advertisement.

Reliability
The reliability of the FAQLQ-TF was assessed by administering the questionnaire to 34 adolescents on 2 occasions 10-14 days apart.

Convergent and discriminant validity
To investigate convergent and discriminant validity, a generic HRQL questionnaire was administered: the Child Health Questionnaire-Child Form (CHQ-CF87) [28;29]. This questionnaire is self-administered by adolescents and contains 87 items divided into twelve scales. We expected weak correlation coefficients (0.20-0.40) for the FAQLQ-TF with the CHQ-CF87.

Statistical analyses
The raw FAQLQ-TF and FAIM scores 0 to 6 were recoded as 1 to 7. The total FAQLQ-TF score is the mean score of all items with a range of 1 'no impairment' to 7 'maximal impairment'. To assess construct validity, Spearman's correlation coefficients were calculated between the FAQLQ-TF and the FAIM. The allocation of the items of FAQLQ-TF into domains was based on factor analysis (principal component analysis with Varimax rotation) [30] and face validity determined by a clinical expert panel (BMJFdB, JNGOE and AEJD) [14;31]. To investigate the internal consistency of the FAQLQ-TF and the domains, Cronbach's α were calculated. An α greater than 0.70 indicates good internal consistency [32]. The Mann-Whitney test was used for measuring the discriminative ability of the FAQLQ-TF. The reliability of the FAQLQ-TF was assessed by calculating the intraclass correlation coefficient of the repeated FAQLQ-TF measurement [33]. Finally, convergent and discriminant validity were assessed by calculating Spearman's correlation coefficients between the FAQLQ-TF and the CHQ-CF87 scales. Statistical analyses were performed with SPSS for Windows 14.0 (SPSS Inc., Chicago, IL, USA).

Results

Development
Descriptive characteristics of the adolescents involved in the item generation and item reduction are shown in Table 1. The extended item questionnaire was returned by 46 adolescents (response rate 90%). The OI scores of all 166 items of the extended item questionnaire ranged from 0.00 to 2.89. The item reduction resulted in the selection of 28 items (OI$\geq$1.37) for the FAQLQ-TF (Table 2).

Cross-sectional validation

Participants
The questionnaire package including the FAQLQ-TF, the FAIM and the CHQ-CF87 were returned by 75 adolescents (response rate 77%). One adolescent

Table 1. Descriptive characteristics of the adolescents involved in the item generation, item reduction and cross-sectional validation.

	Item generation	Item reduction	Cross-sectional validation
Participants (n)	10	46	74
Sex (m/f)	4/6	23/23	34/40
Age, mean in years (SD)	14.2 (1.5)	14.9 (1.4)	14.7 (1.3)
Food allergy, n (%)			
Peanut	7 (70)	36 (78)	57 (77)
Tree nuts	8 (80)	33 (72)	56 (76)
Egg	3 (30)	17 (37)	26 (35)
Milk	5 (50)	15 (33)	29 (39)
Fish	2 (20)	8 (17)	13 (18)
Shell fish	1 (1)	10 (22)	12 (16)
Wheat	0	4 (9)	5 (7)
Sesame	0	7 (15)	8 (11)
Soy	3 (30)	11 (26)	17 (23)
Celery	0	4 (9)	3 (4)
Number of food allergies, n (%)			
1 food	3 (30)	10 (22)	12 (16)
2 foods	0	16 (35)	31 (42)
3 foods	1 (10)	2 (4)	8 (11)
>3 foods	6 (60)	17 (33)	23 (31)
Type of symptoms, n (%)			
Cardiovascular[1]	4 (40)	9 (20)	17 (23)
Respiratory tract[2]	3 (30)	26 (58)	39 (53)
Gastrointestinal tract[3]	2 (20)	4 (9)	11 (15)
Skin[4]	1 (10)	4 (9)	4 (5)
Other[5]	0	2 (4)	3 (4)

[1] dizziness, feeling your heart beat fast, loss of vision, inability to stand, light headedness, collapse, loss of consciousness / passing out. [2] tightening throat, difficulty swallowing, hoarseness / hoarse voice, difficulty breathing in, shortness of breath, wheezing, cough. [3] sick to your stomach, stomach cramps, vomiting, diarrhea. [4] itchy skin, red rash, hives, worsening eczema, swelling of the skin. [5] oral allergy, swollen tongue or lips, symptoms of the nose or eyes.

was excluded because the descriptive characteristics were missing from the questionnaire, resulting in 74 assessable questionnaires for the cross-sectional validation. Forty-three adolescents (58%) were recruited from our clinic, of which 19 (26%) had a food allergy confirmed by a DBPCFC. The other adolescents from our clinic had a physician-diagnosed food allergy (skin prick and/or blood test) and the majority was awaiting DBPCFC. All adolescents recruited by advertisement (42%) reported physician-diagnosed food allergies. Descriptive characteristics of the adolescents involved in the cross-sectional validation are shown in Table 1. There were no significant differences in descriptive characteristics between boys and girls, between adolescents recruited from our clinic and adolescents recruited by advertisement or between adolescents with a physician-diagnosed food allergy and adolescents with a food allergy diagnosed by DBPCFC.

Table 2. Selected items for the FAQLQ-TF.

Item	%	MI	OI
Always be alert as to what you are eating	91	3.17	2.89
Change of ingredients of a product	87	3.30	2.87
Able to eat fewer products	91	3.12	2.85
Having to read labels	93	2.98	2.78
Troublesome for those with whom you are eating if you have an allergic reaction	80	3.41	2.74
Hesitate eating a product when you have doubts about it	96	2.77	2.65
Label states: "May contain traces of…."	76	3.29	2.50
Refusing treats at school or work	85	2.82	2.39
Limited as to the products you can buy	96	2.45	2.35
Less able to taste or try various products when eating out	83	2.61	2.15
Frightened of an allergic reaction	54	3.68	2.00
Checking personally whether you can eat something when eating out	85	2.31	1.96
Refusing many things during social activities	65	2.93	1.91
Being careful about touching certain foods	67	2.81	1.89
Disappoint people when they are making an effort to accommodate your food allergy	57	3.35	1.89
Frightened of accidentally eating something wrong	61	2.96	1.80
Frightened of eating something you have never eaten before	59	2.85	1.67
The labeling of the bulk packaging (for example box or bag) is different than the individual packages	57	2.92	1.65
The feeling that you have less control of what you eat when eating out	65	2.53	1.65
Disappointed when people do not take your food allergy into account	57	2.77	1.57
Less able to spontaneously accept an invitation to stay for a meal	52	2.92	1.52
Carrying an Epipen	63	2.41	1.52
People must accommodate you when you visit them	54	2.68	1.46
Having to explain to people around you that you have a food allergy	87	1.68	1.46
During social activities your food allergy is not taken into account	39	3.67	1.43
During social activities others can eat the food to which you are allergic	91	1.57	1.43
Not knowing how things taste which you can't eat	48	2.95	1.41
Feel discouraged during an allergic reaction	39	3.50	1.37

MI, mean importance. OI, overall importance.

Construct validity

Most items of the FAQLQ-TF correlated significantly with at least one of the FAIM questions and with the mean of the FAIM questions. Five items did not correlate with any of the FAIM questions and were therefore excluded from the questionnaire. The validated FAQLQ-TF therefore consists of 23 questions. As expected, we found moderate correlation coefficients between the FAQLQ-TF and the FAIM. The total FAQLQ-TF score correlated significantly with the mean FAIM (rho 0.57, $p<0.001$) and with the individual FAIM questions (Table 3). This significant correlation coefficient was found for adolescents with a food allergy diagnosed by DBPCFC and for adolescents with a physician-diagnosed food allergy (total FAQLQ-TF score

Table 3. Spearman correlation coefficients for the FAQLQ-TF with the FAIM and internal consistency (Cronbach'sα) of the FAQLQ-TF.

	FAIM							α
	EO1	EO2	EO3	EO4	IM1	IM2	Mean	
Total FAQLQ-TF	**0.44**	**0.29**	0.15	**0.50**	**0.41**	**0.54**	**0.57**	0.92
Allergen Avoidance & Dietary Restrictions (AADR)								0.89
Refuse treats at school or work	**0.29**	0.22	-0.12	**0.46**	0.13	0.16	**0.27**	
Able to eat fewer products	**0.37**	0.12	0.08	**0.46**	**0.27**	**0.28**	**0.35**	
Limited as to the products you can buy	**0.28**	0.09	0.01	**0.34**	**0.34**	**0.41**	**0.34**	
Less able to taste or try various products when eating out	**0.38**	**0.33**	0.14	**0.46**	0.25	**0.38**	**0.49**	
Hesitate eating a product when you have doubts about it	**0.30**	0.15	-0.03	0.32	0.14	**0.26**	**0.27**	
Less able to spontaneously accept an invitation to stay for a meal	0.21	**0.26**	0.00	0.21	0.25	0.17	**0.30**	
Always be alert as to what you are eating	**0.44**	0.19	0.19	0.32	0.11	0.19	**0.33**	
Checking personally whether you can eat something when eating out	**0.24**	**0.29**	0.18	0.33	0.18	**0.44**	**0.39**	
Having to read labels*	**0.29**	0.06	0.10	**0.37**	0.18	**0.35**	**0.27**	
Having to explain to people around you that you have a food allergy*	0.16	0.14	0.20	**0.43**	0.07	**0.45**	**0.27**	
Emotional Impact (EI)								0.81
Frightened of eating something you have never eaten before	**0.30**	0.23	0.19	**0.45**	**0.45**	**0.41**	**0.48**	
Frightened of an allergic reaction	**0.33**	**0.31**	0.15	**0.40**	0.20	**0.27**	**0.42**	
Frightened of accidentally eating something wrong	**0.37**	**0.28**	0.20	**0.46**	**0.41**	**0.45**	**0.53**	
Feel discouraged during an allergic reaction	**0.36**	0.10	0.21	**0.34**	0.03	0.14	0.18	
The feeling that you have less control of what you eat when eating out	**0.32**	0.05	0.09	**0.36**	**0.40**	**0.38**	**0.38**	
Disappointed when people do not take your food allergy into account	0.17	**0.29**	0.12	0.51	**0.34**	**0.38**	**0.43**	
Carrying an Epipen	0.14	**0.41**	0.30	0.33	-0.20	-0.12	0.15	
Risk of Accidental Exposure (RAE)								0.81
Change of ingredients of a product	**0.33**	-0.08	0.02	0.33	**0.43**	**0.30**	**0.27**	
The labeling of the bulk packaging (for example box or bag) is different than the individual packages	0.16	0.01	0.15	0.11	**0.30**	0.14	0.20	
Label states: "May contain traces of…."	**0.40**	0.10	0.14	0.28	**0.33**	**0.42**	**0.40**	
Being careful about touching certain foods	0.20	0.08	-0.07	**0.46**	0.27	**0.49**	**0.29**	
During social activities your food allergy is not taken into account	0.21	0.10	-0.11	**0.58**	**0.34**	**0.46**	**0.34**	
During social activities others can eat the food to which you are allergic**	**0.38**	0.18	0.06	**0.40**	**0.31**	**0.39**	**0.42**	

p<0.05 is shown in bold. EO1, Chance of accidental exposure. EO2, Chance of severe reaction when accidentally exposed. EO3, Chance of dying when accidentally exposed. EO4, Chance of not acting effectively when accidentally exposed. IM1, Number of foods one needs to avoid. IM2, Impact of food allergy on social life. Based on face validity, the expert panel allocated *items from EI to AADR and **item from AADR to RAE.

with the mean FAIM, rho 0.76, p<0.001 and rho 0.52, p<0.001, respectively). These results support the construct validity of the FAQLQ-TF. That is, the FAQLQ-TF measures that part of quality of life that is affected by food allergy. Expectation of Outcome question 3 (EO3) did not correlate with any of the individual HRQL items and is thus unlikely to be an appropriate independent measure for food allergy in adolescents. Therefore, we excluded this question from further analyses.

Domain structure and internal consistency

The 23 items of the FAQLQ-TF were subjected to factor analysis (principal component analysis), which revealed 5 factors with eigenvalues >1. To aid in the interpretation of these factors, Varimax rotation was performed for 5, 4 and 3 factors. These groupings were reviewed by an expert panel, and based on face validity the grouping of 3 factors made the most sense. This grouping revealed the following domains: Allergen Avoidance and Dietary Restrictions, Emotional Impact and Risk of Accidental Exposure. These three factors showed a number of strong loadings; all exceed 0.300, which is regarded as an acceptable criterion [30]. The expert panel allocated 3 items to a more appropriate domain based on face validity. The FAQLQ-TF and the domains had excellent internal consistency with Cronbach's α exceeding 0.70 (Table 3).

Discriminative ability

Adolescents who reported 2 or more food allergies reported a significantly more impaired HRQL than adolescents who reported only 1 food allergy (total FAQLQ-TF score 4.3 vs. 3.5; p=0.037). There was no significant difference in total FAQLQ-TF score between adolescents who reported anaphylaxis (cardiovascular symptoms) and adolescents who did not report anaphylaxis (4.5 vs. 4.0; p=0.184) or between boys and girls (4.0 vs. 4.3; p=0.324). Adolescents who were recruited by advertisement reported a significantly more impaired HRQL than adolescents recruited from our clinic (total FAQLQ-TF score 4.6 vs. 3.9; p=0.015).

Reliability

The total FAQLQ-TF score intraclass correlation coefficient was 0.98 (95% confidence interval, 0.95-0.99), indicating excellent test-retest reliability.

Convergent and discriminant validity

The total FAQLQ-TF score correlated weakly with 6 of the 11 CHQ-CF87 scales. In addition, the domains of the FAQLQ-TF correlated weakly with several CHQ-CF87 scales (Table 4). This indicates that both questionnaires measure constructs that are partly related (i.e. convergent validity). However, as expected the correlations are weak and sometimes even absent because the CHQ-CF87 is a generic quality of life questionnaires and therefore not as sensitive as the disease-specific FAQLQ-TF (i.e. discriminant validity).

Table 4. Spearman's correlation coefficients for the total FAQLQ-TF score and domains of the FAQLQ-TF with the CHQ-CF87 scales.

	Total FAQLQ-TF	Domains of the FAQLQ-TF		
CHQ-CF87 scales		**AADR**	**EI**	**RAE**
Physical functioning	**-0.29**	-0.18	-0.22	**-0.37**
Role functioning- Emotional	-0.15	**-0.23**	0.04	-0.07
Role functioning-Behavior	-0.16	-0.18	-0.12	-0.10
Role functioning-Physical	-0.20	-0.15	**-0.25**	-0.11
Bodily pain	**-0.29**	**-0.27**	**-0.28**	-0.18
General behavior	-0.23	-0.19	**-0.32**	-0.09
Mental health	**-0.33**	**-0.33**	**-0.37**	-0.15
Self esteem	**-0.27**	**-0.27**	**-0.30**	-0.20
General health perceptions	**-0.31**	**-0.27**	**-0.36**	-0.16
Family activities	**-0.43**	**-0.37**	**-0.39**	**-0.35**
Family cohesion	-0.19	**-0.27**	-0.19	0.05

$p<0.05$ is shown in bold. AADR, Allergen Avoidance and Dietary Restrictions. EI, Emotional Impact. RAE, Risk of Accidental Exposure. Correlation coefficients are negative because a high score on the FAQLQ-TF indicates maximal impairment of quality of life, whereas a high score on the CHQ-CF87 indicates better health status.

Discussion

We have developed and validated the first health-related quality of life (HRQL) questionnaire specific for adolescents with food allergy, the Food Allergy Quality of Life Questionnaire-Teenager Form (FAQLQ-TF). We found that the FAQLQ-TF has good construct validity and excellent internal consistency (Table 3). In addition, the FAQLQ-TF discriminates between adolescents who differ in number of food allergies. Finally, the FAQLQ-TF showed convergent/discriminant validity (Table 4), which supports the need for a disease-specific quality of life questionnaire for food allergic adolescents.

It is known that HRQL may be influenced by the current stage of cognitive, social and emotional development of an individual. Therefore, it has been argued that HRQL in adolescents should be measured by means of a specific instrument [14;15]. The FAQLQ-TF was specifically designed for food allergic adolescents aged 13 to 17 years. Age appropriateness was ensured by generating and including only items that were regarded as important by food allergic adolescents (clinical impact method). The FAQLQ-TF focuses on the perceptions of the adolescents themselves, because the questionnaire is self-administered.

Many of the items in this instrument are specific to adolescents. An example is 'Carrying an Epipen'. The Epipen issue in food allergic adolescents is in concordance with the literature. It has been reported that adolescents raise concerns about its size and portability [34], and sometimes adolescents do not carry it based on social circumstances and perceived risks [35]. Despite our age specific approach and the separate development of child and adolescent questionnaires, it is striking that

approximately two thirds of the adolescent questions in the FAQLQ-TF correspond to the child questions in the FAQLQ-CF (B.M.J. Flokstra-de Blok et al., unpublished data, June 2008). Thus, although we generated many age specific items, there are apparently 'general' food allergy items that are important in children and adolescents. Furthermore, we found that the three most important items that impair quality of life were the same in children and teenagers ('Always be alert as to what you are eating', 'The ingredients of a product change', 'Able to eat fewer products').

An unexpected finding was that EO3 (Chance of dying when accidentally exposed) was not correlated with any of the items of the FAQLQ-TF. This may indicate that fear of dying of food allergy is not a driving force of quality of life in adolescents, which may be characteristic and specific for adolescents. It has been reported that adolescents perceived their anaphylaxis as 'no big deal' [34]. In addition, adolescents are at the highest risk of death from food allergy [1-3]. This high risk may be the result of underestimation of the severity of food allergy and the belief of adolescents that they will not die from any cause, including their food allergy. In fact, there were no adolescents in this study who reported 'always (100% chance)' of dying when accidentally exposed, whereas this was reported by 5% of children and 4% of adults in other FAQLQ validation studies (not shown). Although not statistically significant, this is a noteworthy observation. The incorrect belief of immortality of adolescents may result in risk-taking behavior that may increase the risk of dying from a food allergy. Therefore, physicians and other health-care providers should be aware that underestimation of food allergic symptoms may be important when counseling adolescents with food allergy.

When comparing the discriminative results of the FAQLQ-TF with the FAQLQ-CF (B.M.J. Flokstra-de Blok et al., unpublished data, June 2008), 2 interesting observations emerged. First, there was no significant difference in total FAQLQ-TF score between adolescents who reported anaphylaxis (cardiovascular symptoms) and adolescents who did not. The same result was found in children. Secondly, adolescents who were recruited by advertisement reported a significantly more impaired HRQL than adolescents recruited from our clinic. This difference was not significant in children, although a trend was seen. It may be that adolescents experience safety and security by being looked after in the clinic, whereas adolescents outside the clinic experience more uncertainty and insecurity about their food allergy [36]. Most adolescents recruited from our clinic were known to us for many years (mean number of years since first visit 12.5 (SD 5.4)). In addition, it has recently been shown that parental trait anxiety is higher in parents of children with a suspected food allergy who refused to participate in a DBPCFC than parents who did participate (W.T. Zijlstra et al., unpublished data, June 2008). Since it is known that parental anxiety is related to child anxiety [37], it may be that the adolescents in our study recruited by advertisement have higher levels of trait anxiety than adolescents recruited from our clinic and may therefore have more impairment in quality of life.

This study may have some limitations. Firstly, the validation of the FAQLQ-TF was carried out in the Dutch language. The FAQLQ-TF was carefully translated

into English using the guidelines of the World Health Organization. The validity of the English language version of this questionnaire is currently being investigated as well as versions in several other European languages. Our experience with the Dutch Vespid Allergy Quality of Life Questionnaire was that the English translation validated well [24]. It is possible, however, that cultural differences may influence the ability of our questionnaire to identify the most important items for food allergic patients in different cultural or linguistic settings.

Secondly, patients were recruited at our clinic and by advertisement. These patients may differ from each other, for example in terms of level of information about their food allergy. However, we did not find significant differences in the descriptive characteristics between these groups and other possible differences would not have adversely influenced the validation procedure, where a spectrum of severity is beneficial to obtain optimal correlations.

Thirdly, some of the items in this questionnaire are likely to be time sensitive in the long run. For example, new labelling laws could make the labelling items included in this questionnaire obsolete. It is likely that in time, this questionnaire will require some updating and adaptation.

Finally, this report describes only the cross-sectional validation of the FAQLQ-TF. Currently, the longitudinal validation of the questionnaire is being investigated (i.e. the capacity of the FAQLQ-TF to measure differences in HRQL over time).

In summary, we have developed and validated the first HRQL questionnaire specific for food allergic adolescents, the Food Allergy Quality of Life Questionnaire-Teenager Form (FAQLQ-TF). We found that this questionnaire is valid and reliable and it is short and easy to use. The FAQLQ-TF will be thus a suitable questionnaire for clinical research in food allergic adolescents in which HRQL is the outcome of interest.

Acknowledgements

This work was funded by the EU through the EuroPrevall project (FOOD-CT-2005-514000). We would like to thank Dr. GFEC van Linden van den Heuvell, medical psychologist, and Karel Verbeek, linguist, for reviewing the extended item questionnaire and the FAQLQ-TF and Tina van der Velde for performing the test-retest of the FAQLQ-TF.

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Appendix 1: Food Allergy Quality of Life Questionnaire – Teenager Form (13-17 years)

The following questions concern the influence your food allergy has on your quality of life. Answer every question by marking the appropriate box with an 'x'. You may choose from one of the following answers.

0	**1**	**2**	**3**	**4**	**5**	**6**
not	barely	slightly	moderately	quite	very	extremely

How *troublesome* do you find it, because of your food allergy, that you …		0	1	2	3	4	5	6
1	must always be alert as to what you are eating?	☐	☐	☐	☐	☐	☐	☐
2	are able to eat fewer products?	☐	☐	☐	☐	☐	☐	☐
3	are limited as to the products you can buy?	☐	☐	☐	☐	☐	☐	☐
4	must read labels?	☐	☐	☐	☐	☐	☐	☐
5	have the feeling that you have less control of what you eat when eating out?	☐	☐	☐	☐	☐	☐	☐
6	are less able to spontaneously accept an invitation to stay for a meal?	☐	☐	☐	☐	☐	☐	☐
7	are less able to taste or try various products when eating out?	☐	☐	☐	☐	☐	☐	☐
8	must check yourself whether you can eat something when eating out?	☐	☐	☐	☐	☐	☐	☐
9	hesitate eating a product when you have doubts about it?	☐	☐	☐	☐	☐	☐	☐
10	must refuse treats at school or work?	☐	☐	☐	☐	☐	☐	☐
11	must be careful about touching certain foods?	☐	☐	☐	☐	☐	☐	☐
12	must carry an Epipen? (If you don't have a Epipen mark an 'x' here ☐)	☐	☐	☐	☐	☐	☐	☐

0	1	2	3	4	5	6
not	barely	slightly	moderately	quite	very	extremely

How *troublesome* is it, because of your food allergy, ...		0	1	2	3	4	5	6
13	that the ingredients of a product change?	☐	☐	☐	☐	☐	☐	☐
14	that the label states: "May contain traces of...."?	☐	☐	☐	☐	☐	☐	☐
15	that the labeling of the bulk packaging (for example box or bag) is different than the individual packages?	☐	☐	☐	☐	☐	☐	☐
16	that you have to explain to people around you that you have a food allergy?	☐	☐	☐	☐	☐	☐	☐
17	that during social activities others can eat the food to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
18	that during social activities your food allergy is not taken into account enough?	☐	☐	☐	☐	☐	☐	☐

How *frightened* are you because of your food allergy ...		0	1	2	3	4	5	6
19	of an allergic reaction?	☐	☐	☐	☐	☐	☐	☐
20	of accidentally eating something wrong?	☐	☐	☐	☐	☐	☐	☐
21	to eat something you have never eaten before?	☐	☐	☐	☐	☐	☐	☐

Answer the following questions:		0	1	2	3	4	5	6
22	How *discouraged* do you feel during an allergic reaction?	☐	☐	☐	☐	☐	☐	☐
23	How *disappointed* are you when people do not take your food allergy into account?	☐	☐	☐	☐	☐	☐	☐

Appendix 2: Food Allergy Independent Measure – Teenager Form (13-17 years)

The following four questions are about the chance that you think you have of something happening to you because of your food allergy. Choose one of the answers provided. This is followed by two more questions about your food allergy. Answer every question by putting an 'x' in the box next to the appropriate answer.

0 never (0% chance)	**1** very small chance	**2** small chance	**3** fair chance	**4** great chance	**5** very great chance	**6** always (100% chance)

How great do you think the chance is that you …		0	1	2	3	4	5	6
a.	will accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
b.	will have a severe reaction if you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
c.	will die if you accidentally eat something to which you are allergic?*	☐	☐	☐	☐	☐	☐	☐
d.	can *not* effectively deal with an allergic reaction should you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐

e. **How many products must you avoid because of your food allergy?**	f. **How great is the impact of your food allergy on your social life?**
☐ almost none	☐ negligibly small
☐ very few	☐ very small
☐ a few	☐ small
☐ some	☐ moderate
☐ many	☐ great
☐ very many	☐ very great
☐ almost all	☐ extremely great

** This Expectation of Outcome question was not correlated with any of the items of the FAQLQ-TF and is thus unlikely to be an appropriate independent measure for food allergy in adolescents. Therefore, this question was excluded from further analyses.*

Chapter 5

Development and validation of the Food Allergy Quality of Life Questionnaire-Adult Form

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Allergy 2009; In press

Abstract

Background:
Health-Related Quality of Life (HRQL) may be affected by food allergy. Presently no disease-specific HRQL questionnaire exists for food allergic adults. Therefore we developed and validated the Food Allergy Quality of Life Questionnaire-Adult Form (FAQLQ-AF) in the Dutch language.

Methods:
Twenty-two food allergic patients (≥18 years) were interviewed and generated 180 HRQL items. The most important items were identified by 54 food allergic patients using the clinical impact method resulting in the FAQLQ-AF containing 29 items (score range 1 'not troubled' to 7 'extremely troubled'). The FAQLQ-AF, the Food Allergy Independent Measure (FAIM) and a generic HRQL questionnaire (RAND-36) were sent to 100 other food allergic adults for cross-sectional validation of the FAQLQ-AF.

Results:
Cross-sectional validity was assessed by the correlation between FAQLQ-AF and FAIM (rho 0.76, $p<0.001$). The FAQLQ-AF had excellent internal consistency (Cronbach's α 0.97). The FAQLQ-AF discriminated between patients who differ in severity of symptoms (anaphylaxis vs. no anaphylaxis, 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; $p=0.008$). The total FAQLQ-AF score was correlated with one RAND-36 scale (convergent/discriminant validity).

Conclusions:
The FAQLQ-AF is the first disease-specific HRQL questionnaire for food allergic adults and reflects the most important issues that food allergic patients have to face. The questionnaire is valid, reliable and discriminates between patients with different disease characteristics. The FAQLQ-AF is short and easy to use may therefore be a useful tool in clinical research.

Introduction

Food plays an important role in our social and cultural life. In patients with food allergy the ingestion of a particular food may provoke an allergic reaction, which may be fatal for some patients [1-3]. The only proven form of treatment is strict avoidance of the food(s) involved and medications for emergency treatment [4]. Food allergic patients thus need to be continuously alert as to what they are eating in numerous situations and settings. Consequently, daily life of these patients may be seriously disrupted by the required continuous vigilance, the threat of accidental exposure and fear of an allergic reaction and this may have a negative impact on their quality of life.

A few studies have investigated the impact of food allergy on Health-Related Quality of Life (HRQL) [5-11], but all these studies investigated children or adolescents with food allergy or parents with a food allergic child. Only one study investigated HRQL in adults with food allergy and reported that daily life was significantly more disrupted in peanut allergic adults than in adults with a rheumatologic disease [12]. However, in that study a generic HRQL questionnaire was used, which may be not as sensitive as a disease-specific HRQL questionnaire [13]. At present, no validated food-allergy-specific HRQL questionnaire exists for use in adults.

Therefore, we here report the development and cross-sectional validation of the first disease-specific HRQL questionnaire for adults with food allergy, the Food Allergy Quality of Life Questionnaire-Adult Form (FAQLQ-AF). This questionnaire is the last HRQL questionnaire in a series of questionnaires developed in the EuroPrevall project, a European multi-centre research project on food allergy, to cover all age groups of patients with food allergy. It complements the recently developed FAQLQ-PF for parents of food allergic children aged 0 to 12 years and the two self-administered questionnaires; the FAQLQ-CF for children aged 8 to 12 years and the FAQLQ-TF for adolescents aged 13 to 17 years [14-16].

Methods

Participants and Procedure

During all stages of questionnaire development, only patients 18 years or older with a physician-diagnosed food allergy were included. All common food allergies and different types and severities of symptoms were represented. Patients with only oral allergy syndrome were excluded. During the item generation, patients were recruited only from our outpatient allergy clinic. During the item reduction and cross-sectional validation, patients were recruited when attending our outpatient allergy clinic or recruited through food allergy support organizations (the Dutch Foundation for Food Allergy and the Dutch Anaphylaxis Network) and by advertisement in local news papers.

Before the cross-sectional validation, the questionnaire was pretested in three patients. No major problems emerged during this pretest. Thereafter, the FAQLQ-

AF, the Food Allergy Independent Measure (FAIM) and the RAND-36, a generic quality of life questionnaire, were sent to 100 food allergic patients by post. These questionnaires are described in more detail later on. A subset of these patients were previously asked to participate in the item generation (n=20) or item reduction phase (n=59), but were eligible to participate in the validation process since it is independent of the development phase. Descriptive characteristics were elicited regarding age, gender, type and number of food allergies, type of symptoms and diagnosis. For the patients recruited from our clinic, we checked the patient records to determine whether or not the food allergy was diagnosed by a double-blind placebo-controlled food challenge (DBPCFC).

The study was approved by the local medical ethics review commission (METc 2005/051) who deemed that permission from the commission was not required, since this study does not fall under the Medical Research Involving Human Subjects Act.

Development

Item generation

The development and validation of the FAQLQ-AF was based on the methodology used for the development and validation of the FAQLQ-CF and FAQLQ-TF [15;16]. Potential items for the new adult questionnaire were generated by interviewing 22 food allergic patients, reviewing literature and consulting expert opinion. This procedure resulted in an 'extended item questionnaire' of 180 items.

Item reduction

The clinical impact method was used for identifying the most important items of the extended item list [17;18]. The 'extended item questionnaire' was sent to a different group of 63 food allergic patients, who were asked to indicate the importance to them of each applicable item, rated on a 5-point scale. The overall importance (OI) of each item was calculated by multiplying the frequency with which an item was identified as being important (%) with the mean importance using the 5-point scale. The maximal possible OI was 5.0 [19;20]. The items with the greatest OI were selected for the FAQLQ-AF, except one of any pair of items with overlapping content (face validity) and/or an inter-item correlation >0.85. The selected items were worded as questions with a 7-point response scale (ranging from 'not troubled' to 'extremely troubled') [18;20]. A psychologist and a linguist reviewed the FAQLQ-AF for clarity and ease of use.

Cross-sectional validation

Construct validity

Construct validity is usually evaluated by comparing the HRQL questionnaire with an objective measurement of the extent or severity of the disease. However, in disorders not characterized by chronic symptoms, as in food allergy, such an

independent measure is not available. It is has been shown that the perceived expectation of what will happen following exposure can be used as independent measure to evaluate construct validity and instruments developed in this way have proved to be useful and consistent in measuring HRQL [8;14-16;20;21]. Therefore, in order to investigate construct validity of the FAQLQ-AF, correlation coefficients were calculated for the FAQLQ-AF with the Food Allergy Independent Measure (FAIM). The FAIM, which has previously been used to validate the FAQLQ-PF, -CF and -TF [14-16], contains four Expectation of Outcome (EO) questions [8;20;21] and two additional Independent Measure (IM) questions [15;16]. The EO questions are based on the perceived expectation of patients of what will happen following exposure, which is likely to be a driving force of quality of life [21]. The IM questions are based on the same principle and query about the perceived number of foods one needs to avoid and perceived impact on social life. We expected moderate correlation coefficients (0.40-0.60) [22] for the FAQLQ-AF with the FAIM. The validation of the FAQLQ-AF was carried out in the Dutch language. The Dutch FAQLQ-AF and the FAIM were translated into English following the guidelines of the World Health Organization [23]. The English version of the FAQLQ-AF and the FAIM may be found as Appendices 1 and 2.

Convergent and discriminant validity

Additionally, construct validity was further investigated by convergent and discriminant validity. To investigate convergent and discriminant validity, a generic HRQL questionnaire was administered, the RAND-36 [24]. This health profile measure is the Dutch version of the MOS 36-item Short-Form Health Survey (SF-36) [25] and consists of 36 items divided into nine scales: physical functioning, social functioning, role functioning-physical, role functioning-emotional, mental health, vitality, bodily pain, general health and change in health (single item). Because the FAQLQ-AF is a disease-specific questionnaire and the RAND-36 a generic questionnaire, we expected no to weak correlations (0.20-0.40) for the total FAQLQ-AF score with the RAND-36 scales (i.e. discriminant validity). When looking at the FAQLQ-AF domains we expected that Food Allergy related Health (FAH) would correlate better with the RAND-36 scales than the other FAQLQ-AF domains, since this is the most 'generic' FAQLQ-AF domain (i.e convergent validity).

Discriminative ability

To investigate the discriminative ability of the FAQLQ-AF, we compared the total FAQLQ-AF score of patients who reported anaphylaxis (i.e. two or more of the following cardiovascular symptoms: dizziness, palpitations, loss of vision, inability to stand, light headedness, collapse, loss of consciousness) *vs* patients who did not, for men *vs* women, for patients who were recruited from our clinic *vs* patients who were recruited by advertisement and for patients who reported many food allergies *vs* patients who reported few food allergies. We investigated which cut off in number of reported food allergies revealed a significant difference in the total FAQLQ-AF score.

Reliability
The test-retest reliability of the FAQLQ-AF was assessed by administering the questionnaire to 36 patients on two occasions 10-14 days apart.

Statistical analyses
The raw FAQLQ-AF and FAIM scores 0 to 6 were recoded as 1 to 7. The total FAQLQ-AF score is the mean score of all items with a range of 1 'no impairment' to 7 'maximal impairment'. Cross-sectional validity was assessed by calculating Spearman's correlation coefficients between the FAQLQ-AF and the FAIM (individual FAQLQ-AF items with individual FAIM items, individual FAQLQ-AF items with mean FAIM, total FAQLQ-AF score with mean FAIM, and total FAQLQ-AF score with individual FAIM items). Domains were created by performing factor analysis (principal component analysis with Varimax rotation) [26] and face validity determined by a clinical expert panel (BMJFdB, JNGOE and AEJD) [27]. The internal consistency was measured by calculating Cronbach's α. An $\alpha > 0.70$ indicates good internal consistency [28]. Convergent and discriminant validity was assessed by calculating Spearman's correlation coefficients between the FAQLQ-AF and the RAND-36 scales. The discriminative ability was measured by using the Mann-Whitney test. The test-retest reliability was assessed by calculating the intraclass correlation coefficient of the repeated FAQLQ-AF measurement [29]. Statistical analyses were performed with SPSS for Windows 14.0 (SPSS Inc., Chicago, IL, USA).

Results

Development
Descriptive characteristics of the patients involved in the item generation and item reduction are shown in Table 1. The 'extended item questionnaire' was returned by 54 of the 63 adults (response rate 86%). The OI scores of all 180 items of the extended item list ranged from 0.00 to 3.19. The item reduction resulted in the selection of 29 items (OI $\geq$1.61) for the FAQLQ-AF (Table 2).

Cross-sectional validation

Participants
The FAQLQ-AF with the FAIM and the RAND-36 were returned by 80 of the 100 adults (response rate 80%). The questionnaire of one patient was excluded from the analysis because no current food allergies were reported and the questionnaires of seven patients were excluded because no physician-diagnosed food allergy was reported. Thus, 72 questionnaires were assessable for the cross-sectional validation. Forty-two patients (58%) were recruited from our clinic, of which 11 (15%) had a food allergy confirmed by a DBPCFC and three (4%) with an open food challenge (OFC). The other patients from our clinic had a physician-diagnosed

Table 1. Descriptive characteristics of the patients involved in the item generation, item reduction and cross-sectional validation.

	Item generation	Item reduction	Cross-sectional validation
Patients (n)	22	54	72
Gender (m/f)	6/16	20/34	18/54
Age, mean in years (SD)	36.4 (16.5)	39.1 (16.4)	37.2 (14.3)
Food allergy, n (%)			
Peanut	10 (45)	32 (59)	42 (58)
Tree nuts	6 (27)	36 (67)	42 (58)
Egg	4 (18)	13 (24)	16 (22)
Milk	6 (27)	17 (32)	19 (26)
Fish	3 (14)	9 (17)	11 (15)
Shell fish	2 (9)	16 (30)	12 (17)
Wheat	4 (18)	14 (26)	12 (17)
Sesame	3 (14)	12 (22)	13 (18)
Soy	2 (9)	14 (26)	13 (18)
Celery	3 (14)	10 (19)	11 (15)
Number of food allergies, n (%)			
1 food	7 (32)	11 (20)	21 (29)
2 foods	4 (18)	10 (19)	19 (26)
3 foods	5 (23)	15 (28)	14 (19)
>3 foods	6 (27)	18 (33)	18 (25)
Type of symptoms, n (%)			
Cardiovascular[1]	6 (27)	20 (37)	32 (44)
Respiratory tract[2]	7 (32)	21 (39)	29 (40)
Gastrointestinal tract[3]	7 (32)	5 (9)	4 (6)
Skin[4]	2 (9)	8 (15)	4 (6)
Other[5]	0	0	3 (4)

[1] dizziness, feeling your heart beat fast, loss of vision, inability to stand, light headedness, collapse, loss of consciousness / passing out, [2] tightening throat, difficulty swallowing, hoarseness / hoarse voice, difficulty breathing in, shortness of breath, wheezing, cough, [3] sick to your stomach, stomach cramps, vomiting, diarrhoea , [4] itchy skin, red rash, hives, worsening eczema, swelling of the skin, [5] oral allergy, swollen tongue or lips, symptoms of the nose or eyes.

food allergy with a positive history and positive skin prick and/or blood test. All patients recruited by advertisement (42%) reported physician-diagnosed food allergies. Descriptive characteristics of the patients involved in the cross-sectional validation are shown in Table 1. There were no significant differences in descriptive characteristics between men and women (not shown). Patients who were recruited by advertisement reported significantly more food allergies than patients who were recruited from our clinic (p=0.001). Patients with a DBPCFC or OFC diagnosis reported significantly fewer food allergies (p=0.046) and reported significantly more severe symptoms (p=0.046) than patients with a physician-diagnosed food allergy.

Table 2. Selected items for Food Allergy Quality of Life Questionnaire—Adult Form (FAQLQ-AF).

Item	%	MI	OI
Always be alert as to what you are eating	89	3.58	3.19
Change of ingredients of a product	80	3.91	3.11
Able to eat fewer products	96	3.21	3.09
Limited as to the products you can buy	87	3.36	2.93
Frightened of an allergic reaction	81	3.48	2.83
Labels are incomplete	65	3.94	2.56
Feel discouraged during an allergic reaction	69	3.70	2.54
Having to read labels	94	2.65	2.50
Frightened of accidentally eating the wrong food	69	3.62	2.48
Hesitate eating a product when you have doubts about it	91	2.73	2.48
Troublesome for your host or hostess should you have an allergic reaction	67	3.64	2.43
Have the feeling that you have less control of what you eat when eating out	72	3.31	2.39
Apprehensive about eating something you have never eaten before	69	3.38	2.31
Refuse many things during social activities	69	3.24	2.22
The lettering on labels is too small	61	3.61	2.20
Less able to spontaneously accept an invitation to stay for a meal	57	3.77	2.17
Worried that the allergic reactions to foods will become increasingly severe	57	3.65	2.09
Less able to taste or try various products when eating out	72	2.79	2.02
Sometimes frustrate people when they are making an effort to accommodate your food allergy	54	3.72	2.00
People underestimate your problems caused by food allergy	72	2.72	1.96
Label states: "May contain (traces of)…."	48	3.96	1.91
Unclear to which foods you are allergic	46	4.00	1.85
Frightened of an allergic reaction when eating out despite the fact that your dietary restrictions have been discussed beforehand	59	3.09	1.83
Worried about your health	54	3.21	1.72
Ingredients are different in other countries (for example during vacation)	50	3.41	1.70
Eating out less often	44	3.79	1.69
Have to explain to those around you that you have a food allergy	91	1.86	1.69
Check personally whether you can eat something when eating out	67	2.42	1.61
Feel you are being a nuisance because you have a food allergy when eating out	48	3.35	1.61

MI, mean importance. OI, overall importance.

Construct validity

All items of the FAQLQ-AF correlated significantly with at least one of the FAIM questions and all items correlated significantly with the mean of the FAIM questions. Therefore, all 29 selected items were included in the final version of the validated FAQLQ-AF. The total FAQLQ-AF score correlated significantly with the mean FAIM (rho 0.76, $p<0.001$) and with the individual FAIM questions (Table 3). The correlation coefficients for the FAQLQ-AF with the FAIM were the same for patients with a food allergy diagnosed by DBPCFC or OFC and patients with a physician-diagnosed food allergy (total FAQLQ-AF score with the mean FAIM,

rho 0.78, p=0.001 and rho 0.78, p<0.001, respectively). These results support the construct validity of the FAQLQ-AF, i.e. the FAQLQ-AF is measuring quality of life that is affected by food allergy.

Domain structure and internal consistency

Factor analysis (principal component analysis) was performed on the 29 items of the FAQLQ-AF and revealed five components with eigenvalues >1. To aid in the interpretation of these components, Varimax rotation was performed for 5, 4 and 3 factors. An expert panel reviewed these groupings and based on face validity the grouping of four domains made the most sense. This grouping revealed the following domains: Allergen Avoidance and Dietary Restrictions (AADR), Emotional Impact (EI), Risk of Accidental Exposure (RAE) and Food Allergy related Health (FAH). All factors showed a number of strong loadings and were >0.300 which is regarded as an acceptable criterion [26]. Based on face validity, the expert panel allocated a few items to a more appropriate domain. The FAQLQ-AF and the domains had excellent internal consistency which is shown by the Cronbach's α that are all exceeding 0.70 (Table 3).

Convergent and discriminant validity

The total FAQLQ-AF score was weakly correlated with one RAND-36 scale (mental health) and the correlations with the other RAND-36 scales were not significant (Table 4). Given the fact that the FAQLQ-AF is a disease-specific questionnaire, whereas the RAND-36 is a generic questionnaire, these results were expected (discriminant validity). The domains of the FAQLQ-AF showed weak correlation with a few RAND-36 scales. As expected, most correlations with the RAND-36 scales were found for the domain FAH, as this is the most general domain of the disease-specific FAQLQ-AF (convergent validity).

Discriminative ability

Patients who reported anaphylaxis (i.e. cardiovascular symptoms) reported a significantly more impaired HRQL than patients who did not report anaphylaxis (total FAQLQ-AF score 4.9 *vs* 4.1; p=0.041). In addition, the total FAQLQ-AF score of patients who reported more than three food allergies was significantly higher, indicating more impairment in HRQL, than patients who reported three or less food allergies (5.2 *vs* 4.2; p=0.008). The impairment of HRQL did not differ significantly between men and women (total FAQLQ-AF score 4.1 *vs* 4.6; p=0.060) and did not differ significantly between patients who were recruited by advertisement and patients who were recruited from our clinic (4.8 *vs* 4.2; p=0.054).

Reliability

The total FAQLQ-AF score intraclass correlation coefficient was 0.95 (95% confidence interval, 0.91-0.98), indicating excellent test-retest reliability.

Table 3. Spearman correlation coefficients for the FAQLQ-AF with the FAIM and internal consistency (Cronbach's α) of the FAQLQ-AF.

	FAIM							
	EO1	EO2	EO3	EO4	IM1	IM2	Mean	α
Total FAQLQ-AF score	**0.54**	**0.59**	**0.49**	**0.75**	**0.56**	**0.56**	**0.76**	0.97
Allergen Avoidance and Dietary Restrictions (AADR)								0.95
Eating out less often	**0.29**	**0.56**	**0.40**	**0.53**	**0.49**	**0.48**	**0.60**	
Limited as to the products you can buy	**0.38**	**0.35**	0.22	**0.56**	**0.68**	**0.62**	**0.56**	
Check personally whether you can eat something when eating out	**0.39**	**0.45**	**0.32**	**0.75**	**0.53**	**0.51**	**0.57**	
Able to eat fewer products	**0.25**	0.18	0.08	**0.49**	**0.67**	**0.60**	**0.40**	
Less able to taste or try various products when eating out	**0.27**	**0.45**	**0.26**	**0.70**	**0.45**	**0.48**	**0.51**	
Having to read labels	**0.35**	**0.51**	**0.40**	**0.63**	**0.27**	**0.29**	**0.48**	
Always be alert as to what you are eating	**0.38**	**0.45**	**0.36**	**0.54**	**0.52**	**0.48**	**0.57**	
Hesitate eating a product when you have doubts about it	**0.44**	**0.43**	**0.30**	**0.78**	**0.30**	**0.29**	**0.48**	
Refuse many things during social activities *	**0.37**	**0.40**	**0.35**	**0.54**	**0.48**	**0.40**	**0.55**	
Less able to spontaneously accept an invitation to stay for a meal *	**0.28**	**0.35**	**0.25**	**0.57**	**0.62**	**0.52**	**0.51**	
Having to explain to those around you that you have a food allergy *	**0.38**	**0.28**	**0.23**	**0.66**	**0.49**	**0.52**	**0.51**	
Emotional Impact (EI)								0.90
Frightened of accidentally eating the wrong food	**0.42**	**0.58**	**0.53**	**0.77**	0.22	0.23	**0.61**	
Frightened of an allergic reaction	**0.33**	**0.55**	**0.45**	**0.75**	0.08	0.16	**0.49**	
Frightened of an allergic reaction when eating out despite the fact that your dietary restrictions have been discussed beforehand	**0.39**	**0.54**	**0.53**	**0.83**	**0.29**	**0.35**	**0.60**	
Apprehensive about eating something you have never eaten before	**0.34**	**0.57**	**0.37**	**0.59**	**0.25**	**0.34**	**0.55**	
Feel discouraged during an allergic reaction	**0.29**	**0.32**	**0.32**	**0.64**	0.15	0.17	**0.37**	
Have the feeling that you have less control of what you eat when eating out **	**0.45**	**0.58**	**0.49**	**0.68**	**0.47**	**0.47**	**0.68**	
Feel you are being a nuisance because you have a food allergy when eating out **	**0.42**	**0.38**	**0.34**	**0.51**	**0.49**	**0.50**	**0.59**	

Table 3. Continued.

	FAIM							
	EO1	EO2	EO3	EO4	IM1	IM2	Mean	α
Risk of Accidental Exposure (RAE)								0.88
Sometimes frustrate people when they are making an effort to accommodate your food allergy	**0.33**	**0.36**	**0.28**	**0.50**	**0.55**	**0.46**	**0.54**	
People underestimate your problems caused by food allergy	**0.40**	**0.33**	**0.28**	**0.45**	**0.30**	**0.39**	**0.47**	
Change of ingredients of a product ***	**0.35**	**0.44**	**0.41**	**0.44**	**0.53**	**0.48**	**0.62**	
Labels are incomplete ***	**0.37**	**0.42**	**0.27**	**0.44**	**0.36**	**0.39**	**0.50**	
Ingredients are different in other countries (for example during vacation) ***	**0.29**	0.25	0.22	**0.77**	**0.50**	**0.38**	**0.41**	
Label states: "May contain (traces of)…." ****	**0.30**	**0.33**	0.23	**0.69**	0.23	**0.30**	**0.34**	
Troublesome for your host or hostess should you have an allergic reaction ****	**0.38**	**0.45**	**0.48**	**0.63**	0.15	**0.29**	**0.53**	
The lettering on labels is too small ****	**0.35**	0.23	**0.27**	**0.55**	0.04	0.14	**0.30**	
Food Allergy related Health (FAH)								0.77
Worried about your health	**0.52**	**0.38**	**0.28**	**0.54**	**0.37**	**0.37**	**0.55**	
Unclear to which foods you are allergic	**0.36**	0.20	0.23	0.28	**0.45**	**0.48**	**0.43**	
Worried that the allergic reactions to foods will become increasingly severe	**0.54**	**0.35**	**0.34**	**0.51**	**0.27**	**0.47**	**0.59**	

The values given in bold are $p<0.05$. FAQLQ-AF, Food Allergy Quality of life Questionnaire-Adult Form. FAIM, Food Allergy Independent Measure. EO1, Chance of accidental exposure. EO2, Chance of severe reaction when accidentally exposed. EO3, Chance of dying when accidentally exposed. EO4, Chance of not acting effectively when accidentally exposed. IM1, Number of foods one needs to avoid. IM2, Impact of food allergy on social life. Based on face validity, the expert panel allocated *items from RAE to AADR, **items from AADR to EI, ***items from AADR to RAE and ****items from 5th factor to RAE.

Table 4. Spearman's correlation coefficient of the total FAQLQ-AF score and domains of the FAQLQ-AF with the RAND-36 (SF-36) scales.

	Total FAQLQ-AF	Domains of the FAQLQ-AF			
RAND-36 scales		**AADR**	**EI**	**RAE**	**FAH**
Physical functioning	0.10	0.04	0.22	0.03	0.02
Social functioning	-0.22	**-0.26**	-0.09	-0.18	**-0.35**
Role functioning-physical	-0.10	-0.14	-0.02	-0.15	-0.21
Role functioning-emotional	-0.20	-0.18	-0.12	-0.19	**-0.25**
Mental health	**-0.27**	**-0.25**	-0.18	-0.21	**-0.35**
Vitality	-0.18	-0.19	-0.07	-0.14	**-0.27**
Bodily pain	0.01	-0.05	0.16	-0.09	-0.09
General health	-0.06	-0.06	0.12	-0.16	**-0.27**
Change in health	0.10	0.16	0.06	0.01	0.07

The values given in bold are $p<0.05$. FAQLQ-AF, Food allergy Quality of life Questionnaire-Adult Form. AADR, Allergen Avoidance and Dietary Restrictions. EI, Emotional Impact. RAE, Risk of Accidental Exposure. FAH, Food Allergy related Health. Correlation coefficients are negative because a high score on the FAQLQ-AF indicates maximal impairment of quality of life, whereas a high score on the RAND-36 indicates better health status.

Discussion

We here report the development and cross-sectional validation of the first disease-specific HRQL questionnaire for adults with food allergy, the Food Allergy Quality of Life Questionnaire-Adult Form (FAQLQ-AF). Our analysis showed that the FAQLQ-AF has good construct validity (Table 3) and excellent internal consistency. In addition, the FAQLQ-AF discriminates between patients with and without anaphylaxis and between patients who differ in the number of food allergies. Finally, the FAQLQ-AF showed convergent/discriminant validity (Table 4). This supports the need for a disease-specific quality of life questionnaire in food allergic adults.

The content of the FAQLQ-AF reflects the most important issues that food allergic patients have to deal with in their daily life and impairs their quality of life. Consequently, these issues are likely to be important targets for interventions by health care providers, catering industries, food manufacturers and governments aimed at improving quality of life in food allergic patients [30]. An example is the item 'Change of ingredients of a product'. In the item reduction phase it turned out that this was one of the most important items (Table 2). This item indicates that food allergic patients find it very frustrating when a product that was safe to eat, which in some cases are very few, turned out to be unsafe. The impact of this item may be reduced to some extent if, for example, manufacturers would place a warning on the product indicating changed ingredients.

Another notable item of the FAQLQ-AF is 'Unclear to which foods you are allergic'. The inclusion and validation of this item emphasizes the fact that if

uncertainty is left about foods that may cause allergic reactions, this consequently impairs quality of life. Therefore, this item demonstrates the need for proper diagnosis for all suspected food allergies and it stresses the need for education on proper management of food allergy in order to prevent unnecessary impairment of quality of life.

In the discriminative analysis it turned out that patients who reported anaphylaxis had a significantly more impaired quality of life than patients who did not report anaphylaxis. The difference in total FAQLQ-AF score between these two groups was 0.8. It is known from the literature that the minimal importance difference (MID) of HRQL questionnaires with a 7-point scale is approximately 0.5. The MID is the smallest difference in score which patients perceive as beneficial and which would mandate, in absence of troublesome side effects and excessive cost, a change in the patient's management [31]. Therefore, the difference in total FAQLQ-AF score between patients who reported anaphylaxis and patients who did not was not only a statistically significant difference but also a clinically significant difference. The same was true for the difference in total FAQLQ-AF score of patients who reported more than three food allergies versus patients who reported three or less food allergies. Although the MID of 0.5 is a robust estimate for HRQL questionnaires with a 7-point scale, the specific MID of the FAQLQ-AF remains to be estimated in a longitudinal survey.

When looking at the discriminative ability of the previously developed questionnaires for children (FAQLQ-CF) and adolescents (FAQLQ-TF), it turned out that there was no significant difference in quality of life between young patients who reported anaphylaxis and those who did not [15;16]. At that time we speculated that these patients may be too young to realize the potentially life-threatening consequences of severe anaphylactic reactions to food. This hypothesis is confirmed when considering the present results in adults. The difference in total FAQLQ score between patients who reported anaphylaxis and patients who did not increases with age (0.3 in children, 0.5 in teenagers and 0.8 in adults, respectively) and this difference was significant in adults. This suggests that, as individuals age, they become more aware of the severity of symptoms in the past and the possibly life-threatening effect of food allergy. Consequently, these patients may judge their quality of life to be more impaired than patients with less severe food allergic reactions.

Finally, this study may have some limitations. The validation of the FAQLQ-AF was carried out in the Dutch language. The FAQLQ-AF was carefully translated into English using the guidelines of the World Health Organization. The validity of the English language version of this questionnaire is currently being investigated as well as versions in several other European languages. Our experience with the Dutch Vespid Allergy Quality of Life Questionnaire was that the English translation validated well [20]. It is possible, however, that cultural differences may influence the ability of our questionnaire to identify the most important items for food allergic patients in different cultural or linguistic settings. Another limitation may be that we did not independently verify the food allergy diagnosis of patients recruited

through advertisement who reported a physician-diagnosed food allergy. However, all these patients reported an allergy to a common/know food allergen, they reported symptoms that are common/known in food allergy, and they reported strict avoidance of the food to which they think they were allergic. Additionally, this report describes only the cross-sectional validation of the FAQLQ-AF. Currently, the longitudinal validation of the questionnaire is being investigated (i.e. the capacity of the FAQLQ-AF to measure differences in HRQL over time).

In summary, we presented here the first disease-specific HRQL questionnaire for food allergic adults, the Food Allergy Quality of Life Questionnaire-Adult Form (FAQLQ-AF) with very good to excellent measurement properties. Moreover, the questionnaire is short and easy to use. The FAQLQ-AF is thus suitable for studies of adult food allergic patients in which HRQL is the outcome of interest. Examples include investigation of the effect of emerging treatments such as oral immunotherapy and anti-IgE therapy on quality of life. The FAQLQ-AF complements the recently developed FAQLQ-TF (for adolescents aged 13 to 17 years), the FAQLQ-CF (for children aged 8 to 12 years) and the FAQLQ-PF (for parents of food allergic children aged 0 to 12 years) [14-16]. Hence, validated disease-specific HRQL questionnaires are now available for food allergic patients of all age groups.

Acknowledgements

This work was funded by the EU through the EuroPrevall project (FOOD-CT-2005-514000). We would like to thank Niels de Voogd, psychologist, for reviewing the extended item questionnaire and the FAQLQ-AF and Tina van der Velde, medical student, for performing the test-retest of the FAQLQ-AF.

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Appendix 1: Food Allergy Quality of Life Questionnaire – Adult Form (≥ 18 years)

The following questions concern the influence your food allergy has on your quality of life. Answer every question by marking the appropriate box with an 'x'. You may choose from one of the following answers.

0	1	2	3	4	5	6
not	barely	slightly	moderately	quite	very	extremely

How *troublesome* do you find it, because of your food allergy, that you ...		0	1	2	3	4	5	6
1	must always be alert as to what you are eating?	☐	☐	☐	☐	☐	☐	☐
2	are able to eat fewer products?	☐	☐	☐	☐	☐	☐	☐
3	are limited as to the products you can buy?	☐	☐	☐	☐	☐	☐	☐
4	must read labels?	☐	☐	☐	☐	☐	☐	☐
5	have the feeling that you have less control of what you eat when eating out?	☐	☐	☐	☐	☐	☐	☐
6	must refuse many things during social activities?	☐	☐	☐	☐	☐	☐	☐
7	sometimes frustrate people when they are making an effort to accommodate your food allergy?	☐	☐	☐	☐	☐	☐	☐
8	are less able to spontaneously accept an invitation to stay for a meal?	☐	☐	☐	☐	☐	☐	☐
9	are less able to taste or try various products when eating out?	☐	☐	☐	☐	☐	☐	☐
10	can eat out less?	☐	☐	☐	☐	☐	☐	☐
11	must personally check whether you can eat something when eating out?	☐	☐	☐	☐	☐	☐	☐
12	hesitate eating a product when you have doubts about it?	☐	☐	☐	☐	☐	☐	☐

0	1	2	3	4	5	6
not	barely	slightly	moderately	quite	very	extremely

How *troublesome* is it, because of your food allergy, ...		0	1	2	3	4	5	6
13	that the ingredients of a product change?	☐	☐	☐	☐	☐	☐	☐
14	that labels are incomplete?	☐	☐	☐	☐	☐	☐	☐
15	that the lettering on labels is too small?	☐	☐	☐	☐	☐	☐	☐
16	that the label states: "May contain (traces of)...."?	☐	☐	☐	☐	☐	☐	☐
17	that ingredients are different in other countries (for example during vacation)?	☐	☐	☐	☐	☐	☐	☐
18	that people underestimate your problems caused by food allergy?	☐	☐	☐	☐	☐	☐	☐
19	that it is unclear to which foods you are allergic?	☐	☐	☐	☐	☐	☐	☐
20	that you must explain to those around you that you have a food allergy?	☐	☐	☐	☐	☐	☐	☐
21	for your host or hostess should you have an allergic reaction?	☐	☐	☐	☐	☐	☐	☐

How *worried* are you because of your food allergy ...		0	1	2	3	4	5	6
22	about your health?	☐	☐	☐	☐	☐	☐	☐
23	that the allergic reactions to foods will become increasingly severe?	☐	☐	☐	☐	☐	☐	☐

How *frightened* are you because of your food allergy ...		0	1	2	3	4	5	6
24	of an allergic reaction?	☐	☐	☐	☐	☐	☐	☐
25	of accidentally eating the wrong food?	☐	☐	☐	☐	☐	☐	☐
26	of an allergic reaction when eating out despite the fact that your dietary restrictions have been discussed beforehand?	☐	☐	☐	☐	☐	☐	☐

0	1	2	3	4	5	6
not	barely	slightly	moderately	quite	very	extremely

Answer the following questions:		0	1	2	3	4	5	6
27	To what degree do you *feel you are being a nuisance* because you have a food allergy when eating out?	☐	☐	☐	☐	☐	☐	☐
28	How *discouraged* do you feel during an allergic reaction?	☐	☐	☐	☐	☐	☐	☐
29	How *apprehensive* are you about eating something you have never eaten before?	☐	☐	☐	☐	☐	☐	☐

Appendix 2: Food Allergy Independent Measure – Adult Form (≥ 18 years)

The following four questions are about the chance that you think you have of something happening to you because of your food allergy. Choose one of the answers provided. This is followed by two more questions about your food allergy. Answer every question by putting an 'x' in the box next to the appropriate answer.

0	1	2	3	4	5	6
never (0% chance)	very small chance	small chance	fair chance	great chance	very great chance	always (100% chance)

How great do you think the chance is that you …		0	1	2	3	4	5	6
a.	will accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
b.	will have a severe reaction if you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
c.	will die if you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
d.	can *not* effectively deal with an allergic reaction should you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐

e. **How many products must you avoid because of your food allergy?**	f. **How great is the impact of your food allergy on your social life?**
☐ almost none	☐ negligibly small
☐ very few	☐ very small
☐ a few	☐ small
☐ some	☐ moderate
☐ many	☐ great
☐ very many	☐ very great
☐ almost all	☐ extremely great

Chapter 6

Test-retest reliability of the Food Allergy Quality of Life Questionnaires (FAQLQ) for children, adolescents and adults

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Qual of Life Res 2009; 18: 245-251

Abstract

Objective:
The self-administered Food Allergy Quality of Life Questionnaire-Child Form (FAQLQ-CF), -Teenager Form (FAQLQ-TF) and -Adult Form (FAQLQ-AF) were recently developed within EuroPrevall, a multi-centred study of food allergy in Europe. The primary aim of this study was to evaluate the test-retest reliability of the FAQLQ-CF, -TF and -AF.

Methods:
One-hundred-and-one Dutch patients (31 children, 34 adolescents and 36 adults) completed the FAQLQ twice with a 10-14 day interval. The intraclass correlation coefficient (ICC), Lin's concordance correlation coefficient (CCC) and Bland-Altman plots were used to assess test-retest reliability.

Results:
Test-retest reliability was excellent with ICCs and CCCs above 0.907, 0.975 and 0.951 for the FAQLQ-CF, -TF and -AF, respectively. Bland-Altman plots showed that the mean differences of the test and retest were all close to zero for the FAQLQs.

Conclusions:
The FAQLQs are reliable over a short time interval. The FAQLQs are not only excellent tools for group comparison studies, but also for monitoring individual patients.

Introduction

Food allergy affects almost 4% of the general population in westernized countries [1] and it is the primary cause of anaphylaxis presenting to emergency departments [2]. The only proven therapy is careful avoidance of the causal food(s) and provision of medication for emergency treatment [3]. Consequently, patients often fear an allergic reaction and are continuously faced with dietary and social restrictions in their daily lives, which can have a negative impact on quality of life [4-11].

To measure Health-Related Quality of Life (HRQL), disease-specific questionnaires are significantly more sensitive than generic ones and they are important for estimating the general burden of food allergy as well as measuring the response to interventions or future treatments. However, generic HRQL instruments allow comparison of the burden of disease between patient populations with different diseases [12]. Recently, as part of the EuroPrevall project, the first self-administered HRQL questionnaires specific for food allergy have been developed and validated; the Food Allergy Quality of Life Questionnaire-Child Form, -Teenager Form and -Adult Form (FAQLQ-CF, -TF, -AF). The FAQLQs showed good validity, internal consistency and discriminative abilities [13-16], but test-retest reliability was not extensively investigated.

Reliability measures are important to ensure that what the questionnaire is measuring is dependable and repeatable [12] and allow sample sizes to be determined for clinical trials [17]. The aim of this study was therefore to assess the test-retest reliability of the self-administered FAQLQ-CF, -TF and -AF.

Methods

Patients

We contacted Dutch children (8-12 years), adolescents (13-17 years) and adults (≥18 years) with food allergy, who were recruited from our clinic or by advertisement. We included patients with the most prevalent food allergies.

Questionnaires

The FAQLQ-CF contains 24 items and 4 domains, the FAQLQ-TF contains 23 items and 3 domains and the FAQLQ-AF contains 29 items and 4 domains [13-15]. The total FAQLQ score is the sum of all the items divided by the number of items and ranges from 1 (minimal impairment in HRQL) to 7 (maximal impairment in HRQL) [18;19].

Procedures

We sent the FAQLQs by mail to be completed at home. Regarding the FAQLQ-CF, parents were instructed that they were allowed to explain a question when needed, but they were not allowed to tell the child which answer to give. All patients who completed the first questionnaires (test) received the second questionnaires (re-

test) 10-14 days after completion of the first. Patients who did not respond in time were excluded from the study [20;21] as well as patients who reported a clinically important change in disease between the measurements or within two months before the study. We defined a clinically important change in disease which may influence HRQL as a food allergic reaction of grade 3 or 4 according to the Mueller classification [22]. The study was approved by the local medical ethics review commission (METc 2005/051).

Statistical Analysis

Data were analysed using SPSS software for Windows (Version 14.0). To investigate test-retest reliability of the FAQLQs we used the intraclass correlation coefficient (ICC), using a one-way ANOVA [20;21;23]. Values should be above 0.70 for group comparison studies and above 0.90-0.95 for individual measurements over time [24].

As a second measure of test-retest reliability we calculated the Lin's concordance correlation coefficient (CCC). The different components of the CCC (Pearson correlation coefficient (measure of precision), location shift and scale shift (measures of accuracy)), were calculated. We plotted the first measurement against the second measurement and we used major axis analyses to calculate the best fitting line [25].

Visual assessment of test-retest agreement was obtained by use of Bland-Altman plots [26]. Differences between the first and the second measurement were plotted against the mean of the first and the second measurement. Limits of agreement (mean difference +/- 1.96*SD of the difference) were calculated, which reflect the interval within which about 95% of the differences between the two measurements should lie [27;28]. A regression coefficient (r) was calculated to estimate a relationship between the difference and the mean [26].

Results

Patients

We contacted 148 patients, of which 131 patients completed and returned the first questionnaire and 114 responded to the second questionnaire. This resulted in an overall response rate of 77%. A few patients were excluded, resulting in 101 patients that were eligible for analysing test-retest reliability (Table 1). The descriptive characteristics are shown in table 2. Mean duration between the first and second measurement was 11 days for all three age groups.

Analysis of FAQLQs

ICCs were $\geq$ 0.900 for the FAQLQs and CCCs were comparably high. Location shift and scale shift, should all be considered minimal according to Lin's examples [29]. Pearson correlation should be considered moderate in the FAQLQ-CF and good in the FAQLQ-TF and -AF (Table 3). Comparable results were found for the individual domains of the FAQLQs (data not shown).

Table 1. Patient recruitment.

Patients	Children	Adolescents	Adults	Total
Contacted (n)	48	51	49	148
Returned 1st questionnaire (n)	41	47	43	131
Returned 2nd questionnaire (n)	38	38	38	114
Excluded (n)	7	4	2	13*
Analysed (n)	31	34	36	101

* Seven patients (3 children, 3 adolescents, 1 adult) were excluded, because they completed the second questionnaire more than 14 days after completion of the first. One child and 1 adult were excluded because of a grade 3 or 4 allergic reaction between the first and second measurement. One child was excluded because she was aged under 8 years. Two children and 1 adolescent were excluded because they experienced their most severe reaction ever within 2 months before the first measurement.

Figure 1 illustrates the correlation between the first and second measurement. Major axis analysis revealed no significant differences of the slope and intercept of the best fitting line from the concordance line for the FAQLQ-CF and -TF. For the FAQLQ-AF there were significant but modest differences of the slope (1.10, p=0.046) and the intercept (-0.612, p=0.019) of the best fitting line from the concordance line. The slope and intercept of the best fitting line of the FAQLQ-CF, -TF and -AF did not differ significantly from each other.

The Bland-Altman plots are shown in figure 2. About 95% of the differences lie within the 1.96 SD limits of agreement. There was no significant correlation between the mean of both scores and the differences of both scores for the FAQLQ-CF and -TF. There was a significant but modest correlation between the mean of both scores and the differences of both scores for the FAQLQ-AF (r=-0.334; p=0.046). No significant systematic bias was observed, which means that mean differences of both scores were all close to zero. The limits of agreement are most narrow for FAQLQ-TF and wider for FAQLQ-CF and -AF.

Discussion

This article describes the evaluation of the test-retest reliability of the recently developed self-administered FAQLQ-CF, -TF and -AF. Overall, reliability was considered to be excellent for the FAQLQs as measured with the ICC and CCC. Additionally, Bland-Altman plots showed that mean differences were all close to zero, supporting the high reliability of the FAQLQs.

In this study we used ICCs calculated by a one-way ANOVA, CCCs and Bland-Altman plots to assess test-retest reliability. However, different methods can be used to assess test-retest reliability and there is much discussion in literature on the best way to do this [20]. A disadvantage of the ICC is that if patient groups are very

Table 2. Demographics and clinical characteristics.

	Children (n=31)	Adolescents (n=34)	Adults (n=36)
Mean age, years (SD)	10.6 (1.5)	15.0 (1.5)	37.3 (14.5)
Gender, n (%)			
Male	17 (55)	18 (53)	7 (19)
Female	14 (45)	16 (47)	29 (81)
Type food allergy, n (%)			
Peanut	25 (71)	30 (88)	25 (69)
Tree nuts	17 (49)	28 (82)	25 (69)
Milk	15 (43)	15 (44)	15 (42)
Egg	14 (40)	16 (47)	7 (19)
Wheat	5 (14)	4 (12)	7 (19)
Soy	9 (26)	13 (38)	8 (22)
Sesame	7 (20)	9 (26)	6 (17)
Fish	2 (6)	5 (15)	9 (25)
Shell fish	6 (17)	8 (24)	12 (33)
Celery	0 (0)	4 (12)	8 (22)
Fruit	14 (40)	13 (38)	26 (72)
Vegetables	6 (17)	6 (18)	10 (28)
Others	25 (71%)	24 (71)	13 (36)
Number of food allergies, n (%)			
1 food	6 (19)	3 (9)	1 (3)
2 foods	4 (13)	4 (12)	3 (8)
3 foods	4 (13)	8 (24)	10 (28)
> 3 foods	17 (55)	19 (56)	22 (61)
Severity of Symptoms Mueller Classification, n (%)			
Grade 1	6 (19)	2 (6)	3 (8)
Grade 2	2 (6)	3 (9)	3 (8)
Grade 3	17 (55)	18 (53)	13 (36)
Grade 4	6 (19)	9 (26)	17 (47)
Other[1]	0 (0)	2 (6)	0 (0)
Most severe reaction, years ago (SD)	4.6 (3.6)	7.1 (5.4)	5.2 (7.5)
Diagnosed by, n (%)			
Specialist[2]	26 (83)	25 (74)	25 (69)
Dietician	0 (0)	1 (3)	0 (0)
General Practitioner	4 (13)	6 (18)	3 (8)
Alternative Physician	1 (3)	0 (0)	3 (8)
Patient	0 (0)	0 (0)	4 (11)
Parents	0 (0)	2 (6)	1 (3)

[1] Other food allergy types not specified in the Mueller Classification, for example the Oral Allergy Syndrome.
[2] Allergist, Dermatologist or Paediatrician

Table 3. Reliability and agreement measures of the FAQLQs.

	FAQLQ-CF	FAQLQ-TF	FAQLQ-AF
M1 (SD)	4.13 (1.15)	4.37 (1.20)	4.49 (1.44)
M2 (SD)	4.08 (1.34)	4.42 (1.29)	4.34 (1.59)
MB (SD)	4.11 (1.22)	4.40 (1.24)	4.41 (1.50)
MD (SD)	0.045 (0.537)	-0.051 (0.274)	0.147 (0.451)
*Limits of agreement (1.96*SD)*	-1.008 to 1.097	-0.588 to 0.486	-0.737 to 1.031
ICC one-way (95% CI)	0.910 (0.823-0.955)	0.976 (0.952-0.988)	0.952 (0.909-0.975)
Error variance	0.147	0.038	0.102
CCC (95% CI)	0.907 (0.847-0.967)	0.975 (0.959-0.991)	0.951 (0.921-0.981)
Scale shift	1.162	1.077	1.104
Location shift	0.036	-0.041	0.097
Pearson	0.918	0.978	0.960
Kendall's tau-b	0.759	0.888	0.780

M 1 = Total FAQLQ score measurement 1
M 2 = Total FAQLQ score measurement 2
MB = Mean FAQLQ score of both measurements
MD = Mean difference between measurement 1 and 2 (M1-M2)
SD = Standard deviation
CI = Confidence interval
Limits of agreement: MD +/- 1.96*SD of the MD
ICC = Intraclass correlation coefficient
CCC = Concordance correlation coefficient
Scale shift (SD2/SD1)
Location shift: $(M1-M2) \Big/ \sqrt{SD1 * SD2}$

homogeneous, the ICC tends to be low, because the ICC compares variance among patients to total variance. If patient groups are very heterogeneous, the ICC tends to be high. Thus, the ICC would only generalize to similar populations. Additionally, the one-way ICC does not take into account the order in which observations were taken [29]. Therefore, the CCC is a useful additional measure. The CCC takes into account not only mean differences between the first and second measurement, such as ICCs calculated by a one-way ANOVA, but also takes into account variance differences between the first and second measurement by reducing the magnitude of the resulting test-retest reliability estimate. In addition, the CCC is a better tool to distinguish between bias and imprecision [20;29]. There can be large differences in ICC and CCC scores, especially in studies with heterogeneous groups. The similar scores we found in our study reflect that both coefficients worked very well in this population and that results can be generalized to other groups. Bland-Altman plots are very illustrative in assessing test-retest agreement. They were useful to identify some extreme and outlying differences, to analyse the magnitude of the measurement error, which was small, and to visualize a possible relationship between the difference and the mean of both scores [26].

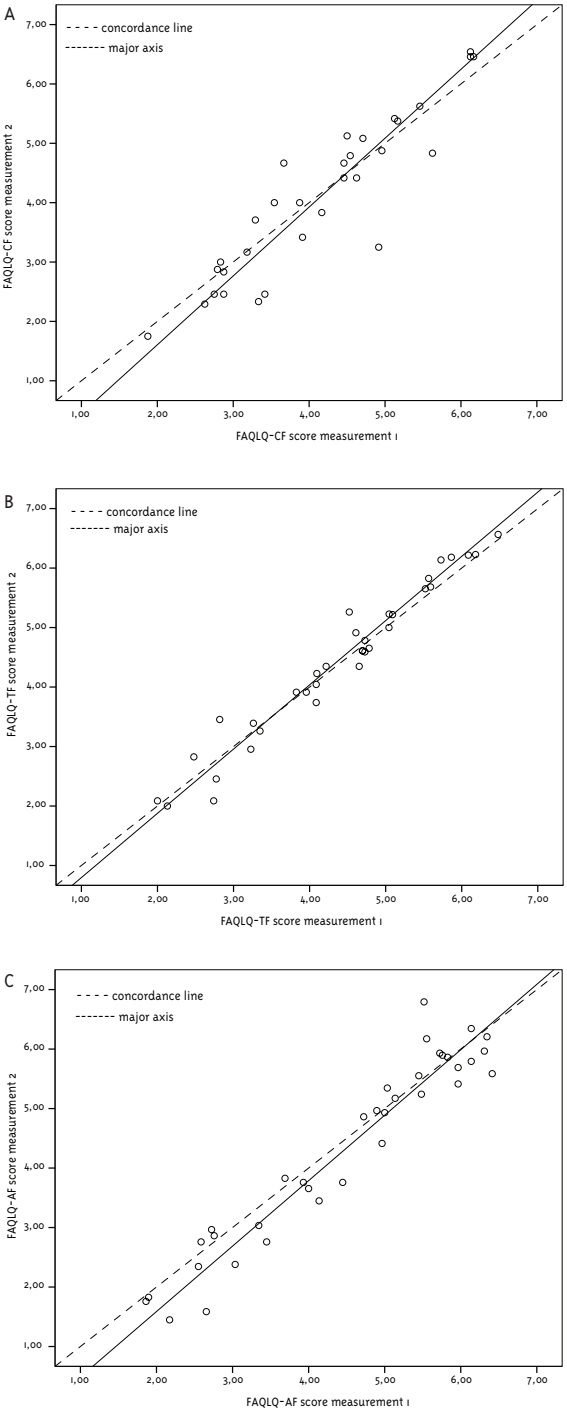

Figure 1. FAQLQ score of the first measurement against FAQLQ score of the second measurement with 45 line through the origin in A children, B adolescents and C adults.

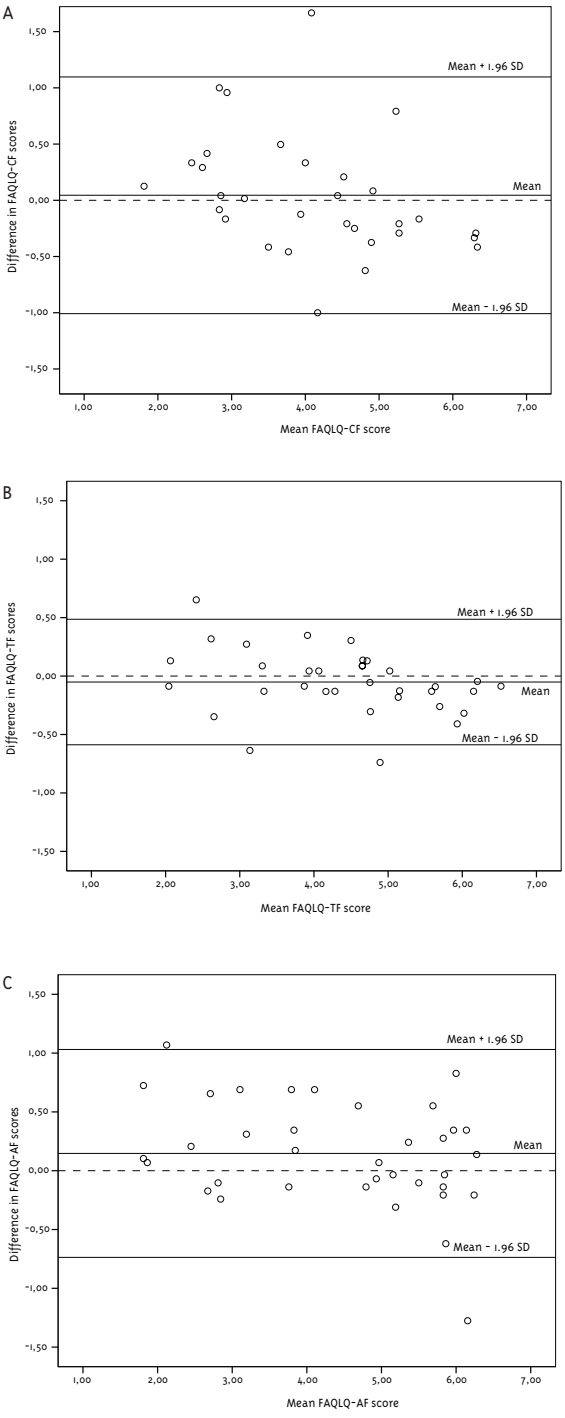

Figure 2. Bland-Altman plots for the FAQLQs in A children, B adolescents and C adults. The mean of both measurements are plotted against the difference of both measurements (calculated as first measurement minus second measurement).

This study may also have some limitations. Firstly, the sample sizes were relatively small. However, we found that the reliability of the questionnaires was very high, which indicates that the sample sizes were adequate and that a greater number of patients would probably not have influenced the outcomes. Another limitation may be that the majority of adults in this study was female. However, we did not find significant differences in the test-retest reliably outcomes between men and women (data not shown). Therefore, we think that the imbalance between men and women did not influence the generalisability of the results of the FAQLQ-AF. Finally, the significant correlation between the first and second measurement of the FAQLQ-AF (figure 1C) and between the mean of both scores and the differences of both scores of the FAQLQ-AF (figure 2C) was an unexpected finding. We think this correlation might be due to an outlier. This assumption was supported by a re-analysis excluding this outlier, which showed that the correlation was no longer significant.

In summary, the FAQLQs clearly showed excellent reliability and are thus promising measures in evaluative studies in patients with food allergy, but also in monitoring individual patients. The high test-retest reliability supports the value of the FAQLQs for clinical trials with relatively small sample sizes. We recommend the use of the FAQLQs in clinical trials of current management strategies of food allergy and they may also be useful when new treatments become available. Currently, the longitudinal validity of the FAQLQs and the validity of several other European language versions of the FAQLQs are being investigated.

Acknowledgements
This work was funded by the EU through the EuroPrevall project (FOOD-CT-2005-514000).

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Chapter 7

Health-related quality of life of food allergic patients: Comparison with other diseases and the general population

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Abstract

Background:
Health-Related Quality of Life (HRQL) has never been measured with generic and disease-specific questionnaires in the same group of food allergic (FA) patients.

Objective:
The aims of this study were to compare generic HRQL of FA patients with the general population and other diseases and to compare HRQL of FA patients as measured with generic and disease-specific questionnaires.

Methods:
Generic HRQL questionnaires (CHQ-CF87 and RAND-36) and disease-specific HRQL questionnaires (FAQLQ-CF, -TF and -AF) were completed by 79 children, 74 adolescents and 72 adults with FA. The generic HRQL scores were compared with scores from published studies on the general population and patients with asthma, irritable bowel syndrome (IBS), diabetes mellitus type I (DM) and rheumatoid arthritis (RA).

Results:
FA children and adolescents reported fewer limitations in school work due to behavioural problems ($p \leq 0.013$), but FA adolescents and adults reported more pain ($p=0.020$), poorer overall health ($p<0.001$), more limitations in social activities ($p<0.001$) and less vitality ($p=0.002$) than individuals from the general population. FA patients reported poorer HRQL than patients with DM, but better HRQL than patients with asthma, IBS and RA. In contrast to the disease-specific questionnaires, high ceiling effects were found for some generic HRQL scales.

Conclusion:
HRQL is impaired in FA adolescents and adults compared to the general population and is intermediate in magnitude between DM and asthma, IBS and RA. Children show the least impact on HRQL from FA. Because of high ceiling effects, generic HRQL questionnaires are less suitable to measure disease-specific, clinically important impairments in food allergy.

Introduction

Currently, there is still no cure available for patients with food allergy. Food allergic patients must carefully avoid the causal foods every day, which may be a great burden to themselves and their families [1;2]. Despite taking precautions, there is always a chance of accidental exposure and for some patients such exposure may be fatal [3] which in turn may provoke even more anxiety. Thus, while food allergic patients may experience symptoms only intermittently, they continuously need to undertake extensive measures in order to prevent exposure to foods to which they are allergic. This has a negative impact on their health-related quality of life (HRQL) [4].

HRQL may be defined as 'the effects of an illness and its consequent therapy upon a patient, as perceived by the patient' [5]. The measurement of HRQL offers the opportunity to study the impact of a disease or the effect of a treatment from the patient's unique perspective. More importantly, HRQL is the only available measure reflecting the ongoing severity of food allergy, since no objective disease parameters are available [6].

There are two major types of questionnaires to measure HRQL: generic and disease-specific questionnaires. Generic questionnaires can be used to evaluate and compare different diseases. The disadvantages of generic questionnaires are that they may not focus adequately on problems specific to a particular disease and that they simultaneously measure the impact of comorbid diseases. Disease-specific instruments are targeted to a specific disease. These disease-specific questionnaires are more likely to detect clinically important changes in patients' HRQL. However, disease-specific questionnaires do not allow comparison between different diseases [7].

In food allergy research, there are only a few studies that have investigated the impact of food allergy on HRQL [8-20]. However, there are no studies that have compared generic HRQL of food allergic patients from childhood to adulthood with generic HRQL of the general population and patients with other chronic diseases. To our knowledge, there are two previous studies that have compared HRQL of food allergic patients with one other chronic disease (rheumathological disease and diabetes mellitus, respectively) [8;10]. However, the later study [10] used non validated disease-specific questionnaires, which makes a comparison between different diseases problematic. The former study [8] used a single Visual Analogue Scale and the Impact on Family Scale, which only covers a single domain of generic HRQL. This study is the only study in the field of food allergy that investigated the HRQL of food allergic adults [8]. All other studies investigated food allergic children. Of these pediatric studies, there was only one study in which adolescents aged 13-21 years completed a self-administered HRQL questionnaire, while in all other pediatric studies, the HRQL questionnaires were completed by the parents. Finally, since self-administered disease-specific HRQL questionnaires for food allergic patients have become available only recently [18-20], the administration of both generic and disease-specific instruments to the same population of food allergic patients has not been possible until now.

The aims of this study were to investigate the impact of food allergy on HRQL measured with self-administered generic HRQL questionnaires in children from the age of 8 years, adolescents and adults and to compare the generic HRQL of these food allergic patients with the generic HRQL of the general population and patients with other diseases. Additionally, we compared HRQL of food allergic patients as measured with generic and disease-specific questionnaires.

Methods

Participants

The current study is part of a larger study on the development and validation of food allergy specific HRQL questionnaires and the measurement of the impact of food allergy on HRQL. This larger study was reviewed by the local medical ethics review commission (METc 2005/051) who deemed that the study did not fall under the range of the Medical Research Involving Human Subjects Act and that therefore approval was not needed. Participants in the present study were part of the studies on the cross-sectional validation of the Food Allergy Quality of Life Questionnaire-Child Form, -Teenager Form and -Adult Form (FAQLQ-CF, -TF and -AF)[18-20]. These participants, aged 8 years and older with a physician-diagnosed food allergy for at least one food, were recruited from our outpatient (paediatric) allergy clinic or were recruited through food allergy support organisations (the Dutch Foundation for Food Allergy and the Dutch Anaphylaxis Network) and by advertisement in local newspapers. All common food allergies and different types and severities of symptoms were represented [18-20].

Procedure

A letter of invitation, the questionnaires (the age appropriate generic and disease-specific HRQL questionnaire) and descriptive questions on age, sex, type and number of food allergies, type of symptoms and diagnosis were sent by mail to be completed at home. The letter of invitation stressed that participation was completely voluntary. Participants were not paid for their participation. The children and their parents were instructed that the children should fill out the questionnaires by themselves. Parents were allowed to explain a question when needed, but they were not allowed to tell the child which answer to give. For completing the descriptive questions parents were allowed to help their child when needed.

Questionnaires

Generic HRQL questionnaires

In children and adolescents, the Child Health Questionnaire-Child Form (CHQ-CF87) was administered [21;22]. This questionnaire is self-administered by the child and contains 87 items divided into twelve scales (Table 1). After recoding the raw

Table 1. CHQ-CF87 and RAND-36 scales, items per scale and definition of the scales.

Generic HRQL scales	No. of items	Definition of the scales
CHQ-CF87		
Physical functioning (PF)	9	Limitations in physical activities
Role functioning-emotional (RE)	3	Limitations in school work or activities with friends due to emotional problems
Role functioning-behaviour (RB)	3	Limitations in school work or activities with friends due to behavioural problems
Role functioning-physical (RP)	3	Limitations in school work or activities with friends due to physical problems
Bodily pain (BP)	2	Severity, frequency of pain and limitations due to pain
General behaviour (BE)	17	The degree to which the child exhibits aggressive, immature or delinquent behaviour
Mental health (MH)	16	The degree of positive and negative feelings, including anxiety, depression, peacefulness and happiness.
Self-esteem (SE)	14	The degree of satisfaction with abilities, looks, family/peer relationship and life overall
General health (GH)	12	Perceptions of overall health
Change in health*	1	Change in health compared to 1 year ago
Family activities (FA)	6	The degree to which the child's health limits or interrupts family activities or is a source of family tension
Family cohesion (FC)	1	The ability of the family to get along with each other
RAND-36		
Physical functioning (PF)	10	Limitations in physical activities
Social functioning (SF)	2	Limitations in social activities
Role functioning-physical (RP)	4	Limitations in work or daily activities due to physical problems
Role functioning-emotional (RE)	3	Limitations in work or daily activities due to emotional problems
Mental health (MH)	5	The degree of positive and negative feelings, including anxiety, depression, peacefulness and happiness.
Vitality (VT)	4	The degree of vitality and liveliness
Bodily pain (BP)	2	Severity, frequency of pain and limitations due to pain
General health (GH)	5	Perceptions of overall health
Change in health (CH)	1	Change in health compared to 1 year ago

* This single-item scale was not used in this study.

scores, scale scores are computed and transformed into a 100-point scale. Higher scores indicate better HRQL.

In adults we administered the RAND-36, which is the Dutch translation of the MOS 36-item Short-Form Health Survey [23;24]. The RAND-36 consists of 36 items divided into nine scales (Table 1). After recoding the raw scores, scale scores are computed and transformed into a 100-point scale. Higher scores indicate better HRQL.

Disease-specific HRQL questionnaires

The disease-specific HRQL questionnaires used in this study were the Food Allergy Quality of Life Questionnaire-Child Form (FAQLQ-CF) for children aged 8-12 years, the Food Allergy Quality of Life Questionnaire-Teenager Form (FAQLQ-TF) for adolescents aged 13-17 years and the Food Allergy Quality of Life Questionnaire-Adult Form (FAQLQ-AF) for adults aged 18 years and older[18-20]. All 3 questionnaires were validated in the Netherlands and showed excellent reliability[25]. These questionnaires consist of 24, 23 and 29 items, respectively. The raw FAQLQ scores 0 to 6 were recoded as 1 to 7. The total score is the mean of all items of each questionnaire and ranges from 1 (minimal impairment of HRQL) to 7 (maximal impairment of HRQL). Thus higher scores indicate poorer HRQL.

Comparative studies

Norm values of the Dutch population were obtained from the validation studies of the generic questionnaires in the Netherlands [22;23]. The original database of the Dutch school population was obtained [22] and used to calculate CHQ-CF87 scores for children and adolescents separately. As comparative diseases we chose asthma, irritable bowel syndrome (IBS), diabetes mellitus type I (DM) and rheumatoid arthritis (RA). These diseases were chosen because they are chronic with sufficient parallels with food allergy and were used as comparative disease in previous studies on HRQL in food allergy [8;10].

Selection of comparative studies

To compare the impact of food allergy on HRQL with the general population and patients with other diseases, we searched PubMed for comparative studies on generic HRQL. Comparative studies were identified through a search from 1998 to 2008 using the search terms 'Child Health Questionnaire Child Form 87' or 'CHQ-CF87' for the children and adolescents and 'RAND-36', 'SF-36' or 'Medical Outcomes Study Short Form 36' for the adults, together with disease-specific terms. Only studies in Dutch populations were included, since the current study of food allergic patients was carried out in the Netherlands. For inclusion in the comparison, the studies had to report the mean (SD) scores for each of the CHQ-CF87 subscales or RAND-36 subscales. Because the focus of the comparison was the effect of disease on HRQL, baseline or pre-treatment scores were required. If multiple studies met the selection criteria, the study with the largest sample size was chosen.

Statistical analysis

One-sample t-tests were used to compare the scores of the food allergic patients on the CHQ-CF87 and RAND-36 with Dutch populations and specific disease populations previously studied. Because we obtained the original database of the Dutch child and adolescent populations [22], we used the Mann-Whitney test to compare the scores of the food allergic children and adolescents on the CHQ-CF87 with the scores of the Dutch child and adolescent populations (not normally

distributed). Additionally, floor and ceiling effects (percentage of patients with minimal or maximal score, respectively) of the generic and disease-specific questionnaires were investigated. The floor and ceiling of the generic CHQ-CF87 and RAND-36 were score 0 and score 100. The floor and ceiling of the disease-specific FAQLQ-CF, -TF and -AF were score 1 and score 7. Statistical analyses were performed with SPSS for Windows 14.0 (SPSS Inc., Chicago, IL, USA).

Results

Participants

The questionnaire packages including the FAQLQ-CF, -TF or -AF and the age appropriate generic HRQL questionnaires were sent to 312 participants divided over the three age groups. Response rates were high: children 84/111 (73%), adolescents 75/98 (77%) and adults 80/100 (80%). A few returned questionnaires were excluded from the analysis because a) no current food allergies were reported (three children and one adult) or b) no physician-diagnosed food allergy was reported (seven adults) or c) the descriptive characteristics were missing (one child and one adolescent) or d) the generic questionnaire was not completed (one child). Therefore, 225 participants were included in the final analysis. Table 2 shows the descriptive characteristics of these participants.

Comparative studies

The following numbers of articles were reviewed for each generic questionnaire and each disease:

- CHQ-CF87, children and adolescents: asthma, 3; IBS, 0; DM, 5; RA, 11;
- RAND-36, adults: asthma, 7; IBS, 1; DM, 19; RA, 16;

A summary of the selected articles (population based and disease based) is shown in Table 3.

CHQ-CF87: food allergy versus population

Food allergic children scored significantly higher on the scale RB ($p=0.005$) than children from the general population [22], indicating better HRQL for the food allergic children on this scale (Figure 1). Also food allergic adolescents scored significantly higher on the scale RB ($p=0.013$), but lower on the scales BP ($p=0.020$) and GH ($p<0.001$) than adolescents from the general population [22], indicating better HRQL on one scale for the food allergic adolescents and poorer HRQL on the other two scales (Figure 2a).

CHQ-CF87: food allergy versus other diseases

No studies in asthma, IBS, DM or RA were found that examined the CHQ-CF87 in children aged 8 to 12 years. Only two studies examined the CHQ-CF87 in adolescents with asthma [26] and DM [27]. Asthmatic adolescents scored significantly

Table 2. Descriptive characteristics of the food allergic participants (n=225).

	Children	Adolescents	Adults
Patients (n)	79	74	72
Sex (m/f)	45/34	34/40	18/54
Age, mean (years)	10.2 (1.3)	14.7 (1.3)	37.2 (14.3)
Age, range (years)	8-12	13-17	18-72
Type of food allergies, n (%)			
Peanut	59 (74)	57 (77)	42 (58)
Tree nut	57 (72)	56 (76)	42 (58)
Egg	29 (37)	26 (35)	16 (22)
Milk	22 (28)	29 (39)	19 (26)
Fish	2 (3)	13 (18)	11 (15)
Shell fish	7 (9)	12 (16)	12 (17)
Wheat	10 (13)	5 (7)	12 (17)
Sesame	14 (18)	8 (11)	13 (18)
Soy	12 (15)	17 (23)	13 (18)
Celery	1 (1)	3 (4)	11 (15)
Fruits	29 (37)	38 (51)	35 (49)
Vegetables	14 (18)	22 (30)	27 (38)
Other*	15 (19)	20 (27)	30 (42)
Number of food allergies, n (%)			
1 food	15 (19)	9 (16)	12 (17)
2 foods	15 (20)	12 (41)	14 (19)
3 foods	16 (20)	15 (11)	8 (11)
>3 foods	32 (41)	38 (51)	38 (53)
Type of symptoms, n (%)			
Cardiovascular symptoms[1]	28 (35)	31 (58)	44 (61)
Respiratory symptoms[2]	56 (71)	61 (82)	60 (83)
Gastrointestinal symptoms[3]	49 (62)	47 (64)	48 (67)
Skin symptoms[4]	69 (87)	60 (81)	55 (76)
Other[5]	66 (84)	66 (89)	62 (86)

* E.g. lupine, kernels and seeds, herbs and spices, meat.

[1] dizziness, feeling your heart beat fast, loss of vision, inability to stand, light headedness, collapse, loss of consciousness / passing out

[2] tightening throat, difficulty swallowing, hoarseness / hoarse voice, difficulty breathing in, shortness of breath, wheezing, cough

[3] nausea, stomach cramps, vomiting, diarrhea

[4] itchy skin, red rash, urticaria, worsening eczema, swelling of the skin

[5] oral allergy, swollen tongue or lips, symptoms of the nose or eyes

Table 3. Description of studies included in the comparison.

Reference	Disease	Patients, n*	Age, mean (SD)	Age, range	Male, %	Sample source
CHQ-CF87						
Raat et al. [22]	Population	444	12.8 (1.7)	9-17	50.5	School children
Mohangoo et al. [26]	Asthma	72	15 (0.7)	14-17	27.8	School children
De Wit et al. [27]	DM	91	14.9 (1.1)	13-16.5	47	Outpatient clinic
RAND-36						
Van de Zee et al. [23]	Population	1063	44.1 (17.5)	18-89	35	Dutch population
Willems et al. [29]	Asthma	27	45.9 (15.9)	NA	33.3	Outpatient clinic
Ten Berg et al. [31]	IBS	169	55.0 (17.1)	NA	22.8	Medical database
Hart et al. [28]	DM	274	38.2 (12.4)	NA	54.4	Outpatient clinic
Rupp et al. [30]	RA	679	59.6 (13.8)	NA	29	Diagnostic register

DM=diabetes mellitus type I
RA=rheumatoid arthritis
IBS= irritable bowel syndrome
NA=not available
*represents the number of patients included in the analysis of the generic HRQL questionnaire

lower on the scales PF (p=0.049), BE, MH, FA and FC (all p<0.001) than those with food allergy, indicating better HRQL for food allergic adolescents than asthmatic adolescents. Adolescents with DM scored significantly higher on to the scales PF (p=0.039), BP (p=0.012), MH (p=0.034) and SE (p=0.014) than those with food allergy, indicating poorer HRQL for food allergic adolescents than diabetic adolescents (Figure 2b).

RAND-36: food allergy versus population

Food allergic adults scored significantly lower on the scales SF (p<0.001), VT (p=0.002) and GH (p<0.001) than adults from the general population [23], indicating poorer HRQL for food allergic adults (Figure 3a).

RAND-36: food allergy versus other diseases

Adults with DM [28] scored significantly higher on five scales than those with food allergy (SF, p<0.001; RP, p=0.014; VT, p=0.002; BP, p=0.001; GH, p<0.001), indicating poorer HRQL for food allergic adults than diabetic adults. Adults with asthma [29] scored significantly lower on all scales, except one (MH), than those with food allergy (all p<0.01), indicating better HRQL for food allergic adults than asthmatic adults. Also adults with RA [30] scored significantly lower on six scales than those with food allergy (PF, p<0.001; RP, p<0.001; RE, p=0.008; VT, p=0.031; BP, p<0.001; GH, p=0.048), indicating better HRQL for food allergic adults than adults with RA. Finally, adults with IBS [31] scored significantly lower on all scales than those with food allergy (all p<0.01), indicating better HRQL for food allergic adults than adults with IBS (Figure 3b).

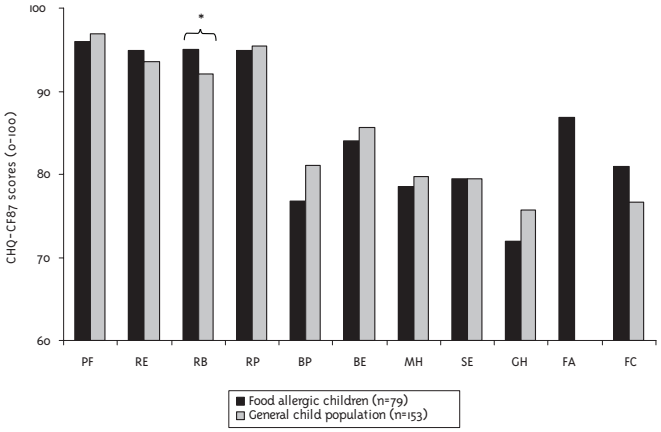

Figure 1. CHQ-CF87 scores of children with food allergy and a sample of children from the general population [22]. *p<0.01. Higher scores indicate better HRQL. FA, not available for the sample of children from the general population. See table 1 for the definition of the scales.

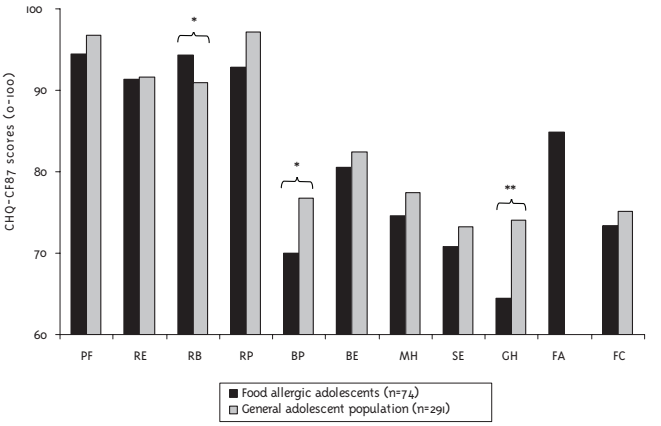

Figure 2a. CHQ-CF87 scores of adolescents with food allergy and a sample of adolescents from the general population[22]. *p<0.05;**p<0.001. Higher scores indicate better HRQL. FA, not available for the sample of adolescents from the general population. See table 1 for the definition of the scales.

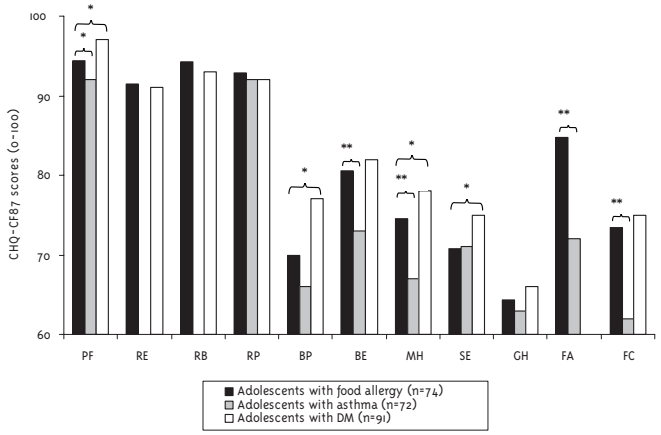

Figure 2b. CHQ-CF87 scores of adolescents with food allergy, asthma [26] and diabetes mellitus type 1 (DM)[27]. *p<0.05; **p<0.01. Higher scores indicate better HRQL. RE and RB not available for asthma, FA not available for DM. See table 1 for the definition of the scales.

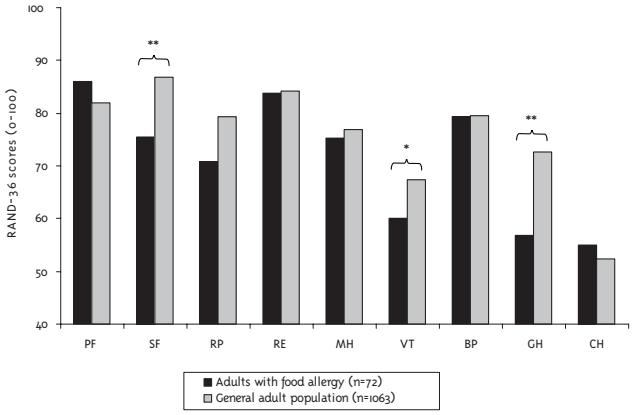

Figure 3a. RAND-36 scales scores of food allergic adults and a sample of adults from the general population [23]. *p<0.01; **p<0.001. Higher scores indicate better HRQL. See table 1 for the definition of the scales.

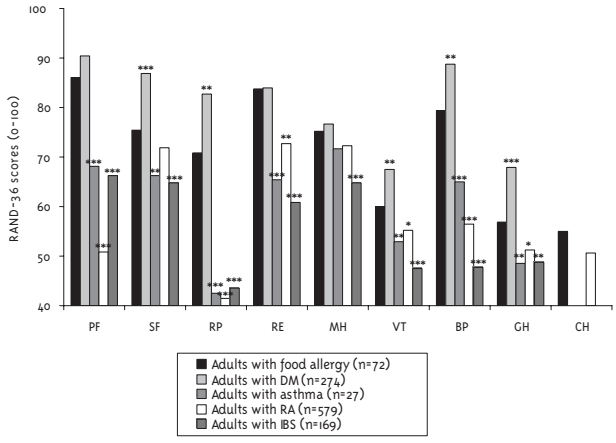

Figure 3b. RAND-36 scales scores of adults with food allergy, diabetes mellitus type 1 (DM) [28], asthma [29], rheumatoid arthritis (RA) [30] and irritable bowel syndrome (IBS)[31]. *p<0.05; **p<0.01; ***p<0.001. Higher scores indicate better HRQL. CH not available for asthma, IBS and DM. See table 1 for the definition of the scales.

Generic versus disease-specific HRQL questionnaires: Floor and ceiling effects

The FAQLQ-CF, -TF and -AF showed minimal if any floor or ceiling effects (Table 4), indicating that almost no food allergic patients reported the minimal score (best HRQL) or maximal score (worst HRQL) on the FAQLQ. In children, the CHQ-CF87 showed almost no floor effects because the minimal score (worst HRQL) was seldom reported. However, remarkable ceiling effects were seen for the scales RE, RB, RP, where more than 80% of the children reported the maximal score (best HRQL). A similar pattern was seen in adolescents. In adults, the RAND-36 showed some floor effects (adults with the minimal score, thus worst HRQL), but more pronounced were the ceiling effects (adults with the maximal score, thus best HRQL), especially for the scale RE (79%).

Table 4. Percentage of floor and ceiling effects of FAQLQ-CF, -TF and -AF, CHQ-CF87 and RAND-36.

	Children		Adolescents			Adults	
	Floor %	Ceiling %	Floor %	Ceiling %		Floor %	Ceiling %
FAQLQ	1.3	0	0	1.4		1.4	0
CHQ-CF87					*RAND-36*		
PF	0	64.8	0	58.1	PF	0	26.0
RE	1.3	81.0	1.4	73.0	SF	1.4	23.0
RB	0	82.3	0	81.1	RP	19.4	58.3
RP	0	86.1	2.7	85.1	RE	11.1	79.2
BP	0	41.8	1.4	20.3	MH	0	2.8
BE	0	5.1	0	0	VT	0	1.4
MH	0	2.6	0	0	BP	0	37.5
SE	0	6.3	0	0	GH	0	2.8
GH	0	3.8	0	0	CH	1.4	8.3
FA	0	31.6	0	24.3			
FC	0	25.3	0	23.0			

See table 1 for the definition of the scales.
Floor effect = percentage of patients with minimal score.
Ceiling effect = percentage of patients with maximal score.
Floor and ceiling of the FAQLQ-CF, -TF and -AF are score 1 (best HRQL) and 7 (worst HRQL), respectively.
Floor and ceiling of CHQ-CF87 and RAND-36 are score 0 (worst HRQL) and 100 (best HRQL), respectively.

Discussion

In this study we found that food allergic children and adolescents reported less impairment on the scale role functioning-behaviour (RB) than general pediatric and adolescent populations. However, food allergic adolescents reported more impairment on the scales bodily pain (BP) and general health (GH) than a general adolescent population and food allergic adults reported more impairment on the scales self-esteem (SE), vitality (VT) and general health (GH). Compared with other chronic diseases, food allergic patients reported poorer generic HRQL than patients with DM, but better generic HRQL than patients with asthma, IBS and RA. Finally, we found very high ceiling effects for some scales of the generic questionnaires. No significant floor or ceiling effects were found for the disease-specific FAQLQs.

One of the advantages of generic HRQL questionnaires is that they can be used to compare healthy individuals with patients with a chronic disease. We compared food allergic patients with individuals from the general population and found that food allergic children and adolescents reported fewer limitations in school work or activities with friends due to behavioural problems (RB). This may be explained by the fact that having a food allergy demands that the child be conscious of his or her behaviour, especially regarding to situations involving food, with an emphasis on avoidance of impulsive behaviour. These disease managing demands may result

in more consciousness about behaviour in other situations as well, resulting in less behavioural problems than in children of the general population. In addition to RB, trends were seen for food allergic children to report better HRQL scores on RE and FC and also in food allergic adolescents and adults to report better HRQL scores on the scales RB and PF, respectively. However, the overall trend was that food allergic patients reported poorer HRQL on most scales than the general population. Compared to the older age groups, food allergic children reported the least impact of food allergy on generic HRQL and their scores were comparable to the scores of the children in the general population. As in this age group parents are responsible for the management of the food allergy, children probably do not experience much impact of their food allergy on their generic HRQL. Alternatively, the generic questionnaire used in children may be less responsive than the corresponding questionnaires in adolescents and adults.

Food allergic adolescents reported significantly more pain and limitations due to pain (BP) and poorer perceptions of overall health (GH) than adolescents from the general population. It is remarkable that food allergic adolescent reported significantly lower scores on BP than those from the general population, since pain is not a feature of food allergy. However, the questions included in BP ask about bodily pain or symptoms. While symptoms are generally not a feature of food allergy outside of accidental exposures, they are a feature of frequent comorbid conditions such as asthma [32]. Since generic questionnaires do not separate the impact on HRQL of the disease in question from the impact of comorbid diseases, this may have influenced the responses to questions in this domain. Food allergic adults reported significantly more limitations in social activities (SF), less vitality and liveliness (VT) and poorer perceptions of overall health (GH) than adults from the general population. Overall, food allergic patients tend to report poorer HRQL than individuals from the general population, apart from the exceptions indicated above.

A further advantage of generic HRQL questionnaires is that they can be used to compare different diseases. We compared food allergy with four other chronic diseases and found that food allergic patients reported poorer HRQL than patients with DM, but better HRQL than patients with asthma, IBS and RA. While this may indicate that these diseases differ in their impact on HRQL, other factors may have played a role as well. Firstly, HRQL in adults is age-dependent and it has been found that HRQL as measured with the scales PF, RB, BP and GH decreases with age [23]. On average, the food allergic adults in our study were younger than the adult patients with asthma, IBS and RA, which may have led to diminished HRQL being reported by these patient groups. The adults with DM had approximately the same age as the food allergic adults, and thus this comparison is probably not influenced by the described age effect. Another possibility is that generic questionnaires may be biased to being responsive in diseases characterised by daily chronic symptoms such as asthma, IBS and RA. Conversely, generic HRQL questionnaires tend to ignore limitations of lifestyle and psychological burden caused by disease managing activities more characteristic for diseases such as food allergy and DM. This may

also have influenced the HRQL reported by these patient groups and could have led to an underestimation of the impact on generic HRQL in DM and food allergy.

The disadvantages of generic questionnaires are that they are by design comprehensive, so they may not focus adequately on problems specific to a particular disease and that they do not separate the impact on HRQL of the disease in question from the impact of comorbid diseases. In previous studies on the development and validation of the FAQLQ-CF, -TF and -AF we already showed that the correlations between the generic and disease-specific questionnaires were only low to moderate [18-20]. This indicates that the generic and disease-specific questionnaires are not measuring exactly the same thing. Additionally, we found very high ceiling effects for some scales of the generic questionnaires in this study, which means that a substantial part of the food allergic patients reported no problems in these areas. This indicates that, as expected, some areas measured by generic questionnaires are irrelevant to food allergy. In contrast, no floor or ceiling effects were observed for the disease-specific FAQLQ-CF, -TF and -AF. This indicates that these questionnaires are responsive to the specific concerns of food allergic patients and it underscores the internal validity of these questionnaires. In addition, it illustrates the general desirability of using disease-specific HRQL questionnaires when studying specific diseases.

This study may also have some limitations. We decided to only include comparative studies that were performed in the Netherlands, since the HRQL measurement in food allergic patients was done in the Netherlands. This may decrease the generalisability of the results to other countries and cultures. However, for the comparisons within this study, it was important to include only Dutch studies to prevent bias caused by different languages or cultures. The FAQLQs used in this study will be validated in other countries as well, so they can be used for international disease-specific studies of food allergy. Further comparative studies in other counties and cultures will show if the same patterns are seen as in our study. In addition, it should be mentioned that the comparison between the different diseases is restricted to the patients included in the selected studies. Patients within these different studies could not be perfectly matched on demographic variables which might influence the impact of these diseases on HRQL.

In conclusion, this study showed that food allergic children reported the least impact of food allergy on generic HRQL, which was even better than in children in the general population in some respects. In contrast, food allergic adolescents and adults reported overall poorer generic HRQL than the general population. The HRQL impact of food allergy is intermediate in magnitude between DM and asthma, IBS and RA. Generic HRQL questionnaires may thus be useful to compare the impact of food allergy on HRQL with the general population and other chronic diseases. However, the very high ceiling effects that were found for some generic scales may indicate that generic HRQL questionnaires are not sufficiently responsive to measure disease-specific but potentially clinically important impairments in food allergy. For measuring these disease-specific effects in food allergic patients, it is preferable to use disease-specific questionnaires.

Acknowledgements
This work was funded by the EU through the EuroPrevall project (FOOD-CT-2005-514000).

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Chapter 8

Quality of life in food allergy: valid scales for children and adults

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Curr Opin Allergy Clin Immunol 2009; In press

Abstract

Purpose:
The purpose of this review is to give an overview of how health-related quality of life (HRQL) can be measured in food allergy and to explore recent findings on how food allergy might impact HRQL.

Recent findings:
In addition to the more familiar burdens of having a food allergy, the psychosocial impact of food allergy and information gaps concerning food allergy have received much attention in the recent literature. Recently, reliable and valid disease-specific HRQL questionnaires have become available to measure the impact of food allergy on HRQL in food allergic patients of all ages.

Summary:
Assessment of HRQL could be used by clinicians to get insight in the specific problems patients have to face. In addition, HRQL measurements may be used to measure the effects of an intervention on the patient's quality of life. Finally, HRQL is the only available measure reflecting the ongoing severity of food allergy, since no objective disease parameters are available.

Introduction

Living with a food allergy is increasingly being recognised as being more difficult than is generally appreciated [1]. Management of food allergy includes avoidance of the culprit food in numerous situations which may interfere with daily life [2]. In addition, there is always a chance of accidental exposure which may lead to a (severe) allergic reaction. This may in turn be a source of anxiety [3]. When a severe allergic reaction occurs, prompt and accurate administration of epinephrine may be required which by itself may provoke anxiety about being able to respond adequately [4]. Therefore, food allergy may have a considerable impact on quality of life [5].

What is quality of life?

Although there is no consensus on the definition of quality of life [6], a constructive definition has been drawn up by the World Health Organisation (WHO): "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" [7]. The component of overall quality of life that concerns an individuals' health is called health-related quality of life (HRQL) and may be defined as "the effects of an illness and its consequent therapies upon a patient as perceived by the patient" [8]. HRQL is a multidimensional concept that consists of bio-psycho-social domains such as physical and psychological status and social interaction [6].

How might food allergy influence HRQL?

Since there is no cure available for food allergy, the only form of treatment is strict avoidance of foods causing allergic reactions and provision of emergency treatment. The difficulty of this treatment is that it may take considerable effort in daily life and that success is not guaranteed. There is always a chance of accidental exposure. Consequently, this might influence HRQL [9].

Allergen avoidance and allergic reactions

Allergen avoidance, aiming to prevent allergic reactions, may include numerous actions in different settings in daily life in which food allergic patients have to relay on external factors for their safety. It has been reported that ingredients lists were insufficient for the needs of food allergic patients and that ingredients of pre-packed products were frequently changed which was perceived as frustrating [10]. In addition, it was shown that a considerable percentage of restaurant personnel have insufficient knowledge about food allergy. Despite this, they expressed relatively

high comfort levels in providing safe meals to food allergic patients [11]. The premise that accidental exposure may occur in any situation is underlined by a study that showed that 9% of food allergic patients who had been on board of an airplane reported experiencing an allergic reaction there. Even more alarming was the finding that the information about flying with food allergies was in some cases incomplete or inaccurate [12]. Therefore, in addition to the need of food allergic patients to be vigilant in various situations involving food, they are often reliant on external information which may very well be unreliable.

Anxiety and psychological impact

Food allergy may be a psychological burden with high levels of stress and anxiety for the food allergic patient and, in the case of children, also for their parents [13;14]. Mothers with a food allergic child reported that they experienced parenting such a child as "living with risk" [15]. The pervading theme expressed by adolescents with food allergy was "striving to normalise the experience of being food allergic". These adolescents experienced deprivation, insecurity and fear of severe allergic reactions, but most of them ultimately felt competent in dealing with their food allergy [16]. Lastly, it has been reported that adolescents perceived anaphylaxis as "no big deal" whereas their parents described a large impact on their own day-to-day life [17]. Thus, food allergy may have a considerable psychological impact and may provoke anxiety in food allergic patients and in parents of food allergic children. The lower levels of anxiety sometimes reported by adolescents may not be justified.

Uncertainty and information gaps

Having a food allergy implies being "at risk" for an allergic reaction and this inevitably invokes uncertainty [18]. Moreover, no biological markers are available to predict who will or who will not have an anaphylactic reaction in the future [19]. Uncertainties concerning food allergy may arise from a lack of information [20]. One way to deal with uncertainties caused by lack of information is to join a patient organisation[21;22]. Recently, it was shown that parents themselves had a solid foundation of food allergy knowledge, but that they had concerns about the food allergy knowledge of primary care physicians [23]. The general public had a wide variation in knowledge of food allergy with many misconceptions [24]. Such knowledge gaps, especially among physicians and the general public, may have a negative impact on the HRQL of food allergic patients and parents of food allergic children.

Why is HRQL measurement important?

The importance of measuring HRQL may be addressed from different points of view. First of all, measurement of HRQL gives insight in the impact of disease

from the patient's perspective. It is, for example, possible that two patients with the same objective clinical impairment may have very different degrees of impairment in their HRQL [25]. HRQL assessment could be used by clinicians to get insight in the specific problems patients have to face and to help them coping with those issues [26]. HRQL questionnaires can usually be completed by the patient in less than 15 minutes and are thus suitable for administration just before the clinical interview (e.g. in the waiting room). During the clinical interview, the clinician could discuss areas most affecting HRQL with the patient and help them to manage the mentioned problems. Follow-up measurement over time gives the clinician and patient insight in the effect on HRQL of the chosen management.

In research, HRQL measurements may be used to measure the effects of interventions generally on patients' quality of life, which could help improve the quality of patients' treatment and outcome. HRQL measurements may also be used to compare the effect of different interventions and to compare the impact of different diseases on HRQL [6]. Such HRQL studies may be used by policy makers to improve the allocation of health care resources. Ultimately, combining HRQL data with epidemiologic data on prevalence may give insight in the societal impact of a disease [27].

Finally, with regard of food allergy, it is important to note that there are no objective disease parameters available to measure the ongoing severity of food allergy, such as FEV1 in asthma. One could measure the severity of a food allergic reaction, but allergic reactions occur only when a patient is exposed to a culprit food. Despite the absence of actual symptoms, food allergy has an ongoing severity due to the allergen avoidance requirements and resulting psychosocial burden. HRQL is the only available measure reflecting this ongoing severity of food allergy.

How to measure HRQL?

HRQL can be measured with questionnaires, also called as instruments or scales. There are two types of HRQL questionnaires; generic and disease-specific questionnaires. The major psychometric properties of questionnaires are reliability and validity.

Generic and disease-specific questionnaires

Generic questionnaires are developed for use in different diseases and general populations. Thus, these questionnaires allow comparison between different diseases. The disadvantage is that they may not focus adequately on problems specific to a particular disease and that they also measure the impact of comorbid diseases. Disease-specific instruments are developed for use in a specific population. These questionnaires are much more likely to detect clinically important changes in patients' impairments. The disadvantage is that do not allow comparison between different diseases [25].

Reliability and validity

Reliability refers to the extent to which the questionnaire is repeatable and consistently produces the same results. Reliability is most commonly evaluated by assessment of internal consistency and test-retest analysis (Table 1). Validity is the degree to which the questionnaire measures what it is intended to measure. There are two types of validity; internal and external validity. Internal validity refers to the internal structure of the questionnaires and is usually evaluated by factor analysis, inter-item correlations and floor- and ceiling effects. External validity is the relationship between the questionnaire and an external criterion (e.g. other measures of the same or different dimensions of health) and the most common types are face, content, convergent/discriminant and construct validity [28].

Table 1. Types of reliability and validity commonly used to evaluate HRQL questionnaires.

Reliability		
	Internal consistency	Refers to how well the items of a questionnaire relate to each other and to the total questionnaire. It is most commonly evaluated by Cronbach's alpha. An alpha $\geq$ 0.70 indicates good internal consistency.
	Test-rest reliability	It estimates the reproducibility of the questionnaire over time. The questionnaire is completed on two occasions by the same patients in whom no change in the condition has taken place. It is most commonly evaluated by the intraclass correlation coefficient (ICC). An ICC $\geq$ 0.70 indicates good test-rest reliability.
Validity		
Internal	Factor analysis	Is used to identify groups of items within the questionnaire that relate with each other.
	Inter-item correlations	Correlation between items. Should not be greater than 0.85 to prevent redundancy.
	Floor and ceiling effects	Percentage of patients with minimal or maximal score on the questionnaire, respectively. Floor- and ceiling effects should be minimal.
External	Face validity	A subjective judgement of whether the questionnaire appears to measure what it is supposed to measure.
	Content validity	The extent to which a questionnaire represents all dimensions of a construct. It is also a judgment, but it may be evaluated by the correlation between the questionnaire and the symptom content of a disease.
	Convergent and discriminant validity	The extent to which the questionnaire correlates with measures designed to measure similar constructs and does not correlate with measures designed to measure dissimilar constructs.
	Construct validity	Refers to whether a questionnaire measures the theorized psychological construct (e.g. HRQL). It is evaluated by the correlation between the questionnaire and an independent measure known to be related with the construct or for which there are theoretical grounds for expecting it to be related.

These types of external validity may be ranked based on the rigor of the method of ascertainment. Face validity is determined by expert opinion as to whether the questionnaire seems to measure HRQL related to the disease in question. Since this assessment is subjective, face validity may be considered the least rigorous form of validity. Content validity is also based on subjective assessment of the extent to which a questionnaire represents all dimensions of a construct, but more systematic assessments may be used as well. Therefore, it may be considered to be more rigorous than face validity. Convergent/discriminant validity is assessed by calculating the correlation between the questionnaire and measures of similar or dissimilar constructs. As this is a systematic assessment, this type of validity may be considered as more rigorous than content validity. Finally, since no "gold standard" exists to measure HRQL and to compare a new HRQL questionnaire with, the best achievable form of validity is construct validity, which is ascertained by calculating the correlation between the questionnaire and an independent measure which reflects the severity of the disease in question. As this is a systematic assessment with measures known to be related with the construct, this type of validity may be considered as more rigorous than convergent/discriminant validity (Table 1).

Construct validity is thus usually evaluated by comparing the HRQL questionnaire with an objective measurement of the extent or severity of the disease, and often such an independent measure is directly or indirectly related to the burden of symptoms characterising the disease in question. However, in disorders not characterized by chronic symptoms, as in food allergy, such an independent measure is not available. Therefore is has been shown that the perceived expectation of what will happen following exposure can be used as independent measure to evaluate construct validity as this will be the driving force determining HRQL, and instruments developed in this way have proved to be useful and consistent in measuring HRQL [29].

Finally, for a questionnaire to be reliable and valid in a specific population (e.g. children), it is very important to include patients of the target population in the development of the questionnaire (i.e. item generation and item selection)[30]. This ensures that the questions are of importance for the target population. In addition, the wording of the question should be age appropriate.

Measurement of HRQL in children and adults with food allergy

Measurement of HRQL in food allergy is relatively new research area. The first study on this topic was published in 2000 [31] and the interest in HRQL of food allergy has increased ever since. A few studies reported HRQL of food allergic patients measured with generic questionnaires. However, reliable and valid disease-specific questionnaires to measure HRQL in food allergy have become available only recently.

Table 2. Generic HRQL questionnaires used in food allergic patients.

Questionnaire	No. of items	Domains/ Subscales	Completed by	Used by (Authors, year, country, reference)	Age in years of included food allergic patients
Child Health Questionnaire-Parent Form (CHQ-PF28) and (CHQ-PF50)	28 / 50	Physical functioning Role-social/emotional, behavioural Role-social/physical Bodily pain General behaviour Mental health Self-esteem General health Parental impact-emotional Parental impact-time Family activities Family cohesion Change in health	Parent	Primeau et al., 2000, Canada [31] Sicherer et al., 2001, US [52] Marklund et al., 2006, Sweden [53] Östblom et al, 2008, Sweden [48]	≤ 18 5-18 8-19 9
Child Health Questionnaire-Child Form (CHQ-CF87)	87	Physical functioning Role functioning-emotional Role functioning-behaviour Role functioning-physical Bodily pain General behaviour Mental health Self-esteem General health Family activities Family cohesion Change in health	Child	Flokstra-de Blok et al., 2009, the Netherlands [50] Flokstra-de Blok et al., 2008, the Netherlands [51]	8-12 13-17
Medical Outcome Trust Short Form 36 Health Survey (SF-36) or (RAND-36)	36	Physical functioning Social functioning Role functioning-physical Role functioning-emotional Mental health Vitality Bodily pain General health Change in health	Patient	Primeau et al., 2000, Canada [31] Marklund et al., 2004, Sweden [54] Flokstra-de Blok et al., 2009, the Netherlands [42]	18-45 13-21 18-54
Impact on Family scale (IOF)	24	Familial/social Personal strain Financial Burden Mastery	Patient/ parent	Primeau et al., 2000, Canada [31]	18-45 / ≤ 18
Visual Analogue Scale (VAS) (i.e.thermometer)	1	n.a.	Patient/ parent	Primeau et al., 2000, Canada [31]	18-45 / ≤ 18

n.a. not applicable

Generic HRQL questionnaires used in food allergic patients

Table 2 gives an overview of the generic HRQL questionnaires used in the field of food allergy. The Child Health Questionnaires (CHQ-CF28, CHQ-CF50 and CHQ-CF87) and the Medical Outcome Trust Short Form 36 Health Survey (SF-36 or RAND-36) are generic HRQL questionnaires for children and adults, respectively, that are reliable and well validated in many languages and that have extensively been used in social-medical research [32-37].

The Impact on Family (IOF) scale has been developed to assess the impact of chronic childhood conditions on the family. The original questionnaire has shown to be internally consistent with an acceptable factor structure [38]. More recently, the IOF has been revised and has shown an acceptable level of construct validity [39;40].

The Visual Analogue Scale (VAS) has been adapted from the EQ-5D [41]. The VAS is a vertical line (i.e. thermometer) with the end-points labelled 'no disruption' (score 0) and 'most disruption imaginable' (score 100) and patients are asked to rate how much disruption they experience in their daily activities due to their disease [31].

As can be seen in Table 2, only two studies investigated the generic HRQL of food allergic adults [31;42].

Disease-specific HRQL questionnaires available for use in food allergic patients

During the last years a few disease-specific HRQL questionnaires have been developed and used in food allergy research. However, not all questionnaires have been extensively validated and therefore sometimes caution is needed when interpreting results obtained with these questionnaires. Table 3 summarises disease-specific HRQL questionnaires for use in food allergic patients that are available in the literature. Other disease-specific HRQL questionnaires that were not available from the publication are described in the text only.

The first study of disease-specific HRQL in food allergy was done by Avery and colleagues [43]. A questionnaire specially developed for this study and an adapted version of the Vespid Allergy Quality of Life Questionnaire (VQLQ) [44] were completed by the children aged 7-12 years. However, the first questionnaire was not validated. The second questionnaire has been validated in vespid allergy but not in food allergy and it was not described how this questionnaire was adapted.

Thereafter, Arslan and colleagues investigated HRQL in food allergic adults (aged 19-80 years) with the Short-Form Nepean Dyspepsia Index (SF-NDI) [28]. This questionnaire was developed and validated in patients with functional dyspepsia, but showed satisfactory test-retest reliability in food allergic patients. Construct validity was evaluated by correlating the SF-NDI with two gastrointestinal symptom rating scales. Relatively high correlations were found, since all three questionnaires are targeted to gastrointestinal problems. However, food allergic patients may experience symptoms of other systems as well (e.g. skin, respiratory tract, cardiovascular). Moreover, food allergic patients experience symptoms only when they are exposed to a culprit food. Otherwise they are symptom free, but the

Table 3. Disease-specific HRQL questionnaires available for use in food allergic patients.

Questionnaire	No. of items	Domains/ Subscales	Targetage group (years)	Completed by	Reliability	Validity	Patients/ parents included in development	Developed by (Authors, year, country, reference)
Food Allergy Quality of Life-Parental Burden (FAQL-PB)	17	n.a.	0-17	Parent	Internal consistency Test-retest	*Internal:* Inter-item correlations *External:* Face, Content, Convergent/discriminant, Construct	Yes	Cohen et al., 2004, US [45]
Food Allergy Impact Scale (FAIS)	32	Meal preparation Family social activities Caregiver-supervised child social activities Family relations Stress and free time School and structured activities Autonomous social activities Employment and finances	0-18	Parent	Internal consistency	*Internal:* Not tested *External:* Face, Content.	Yes	Bollinger et al., 2006, US [46]
Food Allergy Parent Questionnaire (FAPQ)	18	Parental anxiety/stress Psychosocial impact of allergies Parental coping/competence Family Support	0-18	Parent	Internal consistency	*Internal:* Factor analysis *External:* Face, Content.	No	LeBovidge et al., 2006, US [47]
Food allergy specific questions	23	Items concerning the child Items concerning the patents or entire family	9	Parent	Not tested	Not tested	Yes	Östblom et al, 2008, Sweden [48]
Food Allergy Quality of Life Questionnaire-Parent Form (FAQLQ-PF)	30	Emotional Impact Food-related anxiety Social and dietary limitations	0-12	Parent	Internal consistency Test-retest	*Internal:* Inter-item correlations, Factor analysis, Floor- and ceiling effects *External:* Face, Content, Convergent/discriminant, Construct *	Yes	DunnGalvin et al., 2008, Ireland [49]

Table 3. Continued.

Questionnaire	No. of items	Domains/ Subscales	Targetage group (years)	Completed by	Reliability	Validity	Patients/ parents included in development	Developed by (Authors, year, country, reference)
Food Allergy Quality of Life Questionnaire-Child Form (FAQLQ-CF)	24	Allergen avoidance Risk of accidental exposure Emotional impact Dietary restrictions	8-12	Child	Internal consistency Test-retest	*Internal:* Inter-item correlations Factor analysis *External:* Face, Content, Convergent/discriminant, Construct *	Yes	Flokstra-de Blok et al., 2009, the Netherlands [50]
Food Allergy Quality of Life Questionnaire-Teenager Form (FAQLQ-TF)	23	Allergen avoidance and dietary restrictions Emotional impact Risk of accidental exposure	13-17	Child	Internal consistency Test-retest	*Internal:* Inter-item correlations Factor analysis *External:* Face, Content, Convergent/discriminant, Construct *	Yes	Flokstra-de Blok et al., 2008, the Netherlands [51]
Food Allergy Quality of Life Questionnaire-Adult Form (FAQLQ-AF)	29	Allergen avoidance and dietary restrictions Emotional impact Risk of accidental exposure Food allergy related health	≥ 18	Adult	Internal consistency Test-retest	*Internal:* Inter-item correlations Factor analysiso *External:* Face, Content, Convergent/discriminant, Construct *	Yes	Flokstra-de Blok et al., 2009, the Netherlands [42]

* longitudinal validation and validation in different languages underway
n.a. not applicable

considerable efforts they have to make to avoid the culprit food influences their daily life. This impact on daily life is not captured by the SF-NDI.

The first validated disease-specific HRQL questionnaire for food allergy became available in 2004: the Food Allergy Quality of Life-Parental Burden (FAQL-PB) [45]. This questionnaire is administered to parents and measures the parental burden associated with having a food allergic child. The questionnaire has shown to be reliable and valid (Table 3). While being useful and well designed, this instrument is not able to measure HRQL of the food allergic children, which may be an important outcome measure in clinical research.

Recently, the Food Allergy Impact Scale (FAIS) and the Food Allergy Parent Questionnaire (FAPQ) were developed. The FAIS measures the impact of food allergy on daily activities of food allergic children and their families and is completed by the parent [46]. It showed acceptable internal consistency and preliminary support for the external validity (face and content validity), but internal validity was not tested (Table 3). Further study of construct validity and internal validity is desirable to investigate the degree to which the FAIS measure what it is intended to measure.

The FAPQ measures the parental adjustment to and coping with children's food allergy and is completed by the parent [47]. The subscales 'parental anxiety/ stress' and 'psychosocial impact of allergies' showed good internal consistency, but the subscales 'parental coping/competence' and 'family support' did not. Internal validity evaluated by factor analysis was acceptable and preliminary support for the external validity (face and content validity) was shown (Table 3). Another limitation was that the items of the FAPQ were generated based only on the clinical experience of the authors and that no patients/parents were included during the development. Also the FAPQ needs further study of the construct validity in order to investigate the degree to which the FAIS measure what it is intended to measure.

More recently, two studies were published on the impact of food allergy on quality of life in children and the impact on daily life in food allergic adults. The first study used disease-specific questions that were specially developed for this study and these questions were completed by the parents [48]. However, these questions were not tested for reliability or validity (Table 3). The second study investigated the impact of food allergy on daily life of adults with two self-designed questions (influence on daily life at home and outside the home) [2]. Again, these questions were not tested for reliability or validity.

Very recently, disease-specific HRQL questionnaires for food allergic patients of all ages (i.e. parents, children, adolescents and adults) have been published [42;49-51]. All four questionnaires have shown to be reliable (internal consistency and test-retest) with an acceptable level of internal validity (factor analysis, inter-item correlation) and external validity (face, content, convergent/ discriminant and construct validity) (Table 3). During the development of these questionnaires, patients of the target age group were the most important source for items generation and item selection. Investigation of the ability to measure differences over time (i.e. longitudinal validation) and validation in different languages of these questionnaires are underway

Conclusion

Food allergy may negatively impact HRQL of food allergic patients and families with a food allergic child in numerous ways. To investigate this impact on HRQL, generic or disease-specific questionnaires may be used. Generic HRQL questionnaires may be not specific enough to measure disease-specific impairments and they also measure the impact of comorbid diseases. Recently, reliable and valid disease-specific questionnaires have become available to measure HRQL in patients with food allergy of all ages. These questionnaires may be used by clinicians to get insight in the specific problems of food allergic patients and in clinical research where HRQL is the outcome of interest.

Acknowledgements
This research is supported by the EU through the EuroPrevall project (FOOD-CT-2005-514000).

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Chapter 9

Summary, discussion and future perspectives

This thesis deals with the development, validation and outcome of disease-specific health-related quality of life (HRQL) questionnaires for patients with food allergy. In this final chapter we provide a general summary of our findings and we will generally discuss these findings. Finally, recommendations for future study will be provided.

The impact of food allergy on HRQL

Since no cure is available, having a food allergy implies being vigilant in numerous situations and setting involving food [1;2]. This need for allergen avoidance may have a considerable impact on daily life. For example, patients have to read labels of pre-packaged products, which may be time consuming and which may cause frustration when labels are insufficient for the needs of food allergic patients [3]. In addition, when eating outside the home, patients always need to ask beforehand whether the offered food contains the allergen that should be avoided, which may be experienced as embarrassing in social situations. However, despite all the effort it may cost to avoid allergens in food, success is not guaranteed [4]. There is always a chance of accidental exposure [5]. For example, when ingredients of pre-packaged products are changed or when the restaurant personnel or the host is not aware of the danger of cross-contamination of allergens in food [6]. Finally, when a severe allergic reaction occurs, prompt and accurate administration of epinephrine may be required which by itself may provoke anxiety about being able to respond adequately [7]. Therefore, food allergy may have a considerable impact on quality of life [8].

Need for valid HRQL questionnaires for food allergic patients

Although food allergy might have a considerable impact on quality of life, no valid disease-specific HRQL questionnaires were available to measure the impact of food allergy on the patient's quality of life at the beginning of this study (June 2005) **(chapter 2)**. The only well-validated HRQL questionnaire for food allergy available at that time, was the Food Allergy Quality of Life – Parental Burden (FAQL-PB) questionnaire [9]. This questionnaire is completed by parents and measures the parental burden of having a child with food allergy. Although being useful and well designed, this questionnaire is not able to measure the impact of food allergy on HRQL as experienced by the patients themselves. Therefore, there was a need for valid disease-specific HRQL questionnaires that could be self-administered by food allergic patients and in this thesis we describe the development and validation of

these questionnaires. In very young children one can only make use of the proxy ratings of parents. Therefore, in addition and concomitantly to the questionnaires developed in this thesis, a parent-administered questionnaire has been developed as well: the Food Allergy Quality of Life Questionnaire – Parent Form (FAQLQ-PF) [10].

Development, validation and reliability of HRQL questionnaires for food allergic patients

We developed and validated three disease-specific HRQL questionnaires for children (8-12 years), adolescents (13-17 years) and adults (18 years and older) with food allergy (**chapters 3, 4 and 5**) and in addition we investigated the reliability of these three questionnaires (**chapter 6**).

The development phase started with the generation of items for the new questionnaires. The main sources for items were food allergic patients. In semi-structured interviews patients were asked about troublesome aspects of having a food allergy in daily life. In addition, we searched the literature on food allergy and asked clinical experts for additional items. When no important new items emerged, the item generation was considered as complete. This item generation phase was followed by the item reduction phase, in which the obtained long lists of items concerning food allergy were given to other groups of food allergic patients. These patients were asked to indicate whether an item was applicable to them and if so, to rate on a five-point scale how troublesome that particular item was. By following this method, also named as the clinical impact method, we could select the most important items for the questionnaires. This resulted in the following three questionnaires:

- Food Allergy Quality of Life Questionnaire - Child Form (FAQLQ-CF),
- Food Allergy Quality of Life Questionnaire - Teenager Form (FAQLQ-TF),
- Food Allergy Quality of Life Questionnaire - Adult Form (FAQLQ-AF).

The item reduction phase was followed by the cross-sectional validation, in which the newly developed questionnaires were investigated as to their validity. The FAQLQs, the Food Allergy Independent Measure (FAIM, which will be discussed later on) and a generic HRQL questionnaire were sent to other groups of food allergic patients. By calculating correlation coefficients between the FAQLQs and the FAIM we showed acceptable levels of construct validity for all three questionnaires and by calculating correlation coefficients between the FAQLQs and the generic HRQL questionnaire we showed acceptable levels of convergent and discriminant validity for all three questionnaires. Finally, in **chapter 6** we demonstrated, by administrating the questionnaires two times to the same patients within a 10 to 14 day interval, that all three questionnaires showed good test-retest reliability. Such reliability measures are important to ensure that what the questionnaire is measuring is reproducible.

Why three separate questionnaires for three different age groups?

Different issues relating to food allergy may have different impacts at different stages of life. For example, a food allergic child may face problems when treats are given at school, whereas a food allergic adult, for example, may face problems when eating in restaurants. In addition to such practical problems, also the psycho-social impact of food allergy may differ with age. Think for example of peer pressure which may play an important role in adolescence. Therefore, a single questionnaire cannot accurately measure quality of life across all age groups. Consequently, we have developed three questionnaires; one for children aged 8 to 12 years (primary school), one for adolescents aged 13 to 17 years (secondary school) and one for adults 18 years and older.

Moreover, when measuring HRQL in children it is important to take age, maturity and cognitive development into account in the development of the questionnaire [11]. In order to ensure age-appropriateness, we included food allergic children in the development process of the questionnaire. In addition, answer categories were illustrated by faces (smileys) which is appropriate for the cognitive development of the child. Finally, a consultant for sick children reviewed the child questionnaire for clarity and ease of use. Another important issue was to decide the lower limit of age at which a child is able to report on their own quality of life in the form of a self-completed questionnaire. Although the understanding of HRQL is determined by the age, maturity and cognitive development of the child, it has been reported that children 8 years and older are able to understand questions about their HRQL and to give reliable and valid answers [12].

When looking at the content of the final questionnaires for the different age groups, it was striking to see that a considerable part of the items showed overlap. Thus, although we separately interviewed food allergic children, adolescents and adults and generated many age-specific items, there are apparently general food allergy items that are important in all age groups. Moreover, we found that the three most important items, determined during the item reduction phase, were the same for all the three age groups: 'Always be alert as to what you are eating', 'The ingredients of a product change', 'Able to eat fewer products'. Although there was overlap of items, important age-specific items emerged in each questionnaire as well. Examples of items specific for children were: 'Don't get anything when someone is giving treats at school', 'Concerned that you will never get rid of your food allergy', 'Not knowing how things taste which you can't eat' and 'Feel disappointed because you have a food allergy'. Examples of items specific for adolescents were: 'Refuse treats at school or work', 'Carrying an Epipen' and 'During social activities your food allergy is not taken into account'. Examples of items specific for adults were: 'Eating out less often', 'Feel you are being a nuisance because you have a food allergy when eating out', 'Sometimes frustrate people when they are making an effort to accommodate your food allergy' and 'People underestimate your problems caused by food allergy'. Finally, the layout of the child questionnaires

differs significantly from the other two questionnaires since the answer categories in the child questionnaire are illustrated by smileys. Therefore, in conclusion, we think it is important to have three separate questionnaires for three different age groups.

The importance of including patients in the item generation and item reduction

Developing a valid and robust questionnaire is not just putting some questions together [13]. Usually the development of a questionnaire starts with item generation [14]. During the item generation all kinds of possible items for the new questionnaire are assembled. One source or more different sources may be used such as patients, clinicians and the literature [15]. Since a disease-specific HRQL questionnaire intends to measure the impact of a disease as perceived by the patient, it has been argued that patients are the most important source for generating items, because they generate the items that are really a problem as perceived by the patients themselves. Moreover, it is important to include patients that are representative for the patients in whom the final questionnaire will be used [11].

The item generation is usually followed by the item reduction in which the items are reduced to a manageable number for inclusion in the questionnaire. Different methods may be used for the reduction of items, of which the clinical impact method and the psychometric approach (factor analysis) are the most frequently used methods [16]. In the development of the FAQLQs we used the clinical impact method which reveals items that are clinically most important as perceived by food allergic patients. This is in contrast to the method of selecting items based on mathematical linkage between items by performing factor analyses in which items with a low loading on a factor are removed. The latter method has the potential drawback that it may result in excluding items with a high clinical impact [16]. Juniper et al., who also used the clinical impact method for developing the Asthma Quality of Life Questionnaire (AQLQ), showed that the three items of the greatest importance to patients with asthma would have been excluded from the AQLQ if they had used the psychometric approach (factor analysis) [16]. A possible drawback of selecting items based on their clinical importance may be that, when you perform factor analysis on these most important items, the allocation of items into domains does not always make intuitive sense. Therefore, in the development of the FAQLQs we used the clinical impact method for selecting items. Subsequently, the allocation of items into domains was based on factor analysis supplemented by face validity determined by an expert panel.

Cross-sectional validation with the Food Allergy Independent Measure (FAIM)

Once the items are selected for the new questionnaire, it is important to determine whether the individual questions and the total questionnaire measure the things that it are intended to measure, also known as validity. As discussed in the **chapters 3, 4, 5 and 8**, no 'gold standard' HRQL measure exists to which a new HRQL questionnaire could be compared with to investigate validity, which is known as 'criterion' validity in this context [17]. Therefore, construct validity is the best achievable form of validity, which is ascertained by calculating the correlation between the HRQL questionnaire and an independent measure. An independent measure is usually viewed as an important determinant of HRQL, but it is not itself a HRQL item. In addition, it is often an indication of the severity of the disease and it may at the same time be a target for intervention, such as FEV1 in asthma. However, since symptoms occur only upon exposure in anaphylactic disorders, no objective measurement of the extent or ongoing severity of disease exists with which to correlate the new HRQL questionnaire [18].

Therefore, we used the Food Allergy Independent Measure (FAIM) to investigate the construct validity of the FAQLQs, which is based on the concept first described by Oude Elberink et al [19]. The FAIM was developed for this research and includes four Expectation of Outcome (EO) questions and two other independent measure questions. Two of these EO questions were adapted from similar questions previously developed for the validation of the Vespid Allergy Quality of Life (VQLQ) questionnaire (i.e. 'chance of having a severe reaction when stung' and 'chance of dying when accidentally stung') [19] and the validation of the Food Allergy Quality of Life-Parental Burden (FAQL-BP) questionnaire (i.e. 'chance of having a severe reaction when accidentally exposed' and 'chance of dying when accidentally exposed') [9]. These two EO questions have successfully been implemented to validate the VQLQ and the FAQL-PB questionnaire [9;19;20]. For the validation of the FAQLQs we have developed two additional food allergy specific EO questions (i.e. 'chance of accidental exposure' and 'chance of not acting effectively when accidentally exposed') and two additional independent measure questions. The EO questions are based on the perceived expectation of patients of what will happen following exposure which is likely to be a driving force of quality of life [18]. The additional independent measure questions are based on the same principle and ask about the perceived number of foods one needs to avoid and perceived impact on social life.

In addition to the use of the FAIM for the investigation of the validity of the FAQLQs and the individual items of the FAQLQs, we also used the correlation between the individual FAQLQ items and the FAIM for the selection of items for the final questionnaire. That is, if an item of the FAQLQ did not correlate with any of the FAIM questions, than it was excluded from the questionnaire. Our starting point was to include only items that are perceived as important by the patients

themselves (i.e. high overall importance (OI)) which measure that part of quality of life that is affected by food allergy (i.e. correlation with FAIM). If an item does not correlate with any of the FAIM questions, then it should not be in the questionnaire in the first place, whether or not it fits well in the scale or domains. Therefore we investigated the domain structure (factor analysis) and the internal consistency after the investigation of the construct validity. This was also the methodology used in previous studies which produced the VQLQ [19].

Should we use generic HRQL questionnaires in food allergy?

In **chapter 7** we presented the results of the study on HRQL of food allergic patients measured with generic and disease-specific questionnaires. Measurement of generic and disease-specific HRQL in the same group of food allergic patients has never been done before. The aims of this study were to compare generic HRQL of food allergic patients with the general population and other diseases (asthma, irritable bowel syndrome (IBS), diabetes mellitus type I (DM) and rheumatoid arthritis (RA)) and to compare HRQL of food allergic patients as measured with generic and disease-specific questionnaires. We found that food allergic children reported the least impact of food allergy on generic HRQL, which was even better than in children in the general population in some respects. Food allergic adolescents and adults reported overall poorer generic HRQL than the general population. In addition, we found that the generic HRQL impact of food allergy is intermediate in magnitude between DM and asthma, IBS and RA. Moreover, we found very high ceiling effects for some generic scales, which may indicate that generic HRQL questionnaires are not sufficiently sensitive to measure disease-specific clinically important impairments in food allergy. Thus, generic HRQL questionnaires may be useful to compare the impact of food allergy on HRQL with the general population and other chronic diseases. However, for measuring disease-specific effects in food allergic patients, it is preferable to use disease-specific questionnaires.

Although we found that food allergy has a greater impact on generic HRQL than DM, it is remarkable that this is not reflected in the attitudes of governments and societies. For example, if you search in 'Google' for the word 'food allergy', then you get 1,960,000 hits within 0.13 seconds. If you search in 'Google' for the word 'diabetes mellitus', then you get 7,080,000 hits within 0.06 seconds. Although the prevalence of both diseases differ somewhat, approximately 2% for food allergy and approximately 4% for DM [21;22], societal attention for these diseases may be out of proportion to each other. Further comparative studies between food allergy, DM and other chronic diseases will show if the similar differences in HRQL impact are seen as in our study.

Availability of valid disease-specific HRQL questionnaires for food allergic patients

In **chapter 8,** we present a review on how HRQL can be measured in food allergy and we reviewed recent findings on how food allergy might impact HRQL. We found that in addition to the more familiar burdens of having a food allergy, the psycho-social impact of food allergy and information gaps concerning food allergy have received much attention in the recent literature. In addition, we described that the FAQLQs, which we have developed, have become available recently. These are reliable and valid disease-specific HRQL questionnaires to measure the impact of food allergy on HRQL in patients of all ages. The assessment of HRQL could be used by clinicians to get insight in the specific problems patients have to face and HRQL measurements may be used to measure the effects of an intervention on the patient's quality of life. One of the key messages of **chapter 8** was that HRQL is the only available measure that reflects the ongoing severity of food allergy, since no objective disease parameters are available.

Summary of main findings

The main findings of this thesis were as follows:

1) At the beginning of this study (June 2005), there was a need for valid HRQL questionnaires for food allergic patients
2) Disease-specific HRQL questionnaires have been developed for children (8-12 years), adolescents (13-17 years) and adults (18 years and older) with food allergy.
3) These questionnaires showed good validity and reliability.
4) For measuring disease-specific impact of food allergy on HRQL, disease-specific questionnaires may be more useful than generic HRQL questionnaires.
5) The impact of food allergy on HRQL is greater than the impact of diabetes mellitus, but less than the impact of asthma, IBS and rheumatic arthritis as measured with generic HRQL questionnaires.

Recommendations for future study

Following the findings discussed in this thesis, there are a number of studies of interest for the future:

- *Longitudinal validation*. In order to investigate if the FAQLQs are able to measure differences over time, the longitudinal validity of the questionnaires should be investigated. The longitudinal validity could be investigated by administering

the FAQLQ and the FAIM to food allergic patients in whom HRQL is expected to change because of diagnostic and/or therapeutic interventions. The questionnaires should be administered before and a few months after the intervention, so that patients could become accustomed to their new health state. Preliminary data have shown that for some domains HRQL is already significantly improved two months after a diagnostic intervention (i.e. double-blind placebo-controlled food challenge) (DunnGalvin et al., unpublished data, December 2008). Changes in the average score of the FAQLQ are then correlated to changes in the FAIM, comparing values before and after the intervention described. Good correlation between the FAQLQ and FAIM scores validate the instrument longitudinally and simultaneously demonstrate the impact on quality of life of the intervention used.

- *Comparison of the children's FAQLQ-CF scores with their parents' FAQLQ-PF scores.* As discussed earlier, children and parents may differ in their views and judgements concerning HRQL [23], and it would thus be interesting to investigate and compare the scores of children on the FAQLQ-CF with the scores of their parents on the FAQLQ-PF.

- *Determination of the Minimal Importance Difference (MID).* The MID is the smallest difference in score which patients perceive as beneficial and which would mandate, in absence of troublesome side effects and excessive cost, a change in the patient's management. The MID of HRQL questionnaires with a 7-point scale is usually approximately 0.5 [24]. It is important to determine the MID of the FAQLQs, because it gives clinicians and researchers insight into whether a change in the FAQLQ score, for example before and after an intervention, is also a clinically important change.

- *Comparison of informed versus blind administration of follow-up questionnaires.* It would be interesting to investigate if there is a difference in scoring on a follow-up questionnaire when the patients are shown their previous answers (i.e. informed) with the scores generated when there are not shown their previous answers (i.e. blind). It has been suggested that when letting patients see their previous responses, the validity of HRQL questionnaires in clinical trials can be improved [25]. However, when the follow-up measurement was more than three months later, the results of the blind and informed questionnaire showed little difference [26]. These studies were all performed in adults. Therefore, it would be interesting to see if the same is true for children and in food allergic patients.

- *Validation of FAQLQ in other countries.* Before the FAQLQs can be used in other languages and cultures, the questionnaires should be cross-culturally validated in the new language or culture [27]. Forward and backward translation may be used in order to check content comparability. Cross-sectional validation in the new language and cultural setting allows for the assessment of the performance of individual items in that language and culture. Good cross-sectional correlation coefficients indicate validity for that particular language setting. Low correlation coefficients may be encountered if the translation is inaccurate or if the item does not appear to be a problem in the new cultural context. Following successful cross-sectional validation in the new language and cultural setting, the questionnaire could be

incorporation into a longitudinal study in the new language as indicated above.

- *Combine HRQL outcomes with economic measurements.* It would be interesting to combine HRQL outcomes measured with the FAQLQs with economic outcomes measured with the economic questionnaire for food allergy which was also developed within EuroPrevall [28;29]. Interesting questions such as: "Is the social impact of food allergy related to the economic impact of food allergy?" could be investigated. In addition, it would be interesting to investigate if the FAQLQs could be used to calculate Quality-Adjusted Life Years (QALYs). Lamers et al. [30] showed that it is feasible to convert data collected with a disease-specific questionnaire into preferences, which can be used to calculate QALYs. A QALY measures the amount of healthy years gained by a particular health care intervention. QALYs could be used in cost-utility analysis to calculate the ratio of costs to QALYs saved for a particular health care intervention.

- *Combine HRQL outcomes with epidemiological data.* Finally, one of the major aims of the EuroPrevall project is to assess the societal impact of food allergies [31]. In order to realise this, it is important to combine the information from studies on HRQL with epidemiological data on prevalence. This will ultimately give some indication of the magnitude of the societal impact of food allergy in Europe.

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Nederlandse samenvatting

(Summary in Dutch)

Inleiding

Voedselallergie

Voedsel is een essentieel element van ons leven. Het is nodig om in leven te blijven en het is een belangrijk onderdeel van onze culturele identiteit. Mensen met een voedselallergie kunnen ernstig ziek worden na het eten van bepaald voedsel. Ziekmakende reacties ten gevolge van voeding kunnen het resultaat zijn van een voedselallergie, een voedselintolerantie (niet-allergische voedselovergevoeligheid, bijvoorbeeld lactose intolerantie) of een intoxicatie. Bij voedselallergie is er sprake van een abnormale reactie van het immuunsysteem na het eten of drinken van bepaalde voedingsmiddelen. In het lichaam worden specifieke antistoffen (IgE) gemaakt tegen bepaalde eiwitten in de voeding (allergenen). Deze antistoffen binden zich aan bepaalde cellen in het lichaam zoals mestcellen. Wanneer de antistof dan in contact komt met het allergeen kan dit klachten veroorzaken aan de huid, het maagdarmkanaal of de luchtwegen. In het ergste geval kan iemand in shock raken en overlijden. De voedingsmiddelen die de meeste allergische reacties veroorzaken zijn: pinda's, noten, melk, ei, vis en schaaldieren. Voedselallergie komt voor bij ongeveer 2 tot 5% van de kinderen en bij ongeveer 2% van de volwassenen.

Voedselallergie kan helaas nog niet worden genezen. De enige behandeling is strikte vermijding van de voedingsmiddelen waar iemand allergisch voor is. Dit kan het normale dagelijkse leven behoorlijk verstoren. Daarnaast bestaat er, ondanks de strikte vermijding, toch altijd een kans dat men per ongeluk het voedingsmiddel binnen krijgt met als gevolg een (ernstige) allergische reactie. Deze continue onzekerheid kan op zijn beurt weer een bron zijn voor angst. Wanneer een ernstige allergische reactie optreedt, is onmiddellijke en juiste toediening van adrenaline (epinefrine) met een automatische injectiespuit (bijvoorbeeld een Epipen) van groot belang. Deze toediening kan als beangstigend worden ervaren. Al met al kan het hebben van een voedselallergie een behoorlijke negatieve invloed hebben op de kwaliteit van leven.

Kwaliteit van leven

Kwaliteit van leven is een breed begrip. Hoewel er geen overeenstemming bestaat over de definitie van het begrip kwaliteit van leven, heeft de wereld gezondheidsorganisatie (WHO) een opbouwende definitie opgesteld: "de perceptie van een individu van zijn positie in het leven in de context van de cultuur en waardesystemen waarin hij leeft en in relatie tot zijn doelen, verwachtingen, normen en belangen". De component van kwaliteit van leven die betrekking heeft op de gezondheid van een individu, wordt gezondheidsgerelateerde kwaliteit van leven genoemd. In het Engels wordt hiervoor de afkorting HRQL (Health-Related Quality of Life) gebruikt. HRQL wordt gedefinieerd als: "het effect van een ziekte en de bijbehorende behandeling op de patiënt, zoals dit door de patiënt wordt ervaren". HRQL is een multi-dimensioneel concept en bestaat uit biologische/ medische, psychologische en sociale aspecten zoals fysieke en mentale status en sociale interactie.

HRQL kan gemeten worden met vragenlijsten. Er bestaan twee type vragenlijsten: generieke en ziekte specifieke vragenlijsten. Generieke vragenlijsten zijn bruikbaar bij verschillende ziekten en bij de algemene populatie. Met deze vragenlijsten is het dus mogelijk om de invloed op HRQL van verschillende ziekten met elkaar te vergelijken. Het nadeel van generieke vragenlijsten is dat ze niet ingaan op specifieke problemen van een bepaalde ziekte en dat ze ook de invloed meten van andere ziekten wanneer iemand meerdere ziekten heeft. Ziekte specifieke vragenlijsten zijn speciaal ontwikkeld voor een bepaalde ziekte of aandoening. Deze vragenlijsten zijn gevoeliger dan generieke vragenlijsten en hiermee is de kans veel groter dat klinisch belangrijke veranderingen gemeten kunnen worden. Het nadeel is dat er met ziekte specifieke vragenlijsten geen direct vergelijk tussen verschillende ziekten gemaakt kan worden.

Waarom is het meten van HRQL van belang?

Het belang van het meten van HRQL kan bekeken worden vanuit verschillende oogpunten. Ten eerste, geeft het meten van HRQL inzicht in de invloed die een bepaalde ziekte of aandoening heeft op de patiënt, vanuit het perspectief van de patiënt zelf. Het is bijvoorbeeld mogelijk dat twee patiënten met dezelfde ziekte en dezelfde mate van ernst toch verschillende mate van invloed op hun HRQL ervaren en rapporteren. Het meten van HRQL kan door artsen gebruikt worden om inzicht te krijgen in de specifieke problemen waar een patiënt mee wordt geconfronteerd. Zodoende kan de arts de patiënt helpen om beter om te gaan met zijn of haar problemen. HRQL vragenlijsten kunnen vaak in minder dan 15 minuten worden ingevuld en kunnen dus prima ingevuld worden vóór een bezoek aan de arts (bijvoorbeeld in de wachtkamer). Wanneer de HRQL vragenlijst gedurende een bepaalde periode vaker wordt ingevuld, geeft dit de arts en de patiënt bijvoorbeeld inzicht in het effect van de behandeling op HRQL.

In de wetenschap kunnen HRQL vragenlijsten gebruikt worden om het effect van (nieuwe) interventies te onderzoeken. Uiteindelijk kan dit helpen om de kwaliteit van de behandeling en de uitkomsten voor de patiënt te verbeteren. HRQL vragenlijsten kunnen tevens gebruikt worden om de effecten van verschillende interventies op HRQL met elkaar te vergelijken. Dit soort onderzoek kan gebruikt worden door beleidsmakers bij de besluitvorming over toezegging van gezondheidszorggelden.

Ten slotte is het met betrekking tot voedselallergie van belang om stil te staan bij het feit dat er geen objectieve ziekte parameters beschikbaar zijn om de voortdurende ernst van voedselallergie vast te stellen, zoals luchtweggevoeligheid bij astma. Natuurlijk kan men de ernst van een allergische reactie vaststellen, maar allergische reacties komen alleen voor wanneer men de voeding eet waar men allergisch voor is. Ondanks het feit dat mensen met voedselallergie de meeste tijd geen lichamelijke klachten hebben, is er toch een voortdurende ernst die veroorzaakt wordt door de noodzaak om continu bepaalde voedingsmiddelen te vermijden en de psychosociale last die dit met zich meebrengt. HRQL is de enige beschikbare uitkomstmaat die deze voortdurende ernst van voedselallergie kan meten.

Doel van dit proefschrift

Het hoofddoel van dit proefschrift was het ontwikkelen en valideren van ziekte specifieke gezondheidsgerelateerde kwaliteit van leven (HRQL) vragenlijsten voor kinderen (8-12 jaar), adolescenten (13-17 jaar) en volwassenen (18 jaar en ouder) met voedselallergie **(hoofdstuk 3, 4 en 5)**. Dit onderzoek vond plaats in het kader van het EuroPrevall project, een grootschalig multi-disciplinair Europees onderzoek naar voedselallergie. Tevens beschrijft dit proefschrift het onderzoek naar de betrouwbaarheid van deze drie vragenlijsten **(hoofdstuk 6)** en wordt er met behulp van generieke vragenlijsten een vergelijk gemaakt met de algemenen populatie en andere chronische ziekten **(hoofdstuk 7)**. Tenslotte wordt een overzicht gegeven van de huidige kennis op het gebied van voedselallergie en kwaliteit van leven aan het begin van het EuroPrevall project **(hoofdstuk 2)** en tegen het einde van het project **(hoofdstuk 8).**

Samenvatting van de hoofdstukken

Een kader voor het meten van de sociale impact van voedselallergie in Europa

In **hoofdstuk 2** wordt een kader geschetst voor het meten van de sociale impact van voedselallergie in Europa. Voedselallergie (of dit nu door de persoon zelf is vastgesteld of door een arts) is een belangrijk medisch en maatschappelijk probleem in de westerse wereld en het zou wel eens een veel grotere impact op de samenleving kunnen hebben dan tot nu toe gedacht werd. Voor de start van het EuroPrevall project (juni 2005) was de sociale impact van voedselallergie nog nooit eerder systematisch onderzocht met gevalideerde instrumenten. Op dat moment was er slechts één gevalideerde HRQL vragenlijsten beschikbaar, de Food Allergy Quality of Life-Parental Burden (FAQL-PB) vragenlijst. Deze vragenlijst wordt ingevuld door de ouders en meet de kwaliteit van leven die de ouder ervaart die het gevolg is van het hebben van een kind met voedselallergie. Hoewel dit een bruikbare en goed ontwikkelde vragenlijst is, kan men met deze vragenlijst niet de impact van voedselallergie op de kwaliteit van leven meten zoals dit door de patiënt zélf wordt ervaren. Hieruit blijkt dat er vraag is naar gevalideerde ziekte specifieke HRQL vragenlijsten die door de voedselallergische patiënt zélf kunnen worden ingevuld. Deze ziekte specifieke HRQL vragenlijsten zullen ontwikkeld worden in het EuroPrevall project en kunnen vervolgens gebruikt worden om kwaliteit van leven problemen gerelateerd aan voedselallergie te identificeren. Daarnaast kunnen de instrumenten gebruikt worden om de effectiviteit van interventies te onderzoeken. Tevens kunnen zij als leidraad dienen voor de ontwikkeling van nieuw beleid rondom voedselallergie. Het combineren van informatie van kwaliteit van leven studies met epidemiologische informatie over prevalentie, zal uiteindelijk een indicatie kunnen geven van de grootte van de sociale impact van voedselallergie in Europa.

De ontwikkeling en validatie van drie vragenlijsten

In de **hoofdstukken 3, 4 en 5** bespreken we de ontwikkeling en validatie van drie ziekte specifieke HRQL vragenlijsten voor kinderen (8-12 jaar), adolescenten (13-17 jaar) en volwassenen (18 jaar en ouder) met een voedselallergie.

De ontwikkeling van de vragenlijsten startte met het verzamelen van items voor de nieuwe vragenlijsten (item generatie). Voedselallergische patiënten waren de belangrijkste bron voor items. In semi-gestructureerde interviews werden de patiënten gevraagd naar lastige of vervelende aspecten van hun voedselallergie in het dagelijkse leven. Daarnaast hebben we gezocht naar items in de wetenschappelijke literatuur over voedselallergie en hebben we klinische experts op het gebied van voedselallergie gevraagd naar aanvullende items. Op het moment dat er geen nieuwe belangrijke items meer naar voren kwamen, werd de item generatie als voltooid beschouwd.

De item generatie werd gevolgd door de fase van item reductie. In deze fase werd de lange lijst van items over voedselallergie voorgelegd aan een andere groep voedselallergische patiënten. Deze patiënten werd gevraagd om per item aan te geven of dat item ook op hen van toepassing was en zo ja, om aan te geven hoe vervelend dat item was op een schaal van 1 tot 5. Op basis van deze methode, die ook wel de klinische impact methode wordt genoemd, konden we de meest belangrijke items selecteren voor de vragenlijsten. Dit resulteerde in de volgende drie vragenlijsten:

- Food Allergy Quality of Life Questionnaire - Child Form (FAQLQ-CF),
- Food Allergy Quality of Life Questionnaire - Teenager Form (FAQLQ-TF),
- Food Allergy Quality of Life Questionnaire - Adult Form (FAQLQ-AF).

De item reductie fase werd gevolgd door de validatie fase. In deze fase werd onderzocht of de vragenlijsten datgene meten, wat zij behoren te meten (validatie). De beste manier om de validiteit vast te stellen, ook wel criterium validiteit genoemd, is het vergelijken van het nieuwe instrument met de bestaande 'gouden standaard'. Bijvoorbeeld wanneer er een nieuw instrument ontwikkeld is om bloeddruk mee te meten, dan worden de bloeddrukwaarden gemeten met dat nieuwe instrument vergeleken met de bloeddrukwaarden gemeten met het instrument dat momenteel algemeen gebruikt wordt in de medische praktijk. Bij kwaliteit van leven bestaat er echter geen 'gouden standaard'. Daarom is construct validiteit de beste manier om de validiteit van een kwaliteit van leven vragenlijst vast te stellen. Bij construct validiteit wordt de nieuwe vragenlijst vergeleken met een onafhankelijke meting (independent measure) die gerelateerd is aan datgene wat je wil meten (het construct). Bij ziekte specifieke kwaliteit van leven kan dit een meting zijn van de ernst van de ziekte, zoals luchtweggevoeligheid bij astma. Maar voedselallergie wordt niet gekenmerkt door chronische klachten. Zolang men de voedingsmiddelen vermijdt waar men allergisch voor is, heeft men zelfs helemaal géén lichamelijke klachten. Daarom bestaat er bij voedselallergie (en andere ziekten die niet gekenmerkt worden door chronische klachten) geen onafhankelijke meting die de voortdurende mate of ernst van de ziekte kan meten. Om toch de construct validiteit van kwaliteit van leven vragenlijsten voor dit soort ziekten te kunnen evalueren, is gebleken dat de verwachting van wat er zal gebeuren (expectation

of outcome) na blootstelling aan het allergene voedingsmiddel, als onafhankelijke meting gebruikt kan worden. Deze verwachting kan worden gemeten met de Food Allergy Independent Measure (FAIM) welke bestaat uit 6 vragen. Met behulp van het berekenen van correlaties tussen de FAQLQ's en de FAIM hebben we acceptabele niveaus van construct validiteit kunnen aantonen voor alle drie de FAQLQ's. De nieuw ontwikkelde FAQLQ's meten dus wat ze behoren te meten.

Naast de FAQLQ en de FAIM, hebben de patiënten ook een generieke kwaliteit van leven vragenlijst ingevuld (zie ook hoofdstuk 7). Met behulp van het berekenen van correlaties tussen de FAQLQ's en de generieke vragenlijsten hebben we acceptabele niveaus van 'convergent' en 'discriminant' validiteit kunnen aantonen voor alle drie de FAQLQ's. Verder kon worden aangetoond dat alle drie de FAQLQ's een uitstekende interne consistentie hebben. Dit betekent dat alle individuele vragen van de FAQLQ hetzelfde construct meten. Tenslotte hebben we kunnen aantonen dat de FAQLQ's verschillen kunnen meten tussen patiënten met meerdere voedselallergieën en patiënten met slechts enkele voedselallergieën, waarbij de eerste groep een significant slechtere kwaliteit van leven bleek te hebben. De FAQLQ-CF en FAQLQ-TF bleken geen significant verschil te meten tussen patiënten met anafylaxie (de meest ernstige vorm van allergische reacties) en patiënten met mildere vormen van allergische reacties. De FAQLQ-AF bleek dit verschil wel te meten.

We kunnen concluderen dat de FAQLQ's de belangrijkste problemen bevatten waar voedselallergische patiënten mee geconfronteerd worden in het dagelijkse leven. De vragenlijsten zijn valide en kunnen onderscheid meten tussen patiënten met verschillende ziekte karakteristieken. Tenslotte zijn de FAQLQ's kort en gemakkelijk te gebruiken en daarom zeer geschikt voor klinisch onderzoek.

De betrouwbaarheid van de nieuwe vragenlijsten

In **hoofdstuk 6** bespreken we het onderzoek naar de test-hertest betrouwbaarheid van de drie FAQLQ's. Het onderzoeken van de betrouwbaarheid van een vragenlijst is van belang om aan te kunnen tonen dat datgene wat de vragenlijst meet, reproduceerbaar is. Voor dit onderzoek hebben ruim 100 patiënten de vragenlijst twee keer ingevuld met daartussen een tijdsinterval van 10 tot 14 dagen. Deze periode is lang genoeg zodat de mensen hun eerder gegeven antwoorden niet zullen onthouden en kort genoeg zodat er geen grote verandering zullen optreden in kwaliteit van leven. Met het berekenen van verschillende coëfficiënten en grafische weergave hebben we kunnen aantonen dat de antwoorden die gegeven zijn op de twee verschillende tijdstippen goed overeen kwamen. Dit betekent dat alle drie de FAQLQ's betrouwbaar zijn.

Een vergelijk met de algemene populatie en andere chronische ziekten

In **hoofdstuk 7** wordt het onderzoek beschreven waarin we kwaliteit van leven van voedselallergische patiënten hebben gemeten met generieke en ziekte specifieke HRQL vragenlijsten. De scores op de generieke vragenlijsten werden vergeleken met scores van gepubliceerde studies over de algemene populatie en patiënten met astma, prikkelbare darm syndroom, diabetes (type 1) en reuma. We vonden dat de

generieke kwaliteit van leven van voedselallergische patiënten over het algemeen slechter is dan de generieke kwaliteit van leven van de algemene populatie. Echter, zowel kinderen als adolescenten rapporteerden significant minder beperkingen door gedragsproblemen in schoolwerk of activiteiten met vrienden. In vergelijking met andere chronische ziekten, bleken patiënten met diabetes een betere generieke kwaliteit van leven te hebben dan patiënten met voedselallergie. Patiënten met astma, prikkelbare darm syndroom en reuma bleken een slechtere generieke kwaliteit van leven te hebben dan patiënten met een voedselallergie. Tenslotte hebben we bij de voedselallergische patiënten gekeken naar hoe zij de generieke en ziekte specifieke kwaliteit van leven vragenlijsten (de FAQLQ's) hadden ingevuld. Hieruit bleek dat de voedselallergische patiënten bij veel onderdelen van de generieke vragenlijsten de hoogst mogelijke score hadden (ceiling effect). Dit betekent dat deze vragenlijsten minder gevoelig zijn om verschillen in de tijd te meten, men kan immers niet hoger scoren. Dit geeft tegelijkertijd aan dat deze vragenlijsten minder geschikt zijn om specifieke aspecten van voedselallergie te meten.

Kwaliteit van leven bij voedselallergie: valide instrumenten voor kinderen tot volwassen

Hoofdstuk 8 bevat een overzichtsartikel van recente bevindingen over hoe voedselallergie van invloed kan zijn op kwaliteit van leven en het geeft een overzicht van instrumenten die beschikbaar zijn om kwaliteit van leven bij mensen met een voedselallergie te meten. We beschrijven in dit artikel dat er in de recente literatuur, naast meer algemeen bekende lasten van voedselallergie, veel aandacht is besteed aan de psychosociale invloed van voedselallergie en het gebrek aan informatie met betrekking tot voedselallergie op bepaalde gebieden. Bij het overzicht van beschikbare instrumenten voor het meten van kwaliteit van leven bij voedselallergie, concluderen we dat de meeste ziekte specifieke HRQL vragenlijsten, die tot dan toe beschikbaar waren, niet of onvoldoende gevalideerd zijn. Echter zeer recent zijn er betrouwbare en valide ziekte specifieke HRQL vragenlijsten (de FAQLQ's) beschikbaar gekomen om de impact van voedselallergie op kwaliteit van leven te meten bij alle leeftijdsgroepen.

Conclusie

Met het onderzoek beschreven in dit proefschrift hebben we een belangrijke vooruitgang geboekt op het gebied van het meten van kwaliteit van leven bij mensen met een voedselallergie. Er zijn nu valide en betrouwbare kwaliteit van leven vragenlijsten beschikbaar voor voedselallergische patiënten van alle leeftijden. Deze vragenlijsten kunnen enerzijds gebruikt worden door artsen in de praktijk om beter inzicht te krijgen in de kwaliteit van leven van zijn patiënten en de behandeling hier op aan passen. Anderzijds zijn deze vragenlijsten uitermate geschikt om toe te passen in klinisch onderzoek bij voedselallergie waar kwaliteit van leven de uitkomst parameter is. Tenslotte is het van belang om te realiseren dat kwaliteit van leven de enige uitkomst parameter is die de voordurende ernst en impact van voedselallergie kan meten.

Dankwoord

(Acknowledgements)

Na vier jaar onderzoek gedaan te hebben vanuit 'de kelder', dan hier het eindresultaat! Het 'boekje' is af! Maar zelfs al zit je in 'de kelder', promoveren doe je niet alleen en daarom wil ik graag een aantal mensen bedanken.

Allereerst wil ik alle kinderen en hun ouders en alle andere deelnemers hartelijk danken voor hun inzet en voor het invullen van de vragenlijsten. Sommigen hebben zelfs meerdere malen tijdens verschillen onderdelen van mijn onderzoek een vragenlijst ingevuld. Zonder uw en jullie medewerking was dit proefschrift niet tot stand gekomen!

Mijn eerste promotor, Prof. Dr. A.E.J. Dubois.
Beste Ewoud, vier jaar geleden kwam ik binnen als bewegingswetenschapper met nul kennis over voedselallergie en verder had ik wel 'iets' gedaan met kwaliteit van leven in mijn afstudeeronderzoek. Toch ging jij de uitdaging met mij aan en daar ben ik je zeer dankbaar voor. In de afgelopen jaren heb ik veel van je mogen leren op het gebied van voedselallergie, kwaliteit van leven en het doen van onderzoek. Ik bewonder je enorme enthousiasme en toewijding voor je werk en het doen van onderzoek. Het werkt aanstekelijk… Ik heb je snelle en kritische commentaren op mijn manuscripten erg gewaardeerd en wil je bedanken dat ik tussendoor altijd even langs kon komen als ik vast liep of gewoon even van gedachten wilde wisselen over het onderzoek. Ik ben blij dat we onze prettige samenwerking nog een tijdje kunnen voortzetten!

Mijn tweede promotor, Prof. Dr. E.J. Duiverman.
Beste Eric, bedankt voor het vertrouwen in mij toen ik vier jaar geleden binnen kwam. Je inbreng tijdens ons wekelijkse EuroPrevall overleg heb ik altijd zeer op prijs gesteld, vooral je heldere en praktische kijk op het onderzoek. Maar ook je inbreng op het gebied van onderzoek bij kinderen waren zeer waardevol.

Mijn co-promotor, Dr. B.J. Vlieg-Boerstra
Beste Berber, bedankt voor je begeleiding op het gebied van voedselallergie en je praktische kijk op zaken. Als gepromoveerde diëtiste kon ik mij geen betere inhoudsdeskundige wensen. Ook je gezelschap tijdens vele congressen heb ik altijd erg gewaardeerd. Deze promotie is niet alleen voor mij een bijzondere dag, maar ook een beetje voor jou, omdat jij voor het eerst co-promotor bent!

Mijn vierde begeleider, Drs. J.N.G. Oude Elberink.
Beste Hanneke, wat betreft de invulling en praktische uitvoering van het kwaliteit van leven onderzoek was jij, met name in de eerste helft van mijn promotieonderzoek, mijn steun en toeverlaat. Bedankt voor je enthousiasme, spontaniteit en de tijd die je voor me vrij maakte als ik weer eens opzoek moest naar patiënten voor het onderzoek.

Prof. Dr. R. Gerth van Wijk en Prof. Dr. T. van der Molen, hartelijk dank voor het beoordelen van het proefschrift en voor de aanwezigheid tijdens de verdediging van mijn proefschrift. I would like to thank Prof. Dr. L. Frewer for her willingness to be a member of the review committee of this thesis and for her presence at the thesis defence ceremony.

Dear Audrey and Jonathan, I would like to thank you both for your critical comments on my papers and the interesting discussions we had by mail and during the EuroPrevall congresses on how to measure quality of life in food allergy.

Alle medeauteurs wil ik bedanken voor hun bijdrage aan de artikelen. Dear Clare Mills, thank you for your contribution for the 'state-of-the-art' article and your support and kind words during the EuroPrevall congresses. Jan Schouten, bedankt voor je statistische hulp bij het test-hertest artikel. Hein Raat, bedankt voor de beschikbaarstelling van de CHQ-CF87 database en je opbouwende commentaar op het 'generieke' artikel.

Beste Judith en Jantine, de halfjaarlijkse EuroPrevall congressen waren altijd weer een gezellig weerzien. Van hartje Athene en Praag, tot de buitenwijken van Warschau en Berlijn, inmiddels hebben we heel wat Europese steden op ons lijstje staan! Bedankt voor jullie interesse in mijn onderzoek en het meedenken naar oplossingen tijdens EuroPrevall congressen en telefonische vergaderingen. Judith, bedankt voor je inbreng in het 'state-of-the-art' artikel.

Beste Tina, bedankt voor je enthousiasme en vasthoudendheid tijdens en na je wetenschappelijke stage. Dit heeft al geresulteerd in een mooi artikel en misschien binnenkort wel meer! Beste Anouk, ook jij bedankt voor je inzet tijdens je wetenschappelijke stage. Beste Helmi, je deed je wetenschappelijke stage bij Berber, maar ik wil je toch bedanken voor je gezelligheid (en steun toen we allebei ziek waren…) in San Diego. En wij kunnen zeggen dat we in Mexico geweest zijn!

Beste Gerbrich, bedankt voor je inzet voor het Pan-Europese kwaliteit van leven onderzoek en de gezellige "side-seeing" in Berlijn en Praag. Helaas voor mij heb je besloten niet verder te gaan met het Pan-Europese onderzoek. Ik wens je veel succes bij het vervolg van je opleiding tot kinderallergoloog!

De medewerkers van de functieafdelingen van de Allergologie en Kinderallergologie wil ik graag bedanken voor jullie hulp en gastvrijheid bij het zoeken naar voedselallergische patiënten voor mijn onderzoek. Jeanet, fijn dat we een kamer konden delen tijdens de congressen in Miami en Wenen en bedankt voor de gezellige uitstapjes daar!

Beste Erna Botjes en Frans Timmermans, bedankt voor jullie hulp bij het benaderen van voedselallergische patiënten voor mijn onderzoek via de websites van de Stichting Voedselallergie en het Nederlands Anafylaxis Netwerk. Beste Berta en Irene, ook jullie bedankt voor de hulp in de eerste helft van mijn onderzoek bij de zoektocht naar patiënten voor mijn onderzoek.

Beste Arnold Boom, Chiquit Linden van den Heuvell, Niels de Voogd en Karel Verbeek, hartelijk dank voor het beoordelen van de uitgebreide itemlijsten en de FAQLQ's op vorm, inhoud en geschiktheid.

Beste Johan Wempe en Mathieu de Greef, ik wil jullie bedanken voor de begeleiding tijdens mijn eerste stappen in de wereld van de wetenschap. Johan, mede dankzij jou ben ik op deze promotieplek terecht gekomen. Dank daarvoor!

Beste GRIAC collega's, hoewel ik niet trouw elke dinsdagmiddag aanwezig was, wil ik jullie toch bedankt voor de presentaties, commentaren en suggesties tijdens de dinsdagmiddag besprekingen.

Beste Marieke, ik vond het super om jouw paranimf te mogen zijn. Jij hebt mij van heel dichtbij laten zien hoe promoveren moet. Ik hoop dat ik het net zo goed ga doen als jij!

Beste BKK onderzoekers uit de kelder, ik heb de afgelopen jaren met heel veel plezier met jullie in de kelder gezeten! Gewoon gezellig kletsen onder het genot van een taartje bij de verjaardagen, een gangborrel op zijn tijd of serieus advies of overleg over het onderzoek. In het bijzonder wil ik mijn (oud) kamergenootjes Annemieke, Laura, Deirdre en Karin noemen. Samen hebben we grote hoogtepunten en diepe dalen doorgemaakt, zowel in het werk als privé. Bedankt voor de steun in moeilijke dagen en voor het delen van de vreugde op mooie dagen.

Beste Laura en Deirdre, ik vind het helemaal geweldig dat jullie vandaag mijn paranimfen zijn!

Beste Erwin, super leuk dat je vanuit Zuid-Afrika bent overgekomen voor mijn promotie. Ik vind het heel bijzonder dat mijn grote broer straks in de corona zit! Maar niet te moeilijke vragen stellen, hè?!

Lieve pa en ma, bedankt voor jullie onvoorwaardelijke steun en de mogelijkheden die jullie mij hebben geboden om dit te kunnen bereiken. Ik weet zeker dat pa erg trots is. Hij had er natuurlijk gewoon bij moeten zijn. Daarom is dit boekje voor hem.

Last but not least: mijn man Bert, ik weet dat je het niet altijd even leuk vond als ik weer eens een weekje weg was voor een congres, maar toch stond je altijd achter mijn keuzes en wist je mij altijd weer te motiveren als ik het even niet meer zag zitten. Juist jouw niet-medische kijk op mijn onderzoek werkte vaak zeer verhelderend. Lieve Bert, jij bent mijn alles.

About the author

Bertine Margaretha Janine de Blok was born on the 1st of June in 1982 in Havelte, the Netherlands. In 2000 she graduated from secondary school at the CS Vincent van Gogh in Assen and started to study Human Movements Sciences at the University of Groningen. By the end of 2003 she started with research on COPD and pedometers under supervision of Dr. J.B. Wempe, pulmonologist, and Dr. M.H.G. de Greef, human movement scientist. In July 2004 she finished her studies. For one year she continued her research as project co-worker at the pulmonary rehabilitation centre Beatrixoord (University Medical Center Groningen) and at UC Pro Motion in Groningen. In June 2005 she started her PhD research at the department of paediatric pulmonology and paediatric allergology at the University Medical Center Groningen. She investigated health-related quality of life in food allergic patients under supervision of Prof. Dr. A.E.J. Dubois, allergist, Prof. E.J. Duiverman, paediatric pulmonologist, Dr. B.J. Vlieg-Boerstra, research dietician, and Drs. J.N.G. Oude Elberink, allergist. In 2009 she will start working as post doc at the department of paediatric pulmonology and paediatric allergology at the University Medical Center Groningen. She married Bert Flokstra in 2007.

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