Chapter 1

General introduction

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Food allergy

Food allergy was defined by the NIAID-Sponsored Expert Panel as ‘... an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food’ in 2010\(^1\). A food was defined by this expert panel as ‘... any substance – whether processed, semi-processed, or raw – that is intended for human consumption, and includes drinks, chewing gum, food additives, and dietary supplements\(^1\).

All food proteins can theoretically be allergenic, although some features are typically seen in food allergens: low to medium molecular weight (5-70 kD), stability, glycosylation and high solubility in body fluids\(^2\). However, allergies for milk, egg and peanut are most common in children, while allergies for (shell) fish and peanut are most common in adults\(^1\).

How to diagnose food allergy

Food allergy testing should be performed by health-care professionals with food allergy expertise. A detailed medical history and a focused physical examination are essential first steps in order to diagnose food allergy\(^3\). These can be accompanied by a skin-prick test or allergen-specific serum IgE (sIgE) for the suspected food(s) to assist in the identification of food allergens that potentially provoke IgE-mediated food allergic reactions\(^1\). However, these tests alone can not be considered to be diagnostic\(^1\). A double-blind placebo-controlled oral food challenge (DBPCFC) is the gold standard to diagnose food allergy\(^1\). Although undergoing a DBPCFC improves health-related quality of life (HRQL) in all patients\(^4\), many individuals with a self-perceived food allergy have never been tested this way. Previous studies have shown that many misconceptions exist in non-allergist in the way food allergy should be diagnosed\(^5-7\), which may be a reason for many false-positive and false-negative diagnosed individuals. This obviously is an unwanted situation where many individuals suffer from unnecessary dietary restrictions and others may be exposed to extremely dangerous situations.

What is the extent of the problem?

The prevalence of food allergy is estimated to be 3-4% in adults and 3-8% in children\(^8-10\). However, the prevalence of perceived food allergy is much higher\(^9,11-12\). This distinction makes food allergy a complicated topic for research. Inconsistencies in study designs,
methods and used definitions of food allergy make it difficult to interpret the data and generalize conclusions. It is important to be aware of the distinction between DBPCFC-proven and self-perceived food allergy when interpreting prevalence studies.

Previous studies have indicated that the prevalence of food allergy may be different among cultures. This may be due to differences in prevalence of certain food allergies between geographical regions, differences in clinical expression of food allergy or differences associated with ethnicity. These cultural differences in prevalence, clinical expression and also experiencing a certain disease are important motives to perform studies internationally, so that cross-cultural comparisons can be made. All studies in this thesis have been performed in multiple cultures, in order to investigate whether conclusions may be generalized or should be different for different cultures.

It is important to notice that the number of patients suffering from food allergy has increased during the last decades. These prevalence rates may still increase, like the incidence of unnecessary food allergy fatalities. It is therefore important to improve food allergy awareness, identify high-risk patients and make sure that food allergy accidents will be managed adequately.

**Allergy versus intolerance**

Many misconceptions still seem to exist about the pathophysiology of food allergy. Unfortunately, the term food allergy is frequently used popularly when someone dislikes a particular food. Even so, food allergy seems frequently be seen as the most extreme form of food intolerance. However, allergy and intolerance both are adverse reactions towards food with a completely different pathophysiology.

Unlike food intolerance, most food allergic reactions are IgE-mediated and are characterized by an acute onset of symptoms after exposure to the allergenic food, typically within 2 hours. The individual has to be sensitized to the food before such an IgE-mediated reaction can occur. This sensitization involves the production of B cells that are isotype switched to produce antibodies (IgE) specific for proteins in the allergenic food (sIgE). This isotype switching is elicited by TH2 cells which are thought to be the main reason for this immunologic reaction towards the allergenic food. When the sensitized individual is re-exposed to the food, these IgE antibodies will activate
mast cells and basophils, which in turn cause a release of histamine, leukotrienes and cytokines. Histamine and leukotrienes will cause the onset of typical symptoms of the immediate allergic reaction, while the release of cytokines can result in a late phase reaction (which characteristically appears between 2-8 hours after resolution of initial symptoms)\textsuperscript{2,24}.

**Symptoms and severity**
An individual who reacts towards food with an immunologic response may perceive a whole range of symptoms. These symptoms may differ between individuals and also between two different exposures to the food within the same individual. Table 1 shows most common symptoms of a food allergic reaction, which may be present independently.

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Respiratory</th>
<th>Gastrointestinal</th>
<th>Skin</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia</td>
<td>Tightening throat</td>
<td>Nausea</td>
<td>Erythema</td>
<td>Angioedema lips/tongue/palate</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Hoarseness</td>
<td>Abdominal pain</td>
<td>Pruritus</td>
<td>Oral pruritus</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Cough</td>
<td>Vomiting</td>
<td>Urticaria</td>
<td>Eye/nose/mucosal symptoms</td>
</tr>
<tr>
<td>Fainting</td>
<td>Chest tightness</td>
<td>Diarrhea</td>
<td>Angioedema</td>
<td></td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>Dyspnea</td>
<td></td>
<td>Eczematous rash</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wheezing</td>
<td></td>
<td>Flushing</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 - Food allergic symptoms stratified in organ systems

The most extreme variant of any allergic reaction is anaphylaxis. This is a severe allergic reaction that is rapid in onset and may cause death\textsuperscript{25,26}. Food is the most common elicitor of anaphylaxis in children and the second most in adults\textsuperscript{19}. Food allergy related anaphylaxis is an IgE-mediated reaction, which causes a systemic reaction through a rapid release of histamine in the cardiovascular system. In most cases, the reaction will start within minutes with the involvement of the skin, mucosal tissue, or both. These relatively mild symptoms will be followed by respiratory compromise, reduced blood pressure or symptoms of end-organ failure (hypotonia, syncope, incontinence)(Table 2)\textsuperscript{25,26}. 
It is of utmost importance to recognize the unpredictability of food allergic reactions. An initial reaction may be relatively mild. However, subsequent exposures to the same food may cause severe food allergic reactions unexpectedly. Even so, allergic reactions may be biphasic: symptoms may appear again within 72 hours after resolution of initial symptoms, with an incidence of 20 percent in food-related anaphylaxis\textsuperscript{24}.

![Anaphylaxis is highly likely when at least one symptom from Box 1 and one symptom from Box 2 was present during an acute reaction after ingestion of a potential culprit food](attachment)

<table>
<thead>
<tr>
<th>Box 1</th>
<th>Box 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin involvement</td>
<td>Respiratory symptoms</td>
</tr>
<tr>
<td>Mucosal tissue involvement</td>
<td>Cardiovascular symptoms</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 - Definition anaphylaxis

Fortunately, anaphylaxis is extremely uncommon, ranging from 4.5 – 10 cases per 100,000\textsuperscript{19,27,28}, which would imply that there are 167 anaphylaxis cases a year in the Netherlands (based on the population size in 2012). For government, it may therefore not worthwhile investing in emergency medication in public places, school nurses with food allergy expertise, food allergy legislation for restaurant’s staff and public education. However, although food allergic patients do not experience anaphylaxis frequently, they have to live with the idea that anaphylaxis may appear unexpectedly, which significantly impairs quality of life\textsuperscript{29–33}.

**Prevention and management**

There is no intervention available to prevent the development of food allergy. To be specific: maternal diet, breastfeeding, special diets for infants or altered introduction of allergenic foods will not prevent a child to develop a food allergy\textsuperscript{3}. Even so, development of symptoms after accidental ingestion of the allergenic food can not be prevented. Therefore, strict avoidance of the allergenic food(s) is the most important therapy for patients. Education of the patient (and relatives) is especially important in order to achieve this strict avoidance. Education should emphasize food ingredients, reading food package labels and interpretation of these labels. In both the USA and the European Union, regulation requires that the labels of packaged food contain ingredient
statements that list the components of the food. However, the possibility of cross-contamination with allergens in the production and packing of food products remains. This potential cross-contamination is often stated on the products as ‘may contain traces of...’ or ‘manufactured on shared equipment with...’ and is difficult to interpret for food allergic patients. There is currently no legislation for this precautionary labeling, so that manufactures may state a potential risk of cross-contamination with allergens without using any threshold dose. It is therefore difficult to determine the actual risk of consuming the product. This lack of clarity has caused dangerous situations already. Therefore, education should also emphasize recognition of symptoms and management of emergency situations.

In case of accidental exposure, antihistamine can be given to relieve mild symptoms. Additional allergen exposure should be avoided and epinephrine (0.01 mg/Kg in children and 0.30 mg in adults) should be given intramuscularly in the lateral thigh. Thereafter, the patient should be transported to a hospital as soon as possible for further anaphylaxis treatment. When the patient is recovering, observation for 4-8 hours is recommended before discharge. Similarly, the patient should get food allergy education and should be prescribed an epinephrine auto-injector (EAI) for use in future emergency situations. The impact of experiencing anaphylaxis or being prescribed an EAI on quality of life is not known.

**Quality of life in food allergic patients**

Living with a food allergy is difficult in many ways. Most of the time, patients do not have objective symptoms until exposed to the allergenic food. This may cause confusion and misunderstanding in people surrounding these patients. Avoidance of the allergenic food can be difficult for both the patient and his environment. As mentioned before, much confusion exists about the definition of food allergy. The disorder is explained in a whole spectrum of severity and starts with ‘having an aversion for the food’, ‘food intolerance’ and ‘behavioral problems due to food intake’. These stigmata may cause frustration in patients who believe they have a severe food allergy or even experienced severe food allergic reactions. The fact that health-care professionals have little to offer food allergic patients makes it even harder to live with.
Many previous studies have shown that food allergy has a significant impact on quality of life of affected patients and their families. Food allergic patients have reported more pain, poorer overall health, more limitations in social activities and less vitality than people from the general population. Compared to patients with other diseases, food allergic patients reported poorer quality of life than patients with diabetes mellitus, but better quality of life than patients suffering from rheumatoid arthritis, asthma and irritable bowel syndrome.

The fact that food allergic patients and their families must always be alert when they are eating and the resulting feelings of anxiety and insecurity are considered to be most important factors that impair their quality of life. The knowledge that accidentally ingestion of the allergenic food can result in severe and even fatal reactions may make these feelings even stronger.

Until a curative treatment or better emergency treatment is available, health-care professionals should focus on improving health-related quality of life in order to help food allergic patients to cope with their disorder.

**How to measure quality of life**

Quality of life can be measured with generic instruments and disease-specific instruments. Generic instruments are questionnaires developed to measure health-related functioning, including physical, psychological and social themes. These instruments can be used for all kinds of disorders and in healthy people as well. They are especially useful to compare quality of life of patients with different disorders and healthy control groups. A disadvantage of these instruments is that they may be unresponsive and insensitive for specific disorders; disease-specific items are not included in these questionnaires. Disease-specific instruments are developed especially for this purpose and are able to detect small (but potentially important) differences between patients and differences over time in one patient. These disease-specific instruments can not be used for patients with other disorders or healthy controls.

Since food allergic patients do not have daily symptoms and are confronted with specific issues which may impair quality of life, disease-specific instruments were desirable for these patients.
A multinational multicenter research project, sponsored by the European Union, started in 2005 to investigate multiple aspects of food allergy in European countries. This research project, called EuroPrevall, was a great opportunity to build an international database of food allergic patients. One of the aims of EuroPrevall was to investigate the impact of food allergy on health-related quality of life of patients throughout Europe. Therefore, Food Allergy Quality of Life Questionnaires were developed and validated (Table 3).

<table>
<thead>
<tr>
<th>Name</th>
<th>Concerning</th>
<th>Age category</th>
<th>Completed by</th>
<th>Developed in</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAQLQ-AF</td>
<td>Adults</td>
<td>≥18 years</td>
<td>Patient</td>
<td>Netherlands⁵¹</td>
</tr>
<tr>
<td>FAQLQ-TF</td>
<td>Teenagers</td>
<td>13-17 years</td>
<td>Patient</td>
<td>Netherlands⁵⁰</td>
</tr>
<tr>
<td>FAQLQ-CF</td>
<td>Children</td>
<td>8-12 years</td>
<td>Patient</td>
<td>Netherlands⁴⁹</td>
</tr>
<tr>
<td>FAQLQ-PF</td>
<td>Children</td>
<td>0-12 years</td>
<td>Parent</td>
<td>Ireland⁵²</td>
</tr>
<tr>
<td>FAQLQ-PFT</td>
<td>Teenagers</td>
<td>13-17 years</td>
<td>Parent</td>
<td>UK⁵³</td>
</tr>
</tbody>
</table>

Table 3 - Disease-specific instruments for food allergic patients developed within EuroPrevall

**Questionnaire development**

The development and validation of these FAQLQs were performed using established methods:

1. **Item generation phase**

Food allergic patients and a food allergy expert panel discussed which themes and items are important in quality of life in food allergic patients. These discussions were held in focus groups and were performed with patients of different age-groups.

2. **Item reduction phase**

Another group of patients received the list of generated items and determined which items were most important for them, using the clinical impact method.

3. **Cross-sectional validation**

The construct validity of the final questionnaire was investigated by measuring the correlation between the total FAQLQ score and an independent measure, completed by another group of food allergic patients. When the construct validity of a questionnaire is established, it succeeds to measure what it has to measure. For food allergy, the Food
Allergy Independent Measure (FAIM) was developed for this purpose\textsuperscript{51}. This FAIM is yet another questionnaire which measures the self-perceived severity of the food allergy, as reported by the patient himself.

4. *Longitudinal validation*

The longitudinal validity is finally investigated: the ability of the questionnaire to measure differences in quality of life over time. This longitudinal validation still is an ongoing process in the FAQLQs, although some of them were already validated this way\textsuperscript{42,52}.

**Cross-cultural comparison**

The FAQLQs, originally developed and validated in the Netherlands, Ireland and the UK had to be translated for use in other cultures. The World Health Organization (WHO) has developed a translation process that can be used to translate an instrument conceptually equivalent in the target populations\textsuperscript{53}:

1. *Forward translation*

A native speaker of the target language translates the original questionnaire. The translator should preferable be a health-care professional with knowledge of the subject and keeps the age, gender and culture of the target group in mind during this translation.

2. *Backward translation*

A native speaker of the language of the original questionnaire, with reasonable knowledge of the target language, translates the forward translation back into a version of the original language without consulting the original version of the questionnaire.

3. *Expert panel*

The back-translation is then compared with the original version of the questionnaire by a bilingual expert panel, consisting of the two translators and some field experts who can assess the conceptual equivalence of both questionnaires. Suggestions may be made for improvement.
4. **Pre-testing**

After the translation, the questionnaire has to be pre-tested in the target group, which preferably consists of at least 10 participants. The participants are interviewed during or after completing the questionnaire about their understanding and their opinion about the items concerning cultural differences.

5. **Final version**

Based on the pre-test and comments of the participants, minor adjustments are made for the final version of the questionnaire.

After the translation process, validity of the instrument is preferably tested again for use in the new cultural and linguistic setting through a validation study in the target population. This cross-cultural validation process may involve a cross-sectional study in which the construct validity of the instrument is investigated using similar methods as used in the original instrument development study. In food allergy, this validation process may be performed by administering both the FAQLQ and the FAIM in the target population and calculating the correlation between the mean scores obtained for these two instruments by the participants.

An advantage of a cross-cultural validation study is the possibility to compare the outcomes of participants in the study with the outcomes of participants in the original development study. Aim of this cross-cultural comparison is to investigate whether food allergic patients have impaired HRQL in all cultures. If cross-cultural differences exist, it would be interesting to know why, so that interventions can be developed.

**Modifiable factors**

The most important items concerning quality of life in food allergy are included in the FAQLQs, since the items in these instruments were formulated and selected by the patients themselves (although, these patients were from the Netherlands). Based on these items and results of previous studies, allergy themes may be selected that could be of importance and may be modifiable themes for patients in the Netherlands:

One aspect considered to be important for food allergic patients is the understanding and sympathy of others towards their disorder and accompanying lifestyle/restrictions. It is important that primary care physicians recognize the symptoms, know how to
diagnose food allergy, know which patient education is needed and know how to treat food allergic reactions. In the Netherlands, patients are highly dependent on the knowledge, attitudes and beliefs of their general practitioner, since these physicians manage most of the consultations by themselves and are the only ones who can refer patients to specialists. For food allergic children, parents are considered to be most important for the recognition of symptoms, consulting a primary care physician, helping the children with strict allergen avoidance and the immediate treatment of severe reactions. Parental knowledge, attitudes and beliefs are therefore considered to be important for food allergic children. As mentioned before in this general introduction, daily struggles concerning allergen avoidance are important aspects of food allergy related quality of life as reported by the patients themselves. For example visiting a restaurant, going to school/daycare, visiting neighbors, friends or family, and grocery shopping are potentially dangerous matters when suffering from food allergy. Especially the continuous insecurity and anxiety due to fear of severe reactions when eating out have been reported to impair food allergy related quality of life. Understanding and sympathy of people being confronted with these patients and their restrictions may diminish this insecurity and anxiety. Therefore, knowledge, attitudes and beliefs of the general public are considered to be important and potentially modifiable aspects as well.

Another aspect of interest is whether quality of life of food allergic patients can be predicted by patient characteristics. In other words: which food allergic patients suffer most from their disease? Previous studies already showed that self-perceived severity of the disease is an important aspect and other studies have shown gender-related differences. However, no study has ever investigated which patient-related factors are most important. It would be especially interesting to investigate the impact of experiencing anaphylaxis and being prescribed an adrenaline auto-injector on food allergy related quality of life.

Finally, when these cross-sectional measurements are performed, interventions may be developed in order to improve quality of life in food allergic patients. In addition, the effect of these interventions may be measured in different countries using uniform instruments: the translated and validated FAQLQs.
Aims and outline of this thesis

Part I: The first aim of this thesis was to translate and validate the Food Allergy Quality of Life Questionnaires (FAQLQs) for use in different countries. Once cross-sectional validity of these translated FAQLQs was established, the impact of food allergy was investigated in different countries. Cross-cultural comparisons were performed to find out whether having food allergy is experienced differently in patients from different countries. In chapter 2, the FAQLQ-AF was translated and validated for use in the USA. In chapter 3, the same FAQLQ-AF was translated and validated for use in eight European countries. Chapter 4 describes the translation and validation of the FAQLQ-CF in European countries. These three chapters all include a cross-cultural comparison of HRQL between participating countries and the Netherlands.

Part II: Baseline measurements were performed to investigate the knowledge, attitudes and beliefs regarding food allergy among general practitioners (chapter 5), parents (chapter 6) and the general public (chapter 7) in the Netherlands. Results of these studies were compared with data from family doctors, parents and the general public from the USA.

Part III: The final aim of this thesis was to investigate which factors predict health-related quality of life in food allergic patients. The influence of participant characteristics, experiencing anaphylaxis and being prescribed an EAI were investigated in this context and described in chapter 8.

Furthermore, this thesis aims to increase awareness of food allergy in the Netherlands. Readers may hopefully recognize the importance of their knowledge, attitudes and beliefs for the quality of life of food allergic patients. In addition, this thesis aims to increase awareness among physicians regarding the phenomenon health-related quality of life. Many physicians may believe that this is not the most exciting part of medicine, while I believe that it may be the most important issue for their patients. Quality of life is frequently misunderstood as being a subjective measure or easily measurable by asking the patient just one simple question. This image will hopefully be seen as an anachronism after reading this thesis.
REFERENCES


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Food Allergy Quality of Life Questionnaires